REducing INFectiOns thRough Cardiac device Envelope: insight from real world data. The REINFORCE Project

Short title: Effectiveness of antibacterial envelopes in daily practice

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Abbreviations

AF: Atrial Fibrillation

BMI: Body Mass Index

CIED: Cardiac Implantable Electronic Device

CKD: Chronic Kidney Disease

CRT: Cardiac Resynchronization Therapy

CRT-D: Cardiac Resynchronization Therapy defibrillator;

CRT-P Cardiac Resynchronization Therapy Pacemaker

ECG: Electrocardiogram

HF: Heart Failure

HR: Hazard Ratio

ICD: Implantable Cardiac Defibrillator

ICD-DC: dual chamber implantable defibrillator

ICD-SC: single chamber defibrillator;

LVEF: Left Ventricular Ejection Fraction

NNT: number needed to treat

NYHA: New York Heart Association Functional Classification

PADIT: (Prevention of Arrhythmia Device Infection Trial)

PM: PaceMaker

PS: Propensity Score

TIA: Transient Ischemic Attack

VF: Ventricular fibrillation

VT ventricular tachyarrhythmias

Keywords: *Systemic infection, pacemaker, pocket infection, CIED, antibiotic eluting envelope.*

Abstract

Background: Infections resulting from cardiac implantable electronic device (CIED) implantation are severely impacting on patients' and on health care systems. The use of TYRX™ absorbable antibiotic-eluting envelope has proven to decrease major CIED infections within 12 months of CIED surgery.

Aims: to evaluate the impact of the envelope use on infection-related clinical events in a real-world contemporary patient population.

Methods: Data on patients undergoing CIED surgery were collected prospectively by participating centers of the One Hospital ClinicalService project. Patients were divided into two groups according to whether TYRX™ absorbable antibiotic-eluting envelope was used or not.

Results: Out of 1819 patients, 872 (47.9%) were implanted with an absorbable antibiotic-eluting envelope and included in the Envelope group and 947 (52.1%) patients who did not receive an envelope were included in the Control group. Compared to control, patients in the Envelope group had higher thrombo-embolic or hemorrhagic risk, higher BMI, lower LVEF and more comorbidities. During a mean follow-up of 1.4 years, the incidence of infection-related events was significantly higher in the control compared to the Envelope group (2.4% vs 0.8%, p=0.007). The 5-year cumulative incidence of infection-related events was 8.1% in the control and 2.1% in the Envelope group (HR: 0.34, 95%CI: 0.14-0.80, p=0.010).

Conclusions: In our analysis, the use of an absorbable antibiotic-eluting envelope in the general CIED population was associated with a lower risk of systemic and pocket infection.

Introduction

Infections resulting from cardiac implantable electronic device (CIED) implantation are rare but serious complications impacting on patients' outcome and the entire health care system due to hospitalizations, associated complications, increased mortality and costs. [1-5] Recently, a randomized clinical trial [6] and observational studies have demonstrated the efficacy of an absorbable antibiotic-eluting envelope (TYRX™, Medtronic, Minneapolis, US), in reducing the risk of CIED-related infections in particular in case of CIED replacement procedures, upgrades, revisions, or initial cardiac resynchronization therapy - defibrillator implantation [6-10]. Nevertheless, there is still a lack of understanding which patients receive the envelope in the real-world clinical practice, and TYRX™ efficacy in a setting different from a randomized trial. The aim of the present analysis is to describe a

large, unselected population undergoing CIED surgery, and observe TYRX™ efficacy in preventing infection- related events along follow up.

Methods

Project design

Consecutive patients undergoing an initial Medtronic CIED implant, or CIED surgery from August 2016 until May 2022 in the 11 Italian centers participating in the One Hospital ClinicalService project were included in the analysis. One Hospital ClinicalService is a clinical data repository and medical care project designed to describe and improve the quality of diagnostic and therapeutic strategies using technologies and therapies in Italian clinical practice. The project consists of a shared environment for the prospective collection, management, analysis, and reporting of data from patients who have received Medtronic therapies. An independent scientific committee of physicians prospectively identifies key clinical questions on an annual basis for purposes of analysis and publication. A charter assigns the ownership of data to the centers and governs the conduct and relationship of the scientific committee and Medtronic. Medtronic did not have any role in identifying research objectives, interpreting results, or drafting the manuscript. In the REINFORCE (REducing INFectiOns thRough Cardiac device Envelope) project, physicians were prospectively aiming to collect patient and Medtronic device data on risk of infection in patients underwent CIED surgery, and to assess the outcomes including systemic or pocket infection in the setting of the daily clinical practice. This project was approved by each site's Institutional Review Board and Local Ethics Committees and conforms to the principles outlined in the 1975 Declaration of Helsinki as reflected in the *a priori* approval by the institution's human research committee. Each patient included in the One Hospital ClinicalService project provided informed consent for data collection and analysis.

The objective of this research was to describe the patient population who received the antibacterial envelope during Medtronic CIED implantation or CIED surgery, and to assess the impact of the envelope

in preventing infection-related events. The primary efficacy endpoints were defined before the beginning of the analysis and were the incidence of infection-related events (including system infections or pocket infections).

The patient population was divided into two groups. The Envelope group consisted of patients that received an absorbable antibiotic-eluting envelope for the index procedure or a system modification, and the control group included patients who underwent CIED surgery without the use of envelope. Standards of clinical practice at each participating center determined when patients were treated with or without antibiotic eluting envelopes.

Population and procedural characteristics

During the baseline visit several patients' clinical characteristics were collected, including age, sex, NYHA class, CHA2DS2-VASc scores, presence of hypertension, diabetes, previous thromboembolic events, presence of structural heart disease (with the left ventricular ejection fraction (LVEF) measured by echocardiography, presence of renal insufficiency, immunodeficiency. Moreover, the history of procedures on existing pockets was collected (generator replacement, system revision or upgrade including any lead procedure), device type (pacemaker (PM), implantable cardiac defibrillator (ICD), cardiac resynchronization therapy (CRT)), presence of active or abandoned leads and presence of fever in the 48h prior to the procedure. Antibiotic prophylaxis was administered in almost all patients according to the clinical practice of each center; cephalosporins being 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 administrated 2 hours before the incision. All information about any infection-related adverse events occurring during the procedure or during the follow-up was recorded and collected. A pocket infection was defined as superficial cellulitis in the region of the CIED pocket with wound dehiscence, erosion, or purulent drainage or deep incisional (pocket) surgical-site infection or persistent bacteremia according to the definition used in WRAP-IT

trial [6]. A systemic infection was defined as infection (including positive blood cultures and lead vegetations), persistent bacteraemia or endocarditis involving many different parts of the body or more than one body system at the same time with clinical sign like fever.

Follow-up and event collection

Follow-up visits were made in accordance with the clinical practice of each center, including clinic visits for stiches removal or wound control 10-15 days after the surgery, then every 3-6 months in case of ICD or CRT devices and every 6-12 months in case of PM. The standard visit consisted of an assessment of the patient's symptoms, an electrocardiogram (ECG), device interrogation and device pocket examination, and an assessment of the patient's medications. If patients missed the scheduled in-hospital follow-up visits, they or their relatives were contacted by phone; after two unsuccessful attempts at phone contact, information on patients' survival was collected from the National Office of Vital Statistics.

Statistical analysis

Descriptive statistics were used to summarize all results. These include mean and standard deviation and median with interquartile range (IQR) for continuous variables and counts and percentages for categorical variables. Continuous variables were compared between groups using Wilcoxon's test., and categorical variables were compared between groups using the Chi-square test or Fisher's exact test, as appropriate. All statistical tests were based on a two-sided significance level of 0.05. Incidence Rates (IRs) were expressed as number of events / 100 patient-months, and estimated using Poisson regression models, with deviance scaling to correct for over/under-dispersion. Estimates along with their 95% Confidence Intervals (CIs) were reported. Estimated differences between groups were expressed as Incidence Rate Ratios (IRRs), along with their 95% CIs. For all patients, only clinical events after the implant date (start date) during the study period were considered. The end date was the last contact date. Last contact date was defined as the latest date among in-hospital FU dates, telephone contact dates, clinical event dates

system modification date and exit dates. We calculated for each patient the raw PADIT risk scores [14] and the relative risk of infection-related events for each score was estimated and reported as Odds Ratio (OR), together with its 95% CI as a sensitivity analysis. To account for differences in baseline characteristics between envelope and control groups, propensity score (PS) method was utilized to estimate an adjusted risk ratio for infection between envelope and control. The PS method was used to adjust the group's risk ratio in both Poisson and Kaplan-Meier analysis. The propensity scores for each patient were calculated by using a logistic regression model that included PADIT risk score only. PADIT risk score groups (Low, Medium and High) were used as the only match. Additionally, a sensitivity analysis of the primary outcome was performed using inverse probability of treatment weighting (IPTW) on propensity scores. SAS software, version 9.4, (SAS Institute Inc., Cary, NC, USA) was used to perform statistical analyses.

Results

In this analysis, 1819 consecutive subjects underwent an index CIED implantation or system modification in 11 centers. There were 872 (47.9%) subjects in the Envelope group, and 947 (52.1%) in the Control group. The mean percentage of patients treated with envelope per center was 58.6% ± 37.Supplementary table 1

Baseline and Procedural Characteristics

Baseline patient characteristics and procedural data are listed in **Table 1.** There were several differences between the Envelope and Control group, with regard to baseline characteristics. The Envelope group was more likely to be younger, have higher BMI and CHA_2D_2-VASC score, more likely to have a history of heart failure, ventricular arrhythmic episodes, ischemic heart disease, hypertension, diabetes and chronic kidney disease and have lower (LVEF) and to use anticoagulant drugs. Importantly, the groups of patients differed also for infective risk calculated using PADIT score: in the Envelope group, more than 37% of patients were at high risk according to PADIT score, contrary to 11% in the Control group. ($p<0.001$) All other baseline characteristics did not differ, including sex, history of

stroke/TIA, and history of atrial fibrillation (AF). (**Table 1**). Out of 1819 patients, 1817 were in antibiotic prophylaxis during the CIED implant or surgery. In two patients the data was missed.

Out of 1819, 39.7% of patients were implanted with a PM, with a significant difference between the two groups (34.0% and 44.4% in the Envelope and control group, respectively, p<0.001). In the Envelope group, 40.6% of subjects were implanted with a CRT-D, while 26.7% in the Control group received a CRT-D (p<0.001). In the whole population, 1178 (65%) were de-novo patients, while 641 (35%) had a previous CIED implantation.

Infection-related events

During a mean follow up time of 1.4 ± 1.7 years (1.5 ± 1.7 in the Envelope and 1.4 ± 1.6 in the control group, p=0.534), 27/1819 (1.5%) patients experienced a pocket infection, 3 (0.2%) a systemic infection. **Table 2** The Control group had significantly higher overall pocket infection or systemic infection rates as compared with the Envelope group (2.4% (23/947) vs 0.8% (7/872), p=0.007).

All pocket infections resulted in CIED system removal (device and leads). Pocket infection occurred in 5 subjects (0.6%) in the Envelope group and in 22 (2.3%) patients in the Control group, p=0.002, as shown in **Table 2.** Systemic infection occurred in 3 subjects, 2 in the Envelope group and 1 in the control group. Out of those 3 subjects, 2 died as a consequence of the systemic infection. The monthly rate per 100 patients of the composite endpoint of pocket infection and systemic events was 0.04 (95% CI 0.06-0.06) and 0.16 (95% CI 0.14-0.19) in the Envelope and Control group, respectively (p<0.001). The incidence rates confirm the protective effect of the envelope in the Envelope group with respect to infection-related events, with a risk reduction of 62% (IRR: 0.38, 95% CI 0.19-0.38, P<0.001). We adjusted the incidence rates taking into account each center in order to consider the differences in the usage of envelope amongst participating centers between Envelope and Control groups. The findings confirmed the main analysis: The adjusted monthly rate per 100 patients was 0.03 (95% CI 0.02-0.04) and 0.15 (95% CI 0.12-0.18) in the Envelope and Control group, respectively (adjusted IRR: 0.20, 95% CI 0.14-0.28, P<0.001). The unadjusted survival analysis for risk showed the 5-year event rate of 2.1% (95% CI 0.8-5.0%) in the

Envelope group vs 8.1% (95% CI 4.3%-15.0%) in the Control group (HR: 0.34, 95%CI: 0.14-0.80, p=0.010), as shown in **Figure 1** panel A. **Table 3** shows the incidence of infection related events according to PADIT risk scores. Out of 903 patients with a low PADIT score (Score: 0-4), 11 (1.2%) had at least infection-related event: no events occurred in the 271 patients in the envelope cohort, while 11 (1.7%) occurred in the 632 patients in the Control group (p = 0.029). In contrast, out of 433 patients with high PADIT scores (score ≥7), there were 11 events (2.5%): 5 of 325 (1.5%) in the Envelope group, and 6 of 108 (5.6%) in the control group, p=0.022. Out of 1178 patients with de-novo CIED implantation, in 18 (1.5%) occurred a systemic or pocket infection: 3 (0.8%) in the Envelope group vs 15 (1.9%) in the Control group (p=0.130). The monthly rate per 100 patients was 0.04 (95%CI 0.03-0.07) in the Envelope and 0.13 (95% CI 0.11-0.16) in the Control group, p<0.001. **Supplementary table 2A** showed the event rates per group. In the group of patients with previous CIED surgery, systemic or pocket infection occurred in 12 patients: 4(0.8%) in the Envelope group and 8 (4.9%) in the control group, p<0.001. The monthly rate per 100 patients was 0.04 (95% CI: 0.03-0.06) in the Envelope and 0.25 (95% CI 0.19-0.32) in the Control group, p<0.001. **Supplementary table 2 B**

A matched cohort sub-analysis

Propensity score matching, using PADIT score as variable, identified 585 pairs of patients with balanced baseline characteristics with respect to PADIT Score [14]. Baseline characteristics are shown in **Supplementary Table 3**. The mean follow up was 1.5 years with no significant differences between the two groups of patients. The risk of systemic or pocket infection at 60 months post implant was 7.7% (95% CI: 3.7% - 15.4%) in the control group and 1.2% (95% CI: 0.5% - 3.3%) in the Envelope group (HR: 0.28, 95% CI:0.09-0.82, p=0.014) as shown in **Figure 2** panel A. The incidence of infection related events is shown in **Supplementary table 4**.

Additionally, a sensitivity analysis of the primary outcome using IPTW on propensity scores was performed, as shown in **Supplementary table 5 and 6**. The results confirmed the main analysis.

Discussion

Main results

The main findings of the present study are as follows: (1) in contemporary clinical practice, the absorbable antibiotic eluting envelope was more frequently used to prevent infection-related complications in the cohort of patients with higher infective risk scores; (2) use of the antibacterial envelope was associated with a lower risk of the composite endpoint of systemic or pocket infection by more than 60% and when considering a propensity-matched population, the reduction of the risk of the events was higher, (3) these findings were confirmed on long term follow-up.

Patient Population

Infections resulting from CIED implantation are rare but are associated with significant morbidity, mortality and increased cost. [1-4] The majority of infections involve the device pocket, but they can lead to infective endocarditis and progress into systemic infections. [1-4] In some patients with worse prognoses, systemic infection may lead to lead- related endocarditis progressing to pocket infection [15-16]. The rates of infections in the CIED populations ranges from 1% to 19.9% [1-2] and depend on several factors including clinical characteristics and presence of comorbidities, procedural complexity and numbers and times to re-interventions. Recently, a large, randomized study demonstrated the incremental benefit in using an antibacterial envelope in reducing the rate of overall CIED infections by approximately 40%.[6] Moreover, the envelope has been showed to prevent hematoma from transitioning into an infection. [13] In our study, we prospectively collected data on baseline characteristics, envelope usage and infection-related events in consecutive patients during routine clinical practice. The antibacterial envelope was used in 48% of observed patients, and these patients were at higher infective risk (mean PADIT score 5.6 ± 3.1 vs 3.3 ± 2.8 in the Envelope and control group, respectively), with more comorbidities, and more often implanted with CRT-D, compared to the cohort of patients without envelopes. In contrast, the RI-AIAC study showed that in a real-life cohort of patients receiving a CIED, the envelope was used in a few selected cases (2% of enrolled patients). These differences in the use of

envelope could be explained by the older cohort of patients, and the higher percentage of PM implants in the study by Boriani et al. (RI-AIAC), two factors that are related to a lesser infection risk (PADIT). [17]

Our findings showed that among the participating centers the median value of percentage of patients with envelope was 68.3% (I-III Interquartile range: 24%-86%). This heterogeneous situation depended on the choice and clinical practice of each center.

Efficacy/effectiveness in preventing infections

The WRAP-IT study [6] showed the TYRX™ was significantly more effective at preventing infection than standard infection-control strategies alone with an event rate at 1 year of 0.7% and 1.2%, respectively (hazard ratio, 0.60; 95% CI, 0.36 to 0.98; P = 0.04). In our analysis, at 1 year the event rate of systemic or pocket infection was 1.3% (95% CI 0.6% - 2.8%) in the Envelope group and 2.1% (95% CI: 1.2% - 3.6%) in the Control group, increasing at 2.1% (95% CI 0.8% - 5.0%) and 8.1% (95% CI: 3.5% - 10.3%) at the 5th year. This raises the hypotheses that preventing bacterial seeding at any index procedure may prevent pocket infection at a later stage [18]. Interestingly, a long-term analysis of the WRAP-IT trial data [19] showed that infections continued to rise at 12 months post-procedure and that device-related infections are time-dependent and not confined to the 12 months after the index procedure. Although data on repeated procedures (lead repositioning, pocket revision) that might represent further opportunities for pocket infection are missing in both these studies the hypothesis of a sustained benefit of TYRX™ at long term should not be neglected. In our study, when propensity matched populations are considered, the rate of infection-related events increased only in the control group, while in the envelope group remained stable in the first-year post-procedure. These data further support that the use of the antibiotic envelope, on the top of antibiotic prophylaxis, should be included in any peri-operative plan targeted to minimize the infection risk in appropriately selected patients, on the basis of their clinical profile and predicted risk of CIED infections in combination with a series of clinical measures and logistical-organizational features. [11-21]

In this study, the overall incidence of systemic or pocket infection was around 1.6%. In particular, 0.2% was system infection, while 1.5% pocket infection. The large use of antibiotic prophylaxis, standard protocols to prevent infections including chlorhexidine skin preparation and preventive strategies in case of increased risk, may influence these occurrences. The diagnosis of pocket or systemic infection is very challenging. However, in this study, systemic infections are only diagnosticated in case of presence of clinical signs with positive blood cultures and the presence of lead vegetations. In the general CIED population, current data have reported that CIED infection ranged from 0.1–0.7% to 4% depending on the type of device, procedure, and centers. [6,22] When high risk population was assessed, we found that the incidence of infection rose to 5.6% during a mean follow up of 1.4 years.

Our results were in line with the results of previous studies, showing a risk reduction of 62% in the incidence of CIED infection. The WRAP-IT demonstrated a 40% reduction in CIED infections and a 60% reduction in major pocket infections [6] in high-risk patients with a positive cost-effective analysis. Moreover, we also reported a reduction in the incidence in low-risk patients according to PADIT risk score. A reduction in the prize of the envelope might broaden the use of the device after further evidence. More larger and randomized studies are needed to corroborate these early findings.

Cost-Efficacy consideration

The use of the envelope is associated with additional costs which need to be compared to the benefits it provides. [23]A common method to compare costs and benefits is cost-effectiveness analysis. In cost-effectiveness analysis, the incremental costs of an intervention are compared to the willingness to pay threshold for a better health outcome. The antibacterial envelope has been reported to be cost-effective in selected patients at increased risk of infection in Italy based on the WRAP-IT study. The number needed to treat ranged from 35-185 in the different patient groups. The sensitivity analysis showed the risk of infection required for the envelope to be cost-effective was around 2.7% for Italy. [24] In this study, the risk of systemic or pocket infection 5 years post-implant were 8.1% in the control group, 6.0% percentage points higher than in treatment group. This results in a number needed to treat (NNT) per infection

avoided of 15. It is highly suggestive that use of the antibacterial envelope was cost-effective in this real-world cohort of patients with higher infective risk scores than in the above-mentioned cost-effectiveness analysis for Italy.

Limitations

This analysis presents some limitations, including: 1) its non-randomized observational nature, so bias could be present in patient selection and treatment; in particular, selection bias and possible presence of the imbalanced distribution in baseline characteristics may have affected the data set as it is possible that there were factors (e.g., risk of infection, drug therapy, attitude of physicians, economic issues) which influenced envelope usage. To overcome this issue, sensitivity analyses based on the propensity score matching and inverse probability of treatment weighting (IPTW) on propensity scores was additionally conducted to control for this imbalance and potential bias 2) data of infection-related events were collected during in hospital follow-up visits but some events treated in other hospitals may have been missed; 3) Pocket and systemic infection were judged to be adverse event based on the description provided by the physician; 4) the absence of a standardized protocol for the follow up; 5) the envelope group had more comorbidities compared to the control group, though paired-group analyses based on similar PADIT score risk were conducted, and found similar findings; 6) the data were based on the clinical practice of several participating centers with different standard-of-care procedures. No recommendations were provided to the participating centers in terms of pharmacological and antibiotic treatment prior to and following the procedure. However, these limitations are balanced by the accurate picture of real-world clinical patient treatment that these data provide.

Conclusions

In our real-world experience, the use of an absorbable antibiotic-eluting envelope in the general CIED population appeared of clinical value, being associated with a lower risk of the composite endpoint

of systemic and pocket infection. The percentage of infection-related events in the contemporary population was low, around 2% at 1 year and the use of the envelope in clinical practice seemed to be preferred in case of high-risk infection patients. The use of the Envelope was associated with a reduction of infection-related events of more than 60% in high, medium, and low risk populations and its protective effect was maintained over time.

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Compliance with Ethical Standards:

All procedures performed in this project involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest Disclosures

MZ received speeker's fees from Abbott, Biotronik and Boston Scientific; GB 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.

Data Availability Statement

The datasets generated during and/or analysed during the current study are available on reasonable request

Funding sources

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Ethical approval

This project was approved by each site's Institutional Review Board and Local Ethics Committees.

Informed Consent.

Each patient included in the ClinicalService project provided informed consent for data collection and analysis.

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Table 1. Baseline characteristics of the total population and statistical comparisons between the two groups of patients: subjects in the Envelope group versus the Control group.

Baseline Characteristic	TOTAL (n=1819)	Envelope (N = 872)	Control (N = 947)	p-value
Demographics				
Age (yrs/old)	72.8 ± 14.0	72.1 ± 14.1	73.4 ± 13.9	**0.036**
Gender (Male)	69.5% (1263)	69.2% (603)	69.7% (660)	0.830
BMI (kg/m²)	26.7 ± 4.6	27.1 ± 4.7	26.5 ± 4.4	**0.049**
Medical history				

Baseline Characteristic	TOTAL (n=1819)	Envelope (N = 872)	Control (N = 947)	p-value
History of HF	52.1% (947)	64.8% (565)	39.9% (382)	**<0.001**
History of VT/VF	16.2% (294)	18.1% (157)	14.5% (137)	**0.038**
History of AT/AF	38.4% (698)	40.5% (353)	36.5% (345)	0.084
Paroxysmal AF	18.2% (331)	17.4% (151)	18.9% (180)	0.402
Persistent AF	5.4% (98)	6.2% (54)	4.7% (44)	0.190
Permanent AF	14.8% (269)	16.9% (147)	12.8% (122)	**0.014**
Ischemic Heart Disease	34.1% (620)	39.5% (341)	29.0% (279)	**<0.001**
Valvular Disease	32.6% (593)	41.0% (349)	24.7% (244)	**<0.001**
History of Stroke/TIA	4.4% (80)	4.9% (43)	3.9% (37)	0.307
Hypertension	76.6% (1393)	79.4% (691)	74.1% (702)	**0.008**
Diabetes	27.6% (502)	33.8% (294)	22.0% (208)	**<0.001**
Chronic Kidney Disease	25.2% (458)	36.8% (320)	14.0% (138)	**<0.001**
$CHADS_2 \geq 2$	73.2% (1331)	80.4% (701)	66.5% (530)	**<0.001**
CHA_2DS_2-VASc≥4	50.1% (911)	58.9% (513)	42.3% (398)	**<0.001**
COPD	11.5% (209)	12.5% (109)	10.6% (100)	0.209
LVEF (%)	43.4 ± 14.3	40.7 ± 13.2	46.2 ± 14.9	**<0.001**
Risk Score				
PADIT Risk Score	4.4 ± 3.2	5.6 ± 3.1	3.3 ± 2.8	**<0.001***
Low (Score: 0-4)	49.6% (903)	31.1% (271)	66.7% (632)	
Medium (Score: 5-6)	26.6% (483)	31.7% (276)	21.9% (207)	
High (Score: ≥7)	23.8% (433)	37.3% (325)	11.4% (108)	
Implantable device Type				
CRT-D	32.9% (599)	40.6% (352)	26.7% (247)	**<0.001***
CRT-P	8.4% (152)	8.5% (74)	8.3% (78)	
ICD-DC	11.1% (201)	10.3% (90)	11.7% (111)	
ICD-SC	7.9% (143)	6.6% (57)	8.9% (86)	
PM	39.7% (724)	34.0% (299)	44.4% (425)	
De Novo CIED	64.7% (1178)	45% (393)	82.8 % (785)	**<0.001**
De Novo PM	52.9% (623)	51.2% (201)	53.8% (422)	0.457
De Novo ICD	47.1% (555)	48.8% (192)	46.2% (363)	0.457
Previous CIED implantation	35.2% (641)	54.9% (479)	17.1% (162)	**<0.001**
To PM	61.2% (392)	65.0% (308)	52.1% (84)	**0.008**
To ICD	38.8% (249)	35.0% (171)	47.9% (78)	**0.008**
Antiplatelets and Anticoagulant use				
Antiplatelets	33.5% (609)	32.1% (279)	34.7% (330)	0.251
Anticoagulant	35.9% (653)	39.4% (343)	32.6% (310)	**0.004**

* Statistical test conducted between entire Envelope cohort versus Control group on device distribution.

Abbreviations: BMI: Body mass index; HF: heart failure; AF : atrial fibrillation; VT ventricular tachyarrhythmias; VF: Ventricular fibrillation; TIA: transient ischemic attack; LVEF: left ventricular ejection fraction : CRT-D : Cardiac Resynchronization Therapy defibrillator; CRT-P Cardiac Resynchronization Therapy Pacemaker; ICD-DC: dual chamber implantable defibrillator; ICD-SC: single chamber defibrillator; PM: Pacemaker

Table 2. Infective related events of the total population and comparison between the two groups of patients: subjects in the Envelope group versus the Control group.

CLINICAL EVENT	TOTAL (N=1819)	ENVELOPE (N = 872)	CONTROL (N = 947)	P-VALUE
At least one infection-related clinical event (systemic or Pocket infection)	1.6% (30/1819)	0.8% (7/872)	2.4% (23/947)	**0.007**
Pocket infection	1.5% (27/1819)	0.6% (5/872)	2.3% (22/947)	**0.002**
Systemic infection	0.2% (3/1819)	0.2% (2/872)	0.1% (1/947)	0.516

Table 3: Infective related events according to PADIT score.

At least one infection-related clinical event (Pocket or Systemic infection)				
PADIT Score = Low	1.2% (11/903)	0.0% (0/271)	1.7% (11/632)	**0.029**
PADIT Score = Medium	1.7% (8/483)	0.7% (2/276)	2.9% (6/207)	0.064
PADIT Score = High	2.5% (11/433)	1.5% (5/325)	5.6% (6/108)	**0.022**
At least one Pocket infection				
PADIT Score = Low	1.1% (10/903)	0.0% (0/271)	1.6% (10/632)	**0.037**
PADIT Score = Medium	1.7% (8/483)	0.7% (2/276)	2.9% (6/207)	0.064
PADIT Score = High	2.1% (9/433)	0.9% (3/325)	5.6% (6/108)	**0.003**

Figure Legend

Figure 1.
Panel A Cumulative Event Rate of systemic or pocket infection in the Envelope and Control group by Kaplan-Meier estimate.

Figure 2. Cumulative Event Rate of systemic or pocket infection in the propensity matched cohort: Envelope and Control group by Kaplan-Meier estimate.

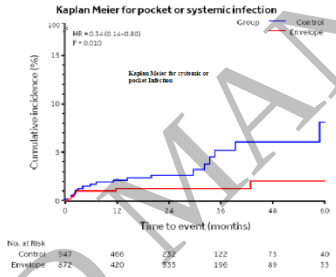


Figure 1
57x46 mm (x DPI)

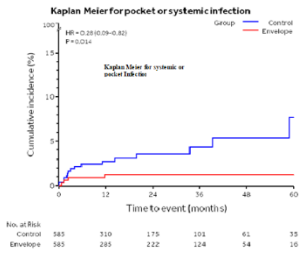
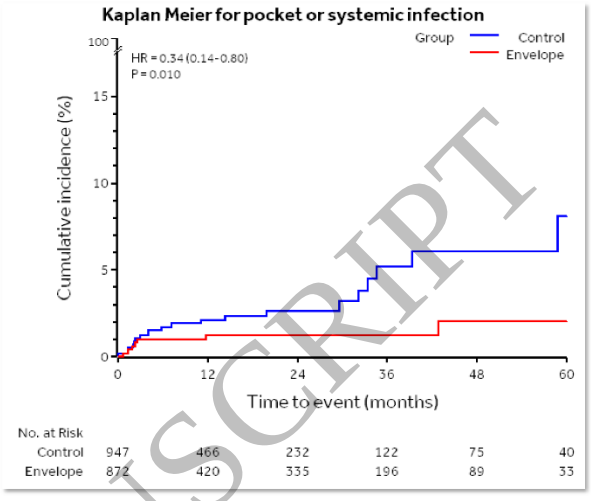


Figure 2
57x46 mm (x DPI)

The use of the Envelope was associated with a reduction of infection-related events of more than 60% in high, medium, and low risk populations and its protective effect was maintained over time.

At least one infection-related clinical event (Pocket or Systemic infection)	TOTAL (n=1819)	Envelope (N = 872)	Control (N = 947)	p-value
PADIT Score = Low	1.2% (11/903)	0.0% (0/271)	1.7% (11/632)	**0.029**
PADIT Score = Medium	1.7% (8/483)	0.7% (2/276)	2.9% (6/207)	0.064
PADIT Score = High	2.5% (11/433)	1.5% (5/325)	5.6% (6/108)	**0.022**

Infective related events (Systemic or pocket infections) according to PADIT score.



Cumulative Event Rate of systemic or pocket infection in the Envelope and Control group by Kaplan-Meier estimate.

Graphical Abstract
180x101 mm (x DPI)