ScienceDirect

Contents lists available at **sciencedirect.com**
Journal homepage: **www.elsevier.com/locate/jval**

Cost-Effectiveness Analyses of an Absorbable Antibacterial Envelope for Use in Patients at Increased Risk of Cardiac Implantable Electronic Device Infection in Germany, Italy, and England

Giuseppe Boriani, MD, Charles Kennergren, MD, PhD, Khaldoun G. Tarakji, MD, MPH, David J. Wright, MD, Fozia Z. Ahmed, MD, Janet M. McComb, MD, Andreas Goette, MD, Thomas Blum, MD, Mauro Biffi, MD, Michelle Green, MSc, Judith Shore, BA, Phuong Lien Carion, PharmD, Bruce L. Wilkoff, MD

ABSTRACT

Objectives: To model the cost-effectiveness of the TYRX Absorbable Antibacterial Envelope when used in patients at increased risk of cardiac implantable electronic device (CIED) infection in the context of 3 European healthcare systems: Germany, Italy, and England.

Methods: A decision tree model with a lifetime horizon was populated using data from the Worldwide Randomized Antibiotic Envelope Infection Prevention Trial, a large multicenter randomized controlled trial. Use of the antibacterial envelope adjunctive to standard of care was compared to standard of care infection prevention alone. Patients in the model were divided into subgroups based on presence of factors known to increase infection risk.

Results: The antibacterial envelope had the most favorable cost-effectiveness profile when patients had previously experienced CIED infection, had a history of immunosuppressive therapy, or had a Prevention of Arrhythmia Device Infection Trial (PADIT) score indicating high risk of infection (scores ≥6) at cost-effectiveness thresholds of €50 000 in Germany (assumed in the absence of an official threshold), €40 000 in Italy, and £30 000 in England. Probabilistic sensitivity analysis indicated that the antibacterial envelope was likely to be cost-effective in patients with other risk factors (including replacement of high power CIEDs, generator replacement with lead modification, and PADIT scores indicating intermediate risk of infection) when used with some device types and in some countries.

Conclusions: The absorbable antibacterial envelope was associated with cost-effectiveness ratios below European benchmarks in selected patients at increased risk of infection, suggesting the envelope provides value for European healthcare systems by reducing CIED infections.

Keywords: antibacterial envelope, cardiac implantable electronic device, cost-utility analysis, infection, randomized controlled trial.

VALUE HEALTH. 2021; ■(■):■–■

Introduction

Cardiac implantable electronic devices (CIED) include pacemakers, implantable cardioverter-defibrillators, and devices for cardiac resynchronization therapy, and they are established treatments for a variety of cardiac arrhythmias.[1] However, infection is a serious complication of CIED implantation that is difficult to diagnose and treat, and these events are associated with prolonged hospital stays, substantial morbidity, and death.[2,3] The mortality risk more than tripled over 12 months of follow-up in a randomized controlled trial (RCT).[4] Standard treatment for major CIED infections includes complete CIED system extraction with extended antibiotic therapy and subsequent reimplantation.[2,3] In addition, management of CIED infections has a large financial impact. Costs associated with hospital treatment, device extraction, and subsequent implantation of a new CIED have been estimated at €21 760-€70 329 in various European countries.[5-11]

The incidence of CIED infections is estimated between 1% and 4% of CIED recipients.[5-8,12-14] In part due to the rising prevalence of certain risk factors among CIED recipients, the rate of CIED infection is reported to be increasing in excess of the implantation rate.[15] An infection risk score was developed from the Prevention of Arrhythmia Device Infection Trial (PADIT), as shown in the Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.021.[16]

Prevention of CIED infections is imperative due to the high clinical and financial burden.[2] The TYRX™ Absorbable Antibacterial Envelope (Medtronic, Inc, Minneapolis, MN) is a sterile,

single-use surgical mesh envelope designed to provide stabilization of an electronic implantable device that contains the antibiotics rifampicin and minocycline.[2]

Efficacy of the envelope was assessed in the Worldwide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT), an RCT of 6983 patients undergoing pocket or lead revision, generator replacement, system upgrade, or an initial CRT-D implantation. Results after 12 months of follow-up demonstrated a hazard ratio (HR) of 0.60 when the envelope was used adjunctive to standard of care (SOC), equating to a 40% reduction in major CIED infections (P = .04), with no increase in procedure- or system-related complications.[17] This effect was sustained in the longer term, with a HR for infection of 0.64 reported after 36 months of follow-up (P = .046).[18] An international consensus document published this year by the European Heart Rhythm Association recommends use of the envelope in patients aligned with the WRAP-IT study population and others with high-risk factors.[3]

The envelope carries a financial impact because it is used adjunctive to SOC. Therefore, health economic analysis is required to determine cost-effectiveness of the envelope.[19,20] Kay et al (2018) previously assessed cost-effectiveness of the envelope compared against SOC from the perspective of the National Health Service (NHS) in England. Data from WRAP-IT were not available at the time of the analysis, so a decision tree model was populated with evidence from a series of observational studies.[21] Results were presented by device type: cardiac resynchronization therapy pacemaker (CRT-P) and defibrillator (CRT-D), implantable cardioverter defibrillator (ICD), and pacemaker (PM) devices. The study found the envelope to be cost-effective at a £30 000 reimbursement threshold at baseline probabilities of infection exceeding 1.65% (CRT-D), 1.95% (CRT-P), 1.87% (PM), and 1.38% (ICD).

The current analysis updates and expands the model presented by Kay et al[21] to estimate whether use of the envelope is cost-effective among patients at increased risk of CIED infection in 3 European countries (Germany, Italy, and England) using 12, 24, and 36-month data from WRAP-IT.

Methods

Model Structure

Based on the model developed by Kay et al (Microsoft Excel), a decision tree structure with a lifetime horizon was used (Fig. 1).[21] A lifetime time horizon was used because CIED infection has an impact on mortality.[18] In brief, the model compared patients receiving the envelope adjunctive to SOC with patients receiving SOC alone. SOC was defined as administration of pre-procedure intravenous antibiotics and use of sterile technique. After implantation all patients were at risk of infection, which resulted in either complete, partial, or no device extraction, where a complete extraction means the CIED device and all its leads are fully removed, and a partial extraction means a lead or leads, or a part of a lead, was left inside the body. Patients experiencing a complete extraction could receive a replacement device or not. Survival and death at 36 months were terminal nodes for all branches, and payoffs were used to capture lifetime costs and benefits of surviving patients.

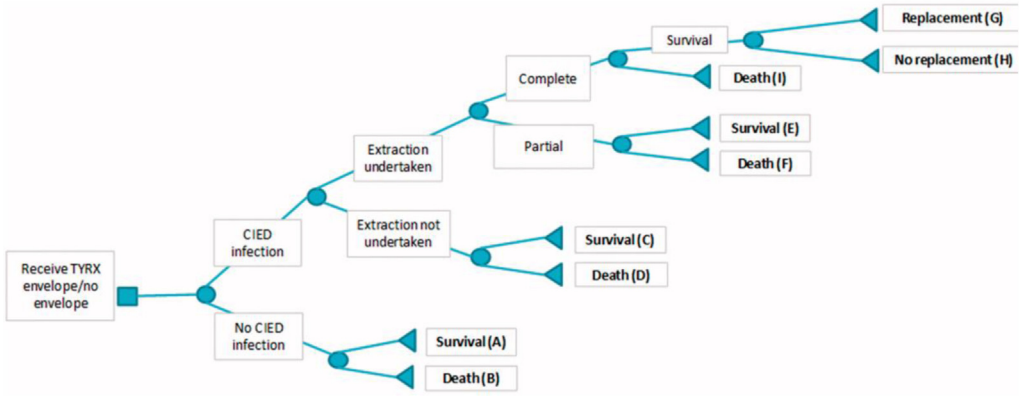
Total costs and outcomes were calculated for each pathway and summed to determine the expected costs and outcomes for each treatment (envelope + SOC vs SOC alone). Additional treatment costs and declines in health-related quality of life (HRQoL) were associated with CIED infections. To capture the long-term impact of infections, lifetime costs and quality-adjusted life-years (QALYs) were assigned to all patients who survived to 36 months. Additional one-off cost and QALY estimates were applied for each patient and varied depending on the type of CIED implanted initially and any subsequent replacement events.

The same structure was used to model cost-effectiveness in Germany, Italy, and England. This was validated with clinical experts from the relevant countries. The analyses adopted the perspective of the German health system, the Italian NHS, and the English NHS and personal social services, respectively. Therefore, the analyses only considered direct costs related to the health and social care systems.

Patient Population

The WRAP-IT study randomized 6983 patients (3495 envelope, 3488 controls) across 25 countries. Only patients at increased risk for CIED infection were enrolled: CIED generator replacement or system upgrade with or without new leads, CIED pocket or lead revision, and initial CRT-D implants. The patient population was divided into subgroups on the basis of risk factors defined using patient characteristics from WRAP-IT and PADIT risk scores.[16,17] Eight subgroups were considered: PADIT score ≥5 points (n = 3068), ≥6 points (n = 1748), or ≥7 points (n = 924); patients with a history of immunosuppressive therapy (n = 51); patients with ≥2 CIED procedures before index procedure (n = 619); patients who experienced a previous CIED infection (>12 months before index

Figure 1. Diagram of model structure (Kay et al[20]).



CIED indicates cardiovascular implantable electronic device.

Table 1. Cost-effectiveness results in each country for people at increased risk of CIED infection receiving high-power devices (lifetime horizon).

Device type	ICER (cost/QALY)		
	Germany	Italy	England
PADIT score ≥5			
CRT-D	€ 66,179	€ 62,381	£57,270
ICD	€ 46,738	€ 42,767	£39,788
PADIT score ≥6			
CRT-D	€ 33,636	€ 29,847	£29,765
ICD	€ 23,889	€ 19,924	£20,476
PADIT score ≥7			
CRT-D	€ 19,300	€ 15,521	£17,654
ICD	€ 13,821	€ 9,864	£11,971
History of immunosuppressive therapy			
CRT-D	€ 5,957	€ 2,226	£6,417
ICD	€ 4,430	€ 522	£4,067
≥ 2 previous CIED procedures			
CRT-D	€ 18,181	€ 14,371	£16,680
ICD	€ 23,273	€ 19,299	£19,950
Previous CIED infection			
CRT-D	€ 6,982	€ 3,176	£7,215
ICD	€ 5,187	€ 1,201	£4,651
Replacement device			
CRT-D	€ 42,912	€ 39,094	£37,581
ICD	€ 30,414	€ 26,421	£25,972
Generator replacement with lead modification			
CRT-D	€ 23,080	€ 19,269	£20,821
ICD	€ 16,536	€ 22,818	£22,926

ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; PADIT, Prevention of Arrhythmia Device Infection Trial; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICD, implantable cardioverter defibrillator; CIED, cardiac implantable electronic device; PM, pacemaker.

procedure, n = 53); and those experiencing a replacement procedure (CRT-D and ICD in W. Europe n = 313) or generator replacement with lead modification (n = 323). Baseline characteristics of the modeled population are in line with those reported in the WRAP-IT trial.[22]

Model Inputs

Tables of model inputs are given in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.021. Targeted searching was used to identify model inputs, and all model inputs and assumptions were validated with clinical experts from each country.

Probability of infection

Risk of major CIED infection within 12, 24, and 36 months of follow-up came from the results of WRAP-IT and PADIT,[16,18] with PADIT results extrapolated to 36 months based on percentage increases shown over the 36-month period in the WRAP-IT trial. Baseline risk differed by device type, with a lower infection risk for low-power devices (CRT-P and PM) and a higher infection risk for high-power devices (CRT-D and ICD) (Table 1). Infection risk differed across geographical locations in WRAP-IT.[23] Where subgroup population sizes were sufficient, risks from the Western Europe cohort only (rather than the full cohort, including US patients) were applied in the model (as reported in Appendix 1, Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.021).

Risk of infection with the envelope was modeled by applying a HR to the baseline risks. HRs calculated from the results of WRAP-IT were applied across all CIEDs as statistical analysis did not demonstrate a significant difference according to device type.[17]

A proportion of patients who experienced initial CIED infections experienced a subsequent infection following treatment (rates of reinfection reported in Appendix 1, Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.021). There was also a proportion of patients who experienced CIED infections that did not meet the WRAP-IT criteria for major infection and, therefore, were adjudicated as experiencing minor infection.[17]

Mortality

All-cause mortality data at 36 months were taken from WRAP-IT.[18] The baseline all-cause mortality rates for patients with and without infection were 41.4% and 18.0%, respectively. Mortality rates for patients with infection were assumed to account for

Table 2. Cost-effectiveness results in each country for people at increased risk of CIED infection receiving low-power devices (lifetime horizon).

Device type	Germany	Italy	England
	ICER (cost/QALY)	ICER (cost/QALY)	ICER (cost/QALY)
PADIT score ≥5			
CRT-P	€43,417	€40,537	£41,690
PM	€45,556	€40,785	£44,017
PADIT score ≥6			
CRT-P	€18,803	€15,930	£20,887
PM	€20,839	€16,075	£23,128
PADIT score ≥7			
CRT-P	€5,665	€2,806	£9,781
PM	€7,641	€2,896	£11,968
History of immunosuppressive therapy			
CRT-P	€9,898	€7,005	£13,368
PM	€13,143	€8,635	£16,502
≥2 previous CIED procedures			
CRT-P	€40,652	€37,705	£39,370
PM	€43,112	€38,296	£41,957
Previous CIED infection			
CRT-P	€11,149	€8,198	£14,438
PM	€13,209	€8,313	£16,722
Generator replacement with lead modification			
CRT-P	€34,717	€31,777	£34,352
PM	€24,322	€19,810	£25,950

ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; PADIT, Prevention of Arrhythmia Device Infection Trial; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICD, implantable cardioverter defibrillator; CIED, cardiac implantable electronic device; PM, pacemaker.

management of the infection (ie, complete, partial, or no extraction) and were applied across all device types.

Health-related quality of life

HRQoL measured in QALYs was captured using EQ-5D data collected at 1, 3, 6, and 12 months of follow-up in WRAP-IT.[17] EQ-5D-3L summary health scores were standardized using UK value sets. Baseline utilities after treatment with CIED differed between device types (CRT-D, 0.81; CRT-P, 0.76; PM, 0.81; ICD, 0.84), but a utility decrement of 0.1 was applied for all patients who experienced infection or reinfection, regardless of device type. A midway change was assumed between the time points at which EQ-5D data were collected. Decrements were applied for 6 months of the model time horizon.

Costs and resource use

The cost of the envelope was €945 in Germany and Italy, and £800 in England. Costs of prophylactic antibiotics (the SOC therapy for preventing infection) were applied as one-off costs each time a patient received a CIED (index and replacement procedures) in both arms of the model. Costs of complete and partial extractions, replacements, additional hospital stays, and courses of antibiotics were applied to patients in both arms of the model who experienced a CIED infection. Resource use parameters (eg, hospital length of stay) were populated using average values from WRAP-IT, including specific resources such as temporary pacing, wearable defibrillators, and leadless devices.[22] Unit costs were taken from diagnostic related group tariffs for Germany; costing studies, hospital pharmacy databases, and expert input for Italy; and NHS databases, the British National Formulary, and costing studies for England (price year 2018/19 with all older costs inflated accordingly). Costs were also applied for patients experiencing a reinfection following no extraction, partial extraction, or complete extraction and replacement. Infection costs occurring after 1 year were discounted in line with the relevant countries' Health Technology Assessment guidelines (3.5% in England, 3.0% in Germany, and 3.0% in Italy).[24]

Lifetime costs and benefits

Lifetime discounted costs and QALYs were applied beyond 36 months. These were dependent on whether a CIED was in place and device type. For example, those patients who had an infection and their device removed, but not replaced, had fewer costs and QALYs applied than those who had a replacement device. Lifetime discounted costs and QALYs were taken from a 2014 English National Institute of Health and Care Excellence technology appraisal of CIEDs and capture the impact of replacement devices as well as treatment waning.[25] Discounting was already applied in the National Institute of Health and Care Excellence appraisal at a rate of 3.5%. The cost of the initial device and procedure was subtracted from lifetime costs because it applied to all patients in the model, not just those surviving beyond 1 year. Costs were converted into euros for the Italian and German models (Euro:GBP 1.129). Lifetime costs were not inflated because, although some costs may

Table 3. Results of risk sharing scenario in Italy, England, and Germany (lifetime horizon).

Device type	ICER (cost/QALY)		
	Germany	Italy	England
High-power devices			
PADIT score ≥5			
CRT-D	€58 480	€52 489	£44 820
ICD	€43 005	€36 478	£32 176
PADIT score ≥6			
CRT-D	€25 934	€19 952	£17 311
ICD	€20 155	€13 633	£12 862
PADIT score ≥7			
CRT-D	€11 615	€5647	£5228
ICD	€10 095	€3586	£4374
History of immunosuppressive therapy			
CRT-D	Dominant	Dominant	Dominant
ICD	€776	Dominant	Dominant
≥2 previous CIED procedures			
CRT-D	€10 392	€4364	£4071
ICD	€19 525	€12 985	£12 304
Previous CIED infection			
CRT-D	Dominant	Dominant	Dominant
ICD	€1410	Dominant	Dominant
Replacement device			
CRT-D	€35 123	€29 087	£24 972
ICD	€26 638	€20 058	£18 264
Generator replacement with lead modification			
CRT-D	€15 291	€9262	£8211
ICD	€23 034	€16 455	£15 218
Low-power devices			
PADIT score ≥5			
CRT-P	€38 399	€36 668	£37 609
PM	€43 603	€37 603	£41 829
PADIT score ≥6			
CRT-P	€13 783	€12 059	£16 804
PM	€18 886	€12 892	£20 939
PADIT score ≥7			
CRT-P	€657	Dominant	£5710
PM	€5691	Dominant	£9785
History of immunosuppressive therapy			
CRT-P	€4951	€3190	£9338
PM	€11 218	€5498	£14 342
≥2 previous CIED procedures			
CRT-P	€35 578	€33 792	£35 227
PM	€41 137	€35 078	£39 736
Previous CIED infection			
CRT-P	€6037	€4256	£10 261
PM	€11 219	€5070	£14 483
Generator replacement with lead modification			
CRT-P	€29 660	€27 878	£30 224
PM	€22 396	€16 673	£23 790

Continued in the next column

Table 3. Continued

ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; PADIT, Prevention of Arrhythmia Device Infection Trial; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICD, implantable cardioverter defibrillator; CIED, cardiac implantable electronic device; PM, pacemaker.

have increased over time (eg, cost of hospitalization), others will have decreased (eg, cost of replacement devices following battery failure).

Model Outputs

Incremental cost-effectiveness ratios (ICERs) were calculated for each type of CIED in each country. The cost-effectiveness thresholds considered were €40 000 per QALY for Italy,[26] €50 000 per QALY for Germany (no official threshold exists, so an assumption was made based on the most commonly cited from a range of European thresholds),[27-29] and £30 000 (€35 564) per QALY for England.[30] These thresholds represent the maximum amount decision makers in each country are willing to pay for 1 additional QALY.

Risk-Sharing Scenario

A risk-sharing program exists for patients who experience a CIED infection up to 36 months after being implanted with an envelope. The manufacturer provides a replacement device, leads, and envelope free of charge. The risk-sharing program was not included in the base case, but the impact of risk sharing on cost-effectiveness was explored in scenario analysis.

Sensitivity Analysis

One-way and 2-way deterministic sensitivity analysis was undertaken to explore the impact on model results of changing individual parameters, including the baseline risk of infection, HR with the envelope, costs of managing infection, and the cost of the envelope.

Probabilistic sensitivity analysis was performed to assess the degree of certainty in the model results, using 10 000 iterations. Probability distributions were based on sampling error estimates (eg, confidence intervals) taken from data sources for base case values where these were available. In the absence of data, standard errors of 10%-20% of the mean were used. Beta distributions were used for probabilities and utilities, gamma for costs, and lognormal for hazard ratios.[31]

Results

Tables 1 and 2 present summaries of cost-effectiveness results in each country over a lifetime horizon, stratified by subgroup and device type. A full breakdown of incremental costs and benefits is shown in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.021.

For both low- and high-power devices, the envelope was more cost-effective in patients with higher PADIT scores (ie, at

Figure 2. Tornado diagram for patients with PADIT score ≥6 for a mix of device types in an English setting.

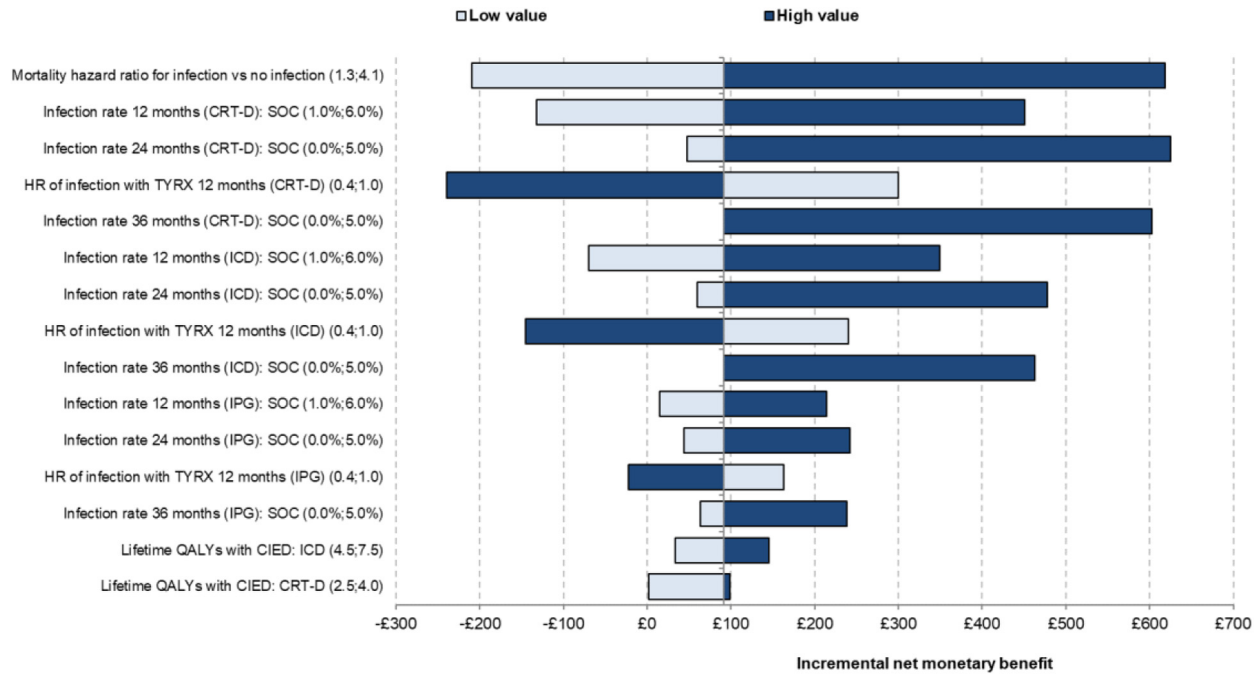
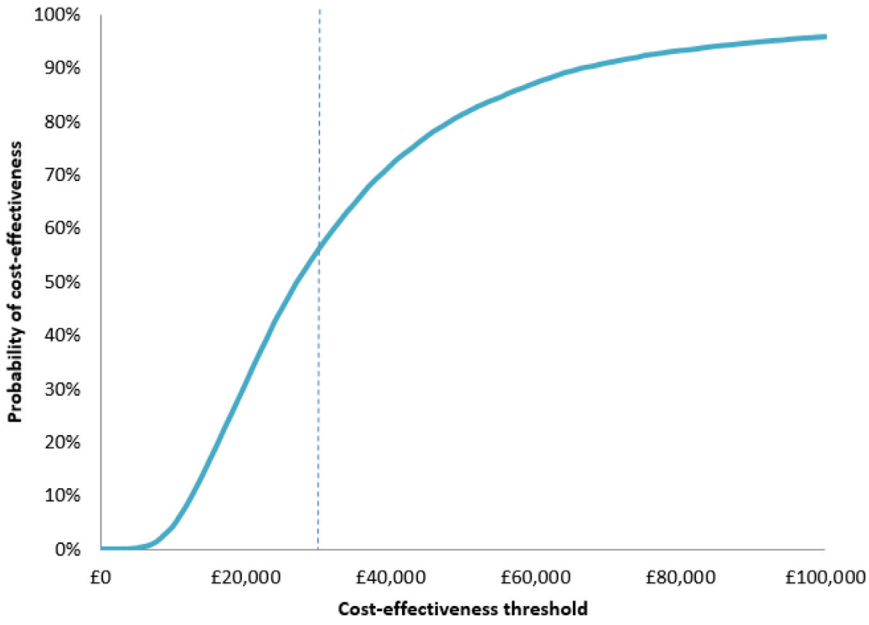


Figure 3. Cost-effectiveness acceptability curve for the PADIT score ≥6 subgroup with a mix of CIED types in the English setting.



higher baseline risk of infection). This was indicated by lower ICER values for patients with higher PADIT scores. ICERs for patients with PADIT scores ≥6 were below the cost-effectiveness thresholds used in the respective countries.

Among the WRAP-IT subgroups, the envelope had a favorable cost-effectiveness profile in all 3 countries in patients with a history of immunosuppressive therapy or previous CIED infection. The envelope was also estimated to be cost-effective in patients experiencing generator replacement with lead modification (with the exception of CRT-P patients in the English analysis) and patients with ≥2 previous CIEDs who received a high-power device.

In the Italian and German adaptations, the envelope was cost-effective at thresholds of €40 000 and €50 000 per QALY, respectively, across all subgroups and device types, with the exception of patients with PADIT scores ≥5 receiving a CRT-D device in Germany or any device in Italy. This is because the

baseline risk of infection in this group was below the threshold required to achieve cost-effectiveness.

Table 3 shows the results of the scenario analysis where the risk-sharing program was applied. Inclusion of the program improved the cost-effectiveness of the envelope, generating ICERs below each countries' respective cost-effectiveness threshold across almost all subgroups and device types. The exceptions were CRT-D patients with PADIT scores ≥5, and English patients receiving low-power devices who had PADIT scores ≥5 or ≥2 previous CIED procedures. The envelope was more effective and less costly than SOC (ie, dominant) for some subgroups and device types, including patients receiving high-power devices who had a history of immunosuppressive therapy or who had experienced a previous CIED infection.

Results of 1-way deterministic sensitivity analysis indicated that the main drivers of model results in all 3 countries were baseline rates of major CIED infections, HR of infection, and HR of mortality associated with the envelope. Figure 2 shows an example tornado diagram for the PADIT score ≥6 subgroup (one of the larger subgroups in WRAP-IT) for a mix of device types in an English setting. Further example tornado diagrams are presented by country and device type for PADIT score ≥6 and high-power replacement device subgroups (the largest subgroups) in Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.021.

Results of probabilistic sensitivity analysis indicated that the likelihood of the envelope being cost-effective at the English threshold of £30 000 per QALY was 21%-77%, depending on the device type and subgroup. At the Italian and German thresholds of €40 000 and €50 000 per QALY, the likelihood of the envelope being cost-effective was 47%-93% and 38%-86%, respectively, depending on the device type and subgroup. Figure 3 shows an example cost-effectiveness acceptability curve for the PADIT score ≥6 subgroup with a mix of CIED types in the English setting. Additional cost-effectiveness planes and cost-effectiveness acceptability curves are presented by country and device type for PADIT score ≥6 and high-power replacement device subgroups in Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.021.

Discussion

The results of this study show that the envelope is likely to be cost-effective over a lifetime horizon when used in patients with specific factors that increase baseline risk of CIED infection, at cost-effectiveness thresholds of €50 000, €40 000, and £30 000 per QALY in Germany, Italy, and England, respectively. This study is the first to use RCT data to model the lifetime impact of the envelope adjunctive to SOC outside of the United States; therefore, these results are likely more representative of the true cost-effectiveness of the envelope than those that have been reported previously.[21]

The envelope had the most favorable cost-effectiveness profile when used in patients who had a history of immunosuppressive therapy, had previously experienced a CIED infection, or had a PADIT score indicating high infection risk (scores ≥6). Analysis of patients with other risk factors (≥2 previous procedures, replacement of high-power devices, generator replacement with lead modification, and intermediate PADIT risk scores) indicated that the envelope was cost-effective for some device types and countries but not others. The combination of patients in subgroups where the envelope was shown to be cost-effective represents approximately 13% of a national CIED population (40% of those with high-power devices and 4% of those with low-power devices).

Cost-effectiveness results in all 3 countries improved when an outcomes-based risk sharing program was included. Outcomes-based risk-sharing programs have been piloted across European healthcare systems, although readiness of healthcare systems to operationalize such contracts remains challenging. Contracts are already in place for the envelope risk-sharing program to be implemented in many hospitals in England and Italy. In Germany, such contracts are yet to be agreed between health insurance companies and manufacturers.

The main drivers of model results were baseline infection rates and HRs of infection and mortality with the envelope. Infection rates from the WRAP-IT and PADIT trials were used in the model to reflect risk of infection in individual patient subgroups.[16-18] The overall CIED infection rate was 1.9% at 36 months in WRAP-IT, which included patients at increased risk of infection (eg, those undergoing pocket or lead revision, generator replacement, system upgrade, or an initial CRT-D implantation).[18] The rate was 0.9% at 12 months in PADIT, which also largely included high-risk patients.[16]

Baseline infection rates are higher in reality than those observed in the WRAP-IT and PADIT trials.[3] Nationwide registry data from Germany demonstrate infection rates of 3.4% and 4.4% 1 year after index high-power device implantation and replacement procedures, respectively.[7] In Denmark, an overall rate of 1.4% at 4 years post-procedure has been reported across subgroups, with higher values for replacement procedures (PM, 2.1%; ICD, 2.3%; CRT-P, 3.4%; CRT-D, 5.0%), index CRT-D procedures (2.4%), and upgrade procedures (2.4-3.94%).[32] In France, infection rates of 0.5-3.9% at 3 years post-procedure have been reported, with higher rates associated with index high-power device implantation (1.6%) and replacement procedures (PM, 1.4%; ICD, 2.9%; CRT-P, 1.3%; CRT-D, 3.9%).[5] Studies conducted in the English population of CIED recipients have reported overall infection rates of 0.6%-1.3%[6] and 3.14% (CRT and ICD only).[8] A worldwide systematic review and meta-analysis reported a CIED infection rate of 1% to 1.3% overall, with substantially higher rates among high-risk patients (eg, odds ratios of infection of 1.9 for device replacements/revisions and 7.84 in patients who had a previous CIED infection).[12]

Infection rates may be underestimated in large RCTs, partly due to the Hawthorne effect (where healthcare staff and patients modify their behavior because they are being observed) leading to provision of better care in the trial setting. In addition, the WRAP-IT study population excluded patients with the highest risk profiles, including those receiving chronic immunosuppressive therapy, requiring dialysis/long-term vascular access, or with a history of CIED infection in the 12 months before enrollment. The envelope was commercially available at the time of the trial, which may also have influenced participation in the trial.[17] Furthermore, use of infection rates from observational studies in sensitivity analyses improved the cost-effectiveness of the envelope in the model results. For all these reasons, it is likely that use of the envelope outside of the RCT setting will result in greater reductions in absolute numbers of infections, and, therefore, the envelope will be more cost-effective in the reality than is indicated by the results presented in this article.

Sensitivity analysis indicated that the baseline risk of infection required for the envelope to be cost-effective was around 2.7% in Italy, 2.5% in Germany, and 3.6% in England (across all device types). Therefore, the envelope would likely be cost-effective in subgroups of high-risk patients with observed infection rates above these thresholds who were not included in the current model. This includes patients with renal failure (overall infection rate, 4.4%[33]), particularly those receiving dialysis, where infection rates of 7.4% at 6 months[34] and 37.5% at 2.6 years of follow-up[35]

are reported in the literature. Patients receiving chronic immunosuppressive therapy or undergoing "early" or "delayed" CIED reimplantation following a previous infection are likely to be especially high-risk[10] and, therefore, could also benefit from use of the envelope.

Mortality and infection data used in the model were taken from WRAP-IT. The same HR of mortality and infection was applied across all subgroups, including patients from PADIT who would not have met eligibility criteria for WRAP-IT. The HR of mortality associated with infection was 2.3 (95% CI 1.3-4.1).[18] This is comparable to a HR of 2.4 reported in The Netherlands.[36]

The results of this analysis represent an update to those presented by Kay et al.[21] The results can be considered more robust because input parameters were populated with evidence from a large RCT, rather than the observational data used in the original model. Data with a longer follow-up period (36 months vs 12 months) were applied before lifetime costs and benefits were added, giving a more accurate measure of short-term costs and benefits associated with the envelope and SOC. The current model also gives more detail on specific patient risk profiles in which use of the envelope is most cost-effective, as well as expanding its focus to 3European healthcare systems (only England was included in the original model). When compared to the results for England reported by Kay et al,[21] the current model showed less favorable (though generally still cost-effective) results in patients receiving high-power devices, where the envelope was cost-saving (ie, dominant) in the original model. This is typical of the gap between observational data (which can overestimate effects) and evidence from RCTs. ICERs were comparable for patients receiving low-power devices.

In line with these results, a recent study from the perspective of the US healthcare system found the envelope to be cost-effective in the population formed by the WRAP-IT inclusion criteria, at an upper threshold of $150 000 per QALY when compared to SOC infection prevention among patients at increased risk of infection.[37] The study also used data from the WRAP-IT trial, although it did not include PADIT score subgroups as adopted in the current model.

The total costs of treating CIED infection in the current model, which were calculated based on resource use data from WRAP-IT, were comparable to those previously reported in Germany (€31 493-€33 777 vs €23 429-€42 921 in the current model) [7] and in England (£14 241-£41 820 vs £14 466-£37 633 in the current model).[6,8-10] Differences can be explained in part by differing resource use associated with CIED infection compared to the current model. If real-world costs of CIED infection are higher than those applied in the model, the envelope is likely to be more cost-effective.

Limitations

A key limitation of the model is the generalizability of data from WRAP-IT to each country due to trial setting and location because the majority of patients included in the trial were from the United States. To mitigate against this, data from Western Europe only were used for subgroups where sample sizes permitted. Long-term costs and QALYs from an English setting were used to predict lifetime outcomes in all 3 countries. A further limitation is that there is some uncertainty around baseline rates of CIED infection in SOC, which could have a large impact on model results. However, as described above, it seems likely that baseline infection rates are higher in reality than those used in the model. Finally, there is uncertainty and variation in the costs of treating CIED infections. This could have an impact on model results, although treatment costs were not identified as a key driver of the analysis.

Conclusions

The absorbable antibacterial envelope was associated with cost-effectiveness ratios below European benchmarks in selected patients at increased risk of infection, suggesting the envelope provides value for European healthcare systems by reducing CIED infections.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2020.12.021.

Article and Author Information

Accepted for Publication: December 14, 2020

Published Online: Month xx, xxxx

doi: https://doi.org/10.1016/j.jval.2020.12.021

Author Affiliations: Department of Biomedical, Metabolic, and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy (Boriani); Sahlgrenska University Hospital, Göteborg, Sweden (Kennergren); Cleveland Clinic, Cleveland, OH, USA (Tarakji, Wilkoff); Liverpool Heart and Chest Hospital, Liverpool, England, UK (Wright); Manchester University NHS Foundation Trust, Manchester, England, UK (Ahmed); The Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, England, UK (McComb); Department of Cardiology and Intensive Care Medicine, Saint Vincenz Hospital, Paderborn, Germany (Goette); Universitaets-Herzzentrum Freiburg Bad Krozingen, Bad Krozingen, Germany (Blum); Policlinico Sant' Orsola – Malpighi, Bologna, Italy (Biffi); York Health Economics Consortium, York, England, UK (Green, Shore); Medtronic International Trading Sàrl, Tolochenaz, Switzerland (Carion).

Correspondence: Professor Giuseppe Boriani, MD, PhD, FESC, Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Via del Pozzo 71, 41125 Modena, Italy. Email: giuseppe.boriani@unimore.it

Author Contributions: *Concept and design*: Boriani, Tarakji, Wright, McComb, Blum, Biffi, Green, Shore, Carion, Wilkoff
Acquisition of data: Biffi, Carion
Analysis and interpretation of data: Boriani, Tarakji, Ahmed, McComb, Goette, Blum, Green, Shore, Carion
Drafting of the manuscript: Boriani, Tarakji, Wright, Ahmed, McComb, Goette, Green, Shore, Carion
Critical revision of paper: Boriani, Kennergren, Tarakji, Wright, Ahmed, Goette, Blum, Biffi, Carion, Wilkoff
Provision of study materials or patients: Kennergren, Biffi, Wilkoff

Conflict of Interest Disclosures: Dr Boriani reports personal fees from Medtronic plc, Boston Scientific, Biotronik, Bayer, Boehringer, of small amount, outside the submitted work.
Dr Kennergren reports personal fees from Biotronik, personal fees from Boston Scientific, personal fees from Medtronic, personal fees from Philips, outside the submitted work.
Dr Tarakji reports personal fees from Medtronic, personal fees from AliveCor, personal fees from Boston Scientific, outside the submitted work.
Dr Wright reports personal fees from Medtronic, personal fees from Medtronic, outside the submitted work.
Dr Ahmed reports grants and personal fees from Medtronic, personal fees from Astrazeneca, personal fees from Pfizer, personal fees from Pharmacosmos, personal fees from Servier, personal fees from Vifor, outside the submitted work.
Dr McComb reports other from Medtronic, during the conduct of the study.

Dr. Goette reports personal fees from Medtronic, personal fees from Boston Scientific, personal fees from Omeicos, personal fees from Daiichi-Sankyo, personal fees from BMS/Pfizer, personal fees from Bohringer Ingelheim, outside the submitted work.
Dr Blum reports other from Medtronic, outside the submitted work.
Dr Biffi has nothing to disclose.
Ms Green reports personal fees from Medtronic Ltd, during the conduct of the study.
Ms Shore reports personal fees from Medtronic Inc, during the conduct of the study.
Dr Carion reports personal fees from Medtronic, during the conduct of the study.
Dr Wilkoff reports personal fees from Medtronic, personal fees from Abbott, personal fees from Philips, outside the submitted work.

Funding/Support: Financial support for this article was provided by Medtronic Inc.

Acknowledgment: The authors are grateful to Benedict Brown, Reece Holbrook, and Jeff Lande from Medtronic for providing their expertise and the necessary WRAP-IT trial statistical analyses, and to Alison Peel from York Health Economics Consortium for providing writing and editorial assistance on the article.

REFERENCES

1. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J*. 2013;34(29):2281–2329.
2. Sandoe JA, Barlow G, Chambers JB, et al. Guidelines for the diagnosis, prevention, and management of implantable cardiac electronic device infection: report of a joint Working Party project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, host organization), British Heart Rhythm Society (BHRS), British Cardiovascular Society (BCS), British Heart Valve Society (BHVS), and British Society for Echocardiography (BSE). *J Antimicrob Chemother*. 2015;70:325–359.
3. Blomström-Lundqvist C, Traykov V, Erba PA, et al. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections—endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID), and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Europace*. 2019;22:515–549.
4. Wilkoff BL, Boriani G, Mittal S, et al. Impact of cardiac implantable electronic device infection: a clinical and economic analysis of the WRAP-IT Trial. *Circ Arrhythm Electrophysiol*. 2020;13(5):e008280.
5. Clementy N, Carion PL, Leotoing LD, et al. Infections and associated costs following cardiovascular implantable electronic device implantations: a nationwide cohort study. *Europace*. 2018;20:1974–1980.
6. Ahsan SY, Saberwal B, Lambiase PD, et al. A simple infection-control protocol to reduce serious cardiac device infections. *Europace*. 2014;16:1482–1489.
7. Ludwig S, Theis C, Brown B, et al. Incidence and costs of cardiac device infections: retrospective analysis using German health claims data. *J Com Eff Res*. 2018;7:483–492.
8. Burnhope E, Rodriguez-Guadarrama Y, Waring M, et al. Economic impact of introducing TYRX amongst patients with heart failure and reduced ejection fraction undergoing implanted cardiac device procedures: a retrospective model based cost analysis. *J Med Econ*. 2019;22:464–470.
9. Brough CEP, Rao A, Haycox AR, et al. Real-world costs of transvenous lead extraction: the challenge for reimbursement. *Europace*. 2019;21:290–297.
10. Ahmed FZ, Fullwood C, Zaman M, et al. Cardiac implantable electronic device (CIED) infections are expensive and associated with prolonged hospitalisation: UK Retrospective Observational Study. *PLoS One*. 2019;14:e0206611-e11.
11. Egea M, Garcia-Urra F, Bellver JA, et al. Economic impact associated with complications of cardiac implantable electronic devices in Spain (Abstract). *EP Europace*. 2018;20(suppl. 1):i180.
12. Polyzos KA, Konstantelias AA, Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. *Europace*. 2015;17:767–777.
13. Kirkfeldt RE, Johansen JB, Nohr EA, et al. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur Heart J*. 2014;35:1186–1194.
14. Eby EL, Bengtson LGS, Johnson MP, et al. Economic impact of cardiac implantable electronic device infections: Cost analysis at one year in a large United States health insurer. *J Med Econ*. 2020:1.
15. Greenspon AJ, Patel JD, Lau E, et al. 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the United States 1993 to 2008. *J Am Coll Cardiol*. 2011;58:1001–1006.
16. Birnie D, Wang J, Alings M, et al. Risk factors for infections involving cardiac implanted electronic devices. *JACC*. 2019;74:2845–2854.
17. Tarakji KG, Mittal S, Kennergren C, et al. Antibacterial envelope to prevent cardiac implantable device infection. *N Engl J Med*. 2019;380:1895–1905.
18. Mittal S, Wilkoff BL, Kennergren C, et al. The World-Wide Randomized Antibiotic Envelope Infection Prevention (WRAP-IT) Trial: long-term follow-up. *Heart Rhythm*. 2020.
19. Boriani G, Maniadakis N, Auricchio A, et al. Health technology assessment in interventional electrophysiology and device therapy: a position paper of the European Heart Rhythm Association. *Eur Heart J*. 2013;34:1869–1874.
20. Maniadakis N, Vardas P, Mantovani LG, et al. Economic evaluation in cardiology. *Europace*. 2011;13:ii3–ii8.
21. Kay G, Eby EL, Brown B, et al. Cost-effectiveness of TYRX absorbable antibacterial envelope for prevention of cardiovascular implantable electronic device infection. *J Med Econ*. 2018;21:294–300.
22. Tarakji KG, Mittal S, Kennergren C, et al. Worldwide Randomized Antibiotic EnveloPe Infection PrevenTion Trial (WRAP-IT). *Am Heart J*. 2016;180:12–21.
23. Kennergren C, Poole J, Wilkoff B, et al. Geographical variations in the incidence of CIED infection and infection prevention strategies: update from the Global WRAP-IT Study. *EHRA presentation*. 2020.
24. Attema AE, Brouwer WBF, Claxton K. Discounting in economic evaluations. *Pharmacoeconomics*. 2018;36:745–758.
25. National Institute for Health and Care Excellence (NICE). *Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure [TA314]*. National Institute for Health and Care Excellence; 2014.
26. Fattore G. Proposta di linee guida per la valutazione economica degli interventi sanitari in Italia. *PharmacoEconomics Italian Research Articles*. 2009;11:83–93.
27. Cameron D, Ubels J, Norström F. On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review. *Glob Health Action*. 2018;11:1447828-28.
28. Stadhouders N, Koolman X, van Dijk C, et al. The marginal benefits of healthcare spending in The Netherlands: estimating cost-effectiveness thresholds using a translog production function. *Health Econ*. 2019;28:1331–1344.
29. van Baal P, Perry-Duxbury M, Bakx P, et al. A cost-effectiveness threshold based on the marginal returns of cardiovascular hospital spending. *Health Econ*. 2019;28:87–100.
30. National Institute for Health and Care Excellence (NICE). *Guide to the methods of technology appraisal*. National Institute for Health and Care Excellence (NICE); 2013.
31. Briggs A, Sculpher M, Claxton K. *Decision Modelling for Health Economic Evaluation*. Oxford University Press; 2006.
32. Olsen T, Jørgensen OD, Nielsen JC, et al. Incidence of device-related infection in 97 750 patients: clinical data from the complete Danish device-cohort (1982-2018). *Eur Heart J*. 2019;40:1862–1869.
33. Sohail MR, Henrikson CA, Braid-Forbes MJ, et al. Mortality and cost associated with cardiovascular implantable electronic device infections. *Arch Intern Med*. 2011;171:1821–1828.
34. Shariff N, Eby E, Adelstein E, et al. Health and economic outcomes associated with use of an antimicrobial envelope as a standard of care for cardiac implantable electronic device implantation. *J Cardiovasc Electrophysiol*. 2015;26:783–789.
35. Romeyer-Bouchard C, Da Costa A, Dauphinot V, et al. Prevalence and risk factors related to infections of cardiac resynchronization therapy devices. *Eur Heart J*. 2009;31:203–210.
36. de Bie MK, van Rees JB, Thijssen J, et al. Cardiac device infections are associated with a significant mortality risk. *Heart Rhythm*. 2012;9:494–498.
37. Wilkoff B, Boriani G, Mittal S, et al. Cost-effectiveness of an antibacterial envelope for CIED infection prevention in the US healthcare system from the WRAP-IT Trial. *Circ Arrhythm Electrophysiol*. 2020;13:e008503.