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SUPPLEMENT PAPER

Infections associated with cardiac electronic implantable devices: economic perspectives and impact of the TYRX™ antibacterial envelope

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Abstract

The occurrence of cardiac implantable electronic devices (CIED) infections and related adverse outcomes have an important financial impact on the healthcare system, with hospitalization length of stay (2–3 weeks on average) being the largest cost driver, including the cost of device system extraction and device replacement accounting for more than half of total costs. In the recent literature, the economic profile of the TYRX™ absorbable antibacterial envelope was analysed taking into account both randomized and non-randomized trial data. Economic analysis found that the envelope is associated with cost-effectiveness ratios below USA and European benchmarks in selected patients at increased risk of infection. Therefore, the TYRX™ envelope, by effectively reducing CIED infections, provides value according to the criteria of affordability currently adopted by USA and European healthcare systems.

Keywords Antibiotics • Cardiac implantable electronic devices • Cost • Cost-effectiveness • Economics • Hospitalization • Infections

Introduction

Infections associated with cardiac implantable electronic devices (CIEDs) are clinically relevant in view of the increasing number of devices implanted owing to population ageing,[1,2] with the number of implants worldwide estimated to be ∼1.5 million per year.[3] Despite the use of antibiotic prophylaxis at the time of device implantation, device-related infection rates increased in recent years, CIED-associated infections rising to alert levels. Cardiac implantable electronic device-related infections have the specific features of infection on prosthetic materials, and are currently recognized as a major concern for health care systems, with over two million cases annually in the USA, causing substantial morbidity and lengthy hospital admissions.[4] Assessments of the incidence, morbidity and mortality are key to improve our knowledge about CIED infections but to have a more complete picture of the adverse impact on the community, the economic consequences also need to be defined. Studies assessing the economic impact of diseases have grown exponentially since the mid-1960s, when the first framework of economic analysis, in the form 'cost-of-illness' evaluations, was defined.[5]

Financial burden of infections associated with cardiac electronic implantable devices

The incidence of infections associated with CIEDs is reported to be ∼1–4%,[6–8] negatively impacting both the patient and health care system due to the need for hospitalization with use of intensive care unit

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stay, expensive diagnostics, prolonged antibiotic therapy, as well as the frequent need for device and lead extraction, and re-implantation. Mortality has been reported as 20–25% at 1 year[9,10] and up to 50% at 3 years despite state-of-the-art infection management, consisting[11] of device and lead removal, antibiotic treatment, and subsequent device and lead re-implantation when indicated. Approximately 3–15% of patients refuse or are considered not suitable for lead extraction and are managed with suppressive antibiotic therapy as a palliative measure.[6,12,13]

Cardiac implantable electronic device infections and their adverse outcomes also heavily impact on healthcare systems. The clinical profile is associated to the overall expenditure, as shown in a retrospective cohort analysis of 5401 Medicare patients which captured an average $62 638 for patients requiring CIED extraction and replacement, $50 079 for those extracted but not re-implanted, $77 397 for patients hospitalized for CIED infection not undergoing removal, and $22 856 for patients who had no infection-related hospitalization.[10] The main driver of cost was represented by hospitalization (included cost of device system extraction and device replacement) and non-extracted patients with infection-related hospitalization actually had the longest hospital stay and the largest use of resources.[10] In 2011, Sohail *et al.*[14] reported on >200 000 Medicare patients admitted for CIED implantation, replacement, or revision during year 2007. A total of 5817 admissions of patients with CIED infection were recorded, with an important burden of hospitalizations and substantial adjusted in-hospital and long-term mortality. The standardized adjusted incremental cost ($14 360–$16 498) and total admission cost ($28 676–$53 349) depended upon device type and was significantly impacted by intensive care stays.[14] More recently an analysis of CIED implants in a MarketScan Commercial Claims and Medicare Supplemental database from the USA during the calendar years 2009–2012 identified a cumulative incidence of infection at 1 year post-implant of 1.18% for initial CIED implants and 2.37% for replacements.[15] Median time to infection was 35 days for initial implants and 23 days for replacements, with incremental healthcare expenditures at 1 year depending on treatment intensity, ranging from $16 651 (no inpatient admission or device procedure) to $279 744 (inpatient admission, device procedure and concomitant sepsis) for initial implants, and from $26 857 to $362 606 for CIED replacement procedures.[15]

The main reports published in the literature on the costs associated with CIED infections, with a focus on Europe, are shown in *Table 1*.[16–22] The important financial burden associated with CIED infections highlighted in North America is confirmed by analyses performed in France, Germany, Spain, and the UK. The direct costs of infections are related to the duration of ICU or non ICU care, diagnostic testing, antibiotic treatment, extraction procedure, post-extraction hospital stay, use of temporary pacing or a wearable external defibrillator, CIED reimplantation procedural, and device costs. The retrospective analyses performed in Europe highlight substantial variability in reported costs, according to the device type, need for extraction, patient profile, and setting of care with frequent occurrence of costs >€30 000 (*Table 1*). There is an urgent need to prevent the occurrence of CIED infections among all higher risk patients.[23]

Economic perspectives and economic analysis: what are the implications for policy makers?

The background of economic analysis in health care is the scarcity of available resources and the inability to meet all demands, which challenges healthcare providers to allocate resources to maximize the outcome in terms of good health, thus justifying the investment made.[24]

Due to rising healthcare costs over time, there is a need for healthcare systems to find ways to obtain the highest value for the financial investments made. This may be defined as the maximum health benefit obtained for a given level of healthcare spending. Other factors such as equity and social justice also need to be considered.[25] Hence, decision-makers—such as clinicians, hospital formulary committees, local or national health technology assessment (HTA) organizations, governmental health departments or health insurance companies—need to develop explicit and reliable assessments of the value of healthcare products and services to make good decisions.[26]

Health economics refers to a discipline of economics that provides standardized methods for estimating the costs and benefits of healthcare interventions.

Different types of economic evaluations have been used in the literature. Cost-minimization analysis is used when the clinical effectiveness of two interventions is equivalent.[4] More frequently, cost-effectiveness analysis (CEA) is employed, since it compares consequences of alternative intervention/strategies, assessed in natural clinical units such as life-years gained. As a derivation of CEA, cost-utility analysis measures health benefit by considering both length and quality of life, usually represented by the quality-adjusted life-year (QALY) (calculated by multiplying the utility as a measure of preference for a person's overall quality of life by the duration of time spent in that situation or health state).[24,27] The QALYs may be compared for different types of interventions to have a basis for decision making on resources allocation. Another type of analysis is cost-benefit analysis, which is rarely applied in healthcare because of concerns with having all health benefits expressed in monetary terms.

Economic evaluations in healthcare often report an incremental cost-effectiveness ratio (ICER), usually but not always expressed as the cost per QALY gained for a new intervention compared to the pre-existing standard of care.[28] In *Figure 1*, the principles of CEA are briefly summarized. Uniquely, the ICER combines comparative data on costs and outcomes into a single metric which represents value for money. A QALY represents years of survival adjusted for quality of life, using a scale of utility ranging from 0 (equivalent to death) to 1 (perfect health).[29] Whether or not a treatment provides sufficient benefits to justify its added costs may be evaluated by comparing the cost per QALY gained with other interventions in a so-called league table, or with a notional cap called the cost-effectiveness threshold. The US Panel on Cost-Effectiveness in Health and Medicine and the National Institute of Health and Care Excellence (NICE) in UK have both endorsed the QALY for their 'reference case', a standardized methodological approach to promote comparability in CEAs of different healthcare interventions.[30,31]

In Germany, the Institute for Quality and Efficiency in Health Care (IQWiG) has defined methods for health economic evaluation which also compare health outcomes and costs between treatments and

Table I **CIED infection associated costs**

Authors (year)	Study design	Country	Study period	Population	Infection associated costs
Ahsan *et al.* (2014)[16]	A retrospective audit of all cardiac device infections in a single tertiary referral institution	UK	2004–2007	2779 CIEDs implants or CIED-related procedures: 30 infections requiring CIEDs removal	Average cost: £30 958.40 per incident infection Cost of cardiac device infection: • PM: £21 908.96 • ICD: £294 162.88 • CRT-D: £126 481.38
Brough *et al.* (2018)[17]	Retrospective, patient level service line analysis of a single UK extraction centre, during a complete financial year	UK	2013–2014	74 patients required transvenous extraction (47 infected and 27 non-infected; 156 leads) • PM: 46% • ICD: 23% • CRT : 31%	Mean cost of extraction: £9228 (±4099): • Infected CIEDs £10 727 (±4178) • Non-infected CIEDs £6619 (±2269) When considering additional costs of device reimplantation: • Overall mean cost: £17 574 (±12 882) • Infected CIEDs £22 615 (±13 343) • Non-infected £8801 (±5007)
Clémenty *et al.* (2018)[18]	Retrospective analysis using medico-administrative hospital discharge database	France	2012–2015	78 267 CIED patients (72% *de novo* implants) 65 553 (84%) PM implantation • SCP: 18% • DCP: 65% • CRT-P: 4% • P-undefined devices: 4% 11 845 (15%) Defibrillators • SCD: 27% • DCD: 20% • CRT-D: 34% • D-undefined devices: 19%	2 years infection *de novo* mean cost per patient • Total CIED: €23 234 ± 50 294 • SCP+DCP: €17 849 ± 14 025 • CRT-P: €25 467 ± 22 894 • SCD+DCD: €25 444 ± 23 560 • CRT-D: €23 966 ± 23 379 2 years infection replacement mean cost per patient • Total CIED: €20 623 ± 18 778 • SCP+DCP: €19 919 ± 18 029 • CRT-P: €16 584 ± 10 461 • SCD+DCD: €19 323 ± 8611 • CRT-D: €27 449 ± 40 485

Continued

Table 1 *Continued*

Authors (year)	Study design	Country	Study period	Population	Infection associated costs
Egea *et al.* (2018)[19]	Cost analysis based on Delphi panel results on health resource utilization associated with the management of chronic pacemaker complications at the hospital level	Spain	2017	NR	Mean cost per infection requiring extraction and considering a 100% reimplantation rate: • PM: €21 196.44 • ICD: €35 496.48 • CRTs: €41 496.44 Cost for inpatient length of stay: • PM: € 13 917.53 Mean cost of intravenous antibiotic treatment previous and after system: €833.23/patient
Ludwig *et al.* (2018)[20]	Case-controlled analysis using PSM in patients with ICD/CRT-D using German health insurance claims data	Germany	2010–2014	158/4699 (3.4%) infections Risk of cardiac device infections 12 months post-implant: 3.4% overall, 2.9% for *de novo* procedures vs. 4.4% for replacement procedures	Mean 3-year incremental expenditure per patient for patients with cardiac devices infections: • €31 493 for *de novo* implant patients • €33 777 for replacement patients. Mean incremental expenditure: €59 419 per patient with a major infection
Ahmed *et al.* (2019)[21]	Retrospective analysis of clinical case records of pts undergoing extraction for CIED infection at a single tertiary cardiothoracic centre	UK	2013–2015	84 CIED patients • CRT-D: 21.4% • ICD : 28.6% • PM : 50.0%	• Median cost of a CIED extraction procedure £1729.95 (£942.41–£3588.90) • Median cost of inpatient stay: £3150 (£700.00–£7700.00) • Median cost outpatient antibiotic therapy:£3.47 (1.96–20.66) • Cost of CIED infection episode according to device type: £5139 (PM) and £24 318 (CRT-D)
Burnhope *et al.* (2019)[22]	Retrospective cohort of HFrEF patients undergoing ICD or CRT procedures	UK	2014–2017	5/157 patients with CIED infection	Average cost of a CIED infection inpatient admission: £41 820 (range £28 377–£56 498)

CIED, cardiac implantable electronic device; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; DCP, dual-chamber pacemaker; ICD, implantable cardioverter-defibrillator; HFrEF, heart failure with reduced ejection fraction; PM, pacemaker; PMS, propensity score matching; SCP, single-chamber pacemaker.

Figure 1 The principles of cost effectiveness analysis in a schematic view.

calculate ICERs, however, IQWiG restricts its analyses to the estimation of 'efficiency frontiers' within individual therapeutic areas.[32] The ICER of a new treatment ('A') is calculated compared to the next effective intervention ('B'), and the ICER should not be higher than that of the existing treatment ('B') compared to its next effective alternative ('C') on the efficiency frontier. While IQWiG does not explicitly exclude QALYs as a measure of health benefit, it criticizes their use based on ethical and methodological grounds. Meanwhile, IQWiG has no need for a universal cost-effectiveness threshold based on QALYs, given its narrower focus on the estimation of efficiency frontiers within individual therapeutic areas.[32]

Cost-effectiveness ratios can be difficult to estimate from clinical studies, with or without the use of QALYs, and the results of such analyses are subject to uncertainty. In practice, reimbursement decisions are multifactorial and rarely based solely on the comparison of a treatment's ICER to another treatment's ICER or a country's cost-effectiveness threshold value.[28] The budget impact for payers and healthcare providers necessarily is critical, and consequently the capability of healthcare systems to create budgetary headroom for new technologies is important, by increasing efficiency and realizing cost-savings.

In the USA, $50 000 per QALY emerged as an early benchmark for a cost-effectiveness threshold, based on the approval in the 1970s by Congress to provide dialysis treatment for patients with end-stage renal disease under the publicly funded Medicare program.[33] It can be argued this value is now out-of-date, first because an inflation adjustment is required and second because the cost of renal dialysis is now much higher: an analysis published 2009 estimated an ICER of $129 090 per QALY gained.[34]

The World Health Organization (WHO) has suggested benchmarks based on the Gross Domestic Product (GDP) per capita in a given country, stating that interventions that avert one disability-adjusted life-year (DALY, similar to a QALY) for less than average per capita income for a given country or region are considered very cost-effective; interventions that cost less than three times average per capita income per DALY averted are still considered cost-effective; and those that exceed this level are considered not cost-effective.[35]

In 2014, the American College of Cardiology/American Heart Association (ACC/AHA) published a statement on cost/value methodology in Clinical Practice Guidelines, which translated the WHO guideline into present-day US dollar values, as shown in *Table* 2.[29]

An ICER (per QALY gained) of <$50 000 was considered highly cost-effective, between $50 000 and $150 000 was considered as intermediate cost effectiveness, and >$150 000 was considered not cost-effective.

Since its inception in 1999, the United Kingdom's National Institute for Health and Care Excellence has used an explicit cost-effectiveness threshold of £20 000–£30 000.[36] This represented 1.1–1.7 times the per-capita GDP in 1999 (GDP £17 720), though it is only 0.6–0.9 times the corresponding value in 2019 (GDP £33 141). Reviews of past NICE decisions suggest the threshold in practice may be higher than stated by NICE, around £35 000–£40 000 per QALY.[37] A multiple of 1–3 times GDP per capita suggests thresholds of £33 100–£99 400.

Official cost-effectiveness thresholds do not exist in Germany, for reasons already explained. In Italy, there is no officially established value, but guidelines from the Italian Health Economics Association (AIES) recommended in 2009 a threshold of €25 000–€40 000 be used.[38]

Per-capita GDP in 2019 was €41 508 in Germany and €29 661 in Italy, so a multiple of 1–3 times GDP per capita suggests thresholds for cost effectiveness of €41 500–€124 500 for Germany and €29 600–€88 900 for Italy.[39]

The economic evaluations allow to assess whether strategies and/or treatments with proven clinical efficacy correspond to good value for money and these analyses are a specific and important component of HTA.[40] The HTA process refers to the systematic evaluation of characteristics, scientific validation, effect, and impact of health technologies and is a multidisciplinary process to evaluate the social, economic, organizational, and ethical issues of a health intervention or health technology, to inform policy decisions.[40] Health technology assessment is particularly important when innovative devices, with new functions are proposed with a need to assess their value and possible implementation.[41] In Europe, the basic principle on which consensus Guidelines are constructed, by the European Society of Cardiology is 'separating science from economics'[42] and therefore while evidence is global, decisions for implementation are made locally and have to be considered at the level of national or regional policymakers. In this perspective, the purpose of HTA is to inform policy decisions about investments, coverage, and reimbursement processes.

Table 2 References for cost effectiveness thresholds

Level of value	ICER (per QALY gained)	USA	UK	Germany	Italy
Official threshold		None	£20 000–£30 000	None	None Proposed €25 000–40 000
High value/highly cost-effective	Less than GDP per capita	<$50 000	£33 100	€41 500	€29 600
Intermediate value/ cost-effective	Between 1 and 3 times GDP per capita	$50 000 to <$150 000	£33 100 to <£99 400	€41 500 to <€124 500	€29 600 to <€88 900
Low value/not cost-effective	Greater than 3 × GDP per capita	>$150 000	>£99 400	>€124 500	>€88 900

US values based on ACC/AHA statement on cost/value methodology.[29]
UK values based on National Institute for Health and Care Excellence methods and WHO guidance.
Italy values based on Italian Health Economics Association (AIES) recommendation and WHO guidance.
ACC/AHA, American College of Cardiology/American Heart Association; GDP, Gross Domestic Product; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WHO, World Health Organization.

Economic analyses of TYRX™ antibacterial envelope

The TYRX™ Absorbable Antibacterial Envelope (Medtronic, Inc., Minneapolis, MN, USA) is a sterile, single-use surgical mesh envelope intended to securely hold a pacemaker pulse generator or defibrillator [implantable cardioverter-defibrillator (ICD)] in order to create a stable environment and that employs the antibiotics rifampicin and minocycline to reduce infections following surgical implant of a pacemaker or defibrillator.[43,44] In Worldwide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT), a randomized, controlled clinical trial, the safety and efficacy of the TYRX™ envelope in reducing the infection rate in patients undergoing CIED replacement or upgrade or initial implantation of a cardiac resynchronization therapy defibrillator (CRT-D) or CIED pocket/lead revision in patients not having pocket assessment in the past 365 days.[44] The primary endpoint (infection resulting in system extraction or revision, long-term antibiotic therapy with infection recurrence, or death, within 12 months) was significantly reduced in the envelope group vs. the control group [0.7% and 1.2%; hazard ratio, 0.60; 95% confidence interval (CI), 0.36–0.98; $P = 0.04$]. The low infection rate in the control group compared to real-world evidence from registries and healthcare administrative/claims datasets has been attributed to certain study exclusion criteria (CIED infection in prior 12 months, haemodialysis or peritoneal dialysis, or treatment with chronic oral immunosuppressive agents), to TYRX™ commercial availability potentially having lead investigators to exclude the highest-risk candidates, to the study operators and centres generally being highly experienced, and to the Hawthorne effect.

According to these results, the international consensus document on how to prevent, diagnose, and treat CIED infections promoted by EHRA[23] reported that the TYRX™ antibiotic envelope is recommended in high-risk situations, as defined in the WRAP-IT study population (patients undergoing pocket or lead revision, generator replacement, system upgrade, or initial CRT-D implantation) and in patients with other high-risk factors such as dialysis or treatment with immunosuppressive agents, and considering also the local CIED infection incidence.

To evaluate the economic implications of the use of the TYRX™ cardiac absorbable antibiotic envelope, a literature review was performed to identify related costs and CEAs. This analysis may be helpful in the assessment and adoption of this innovative technology, and is in accordance with the approach of HTA. A general search was carried out using key words including: 'envelope' or 'TYRX' in combination with 'cost' or 'economic'. This was supplemented with manual review of references in relevant literature. Fifty-eight articles were screened, leading to the selection of five studies that provided comparative cost or cost-effectiveness data for the antibiotic envelope vs. the current standard of care. A summary of these studies is provided in *Table 3*.

Cost-effectiveness analyses based on randomized trial data

Two CEAs have been conducted by clinical study investigators involved in the WRAP-IT.[45,46] Both analyses were based on a prior model[47] and because CEA was pre-specified for the WRAP-IT study, both analyses used prospectively collected data for patients' quality of life (EQ-5D) and healthcare resource use, in addition to clinical endpoints.[43] One study tailored the resource use and cost inputs for the US healthcare system[45] while the second analysis presented data for three European countries (UK, Germany, and Italy).[48]

A decision tree structure with a lifetime horizon was used. The models compare costs and health outcomes for patients receiving the antibacterial envelope adjunctive to 'standard of care' infection prophylaxis, vs. patients treated without the envelope. Total costs and QALYs were calculated for each pathway and ICERs were estimated for the whole study cohort and selected sub-groups. The same structure was used to model cost-effectiveness in the USA as in Germany, Italy, and UK. What changed between the analyses was the (i) country-specific unit costs/prices used; (ii) selection of different

Table 3 Studies containing comparative cost analyses with TYRX™ antibiotic envelope

Authors (year)	Setting	Population	Perspective	Comparison	Time horizon	Results
Boriani *et al.* (2021)[48]	UK, Germany, Italy	High-risk cohorts (WRAP-IT study subgroups and PADIT risk score cohorts)	Healthcare systems (Payers). No indirect costs. Thresholds of €50 000 Germany, €40 000 Italy, £30 000 UK	TYRX™ adjunctive to SoC vs. SoC	Lifetime	*Table 4* for full details. Infection rates SoC: high power replacement 2.9%, PADIT score ≥6 points 3.3% Mortality 3 years: 41.4% (infected), 18.0% (not infected) ICER: TYRX™ cost-effective for ICD and CRT-D replacements, PADIT score ≥6 points (all devices), and some other high-risk groups (all devices)
Wilkoff *et al.* (2020)[46]	USA	High-risk patients (WRAP-IT study population). Included subgroup analyses.	Healthcare system (provider-owned health plan). No indirect costs. Threshold of $150 000.	TYRX™ adjunctive to SoC vs. SoC	Lifetime	Infection rate: 1.2% SoC. TYRX™ hazard ratio 0.6 Mortality 1 year: 14.6% (infected) and 5.2% (not infected) Costs: $37 598 (TYRX™) vs. $36 929 (SoC) QALYs: 6.925 (TYRX™) vs. 6.919 (SoC) ICER: $112 603
Kay *et al.* (2018)[47]	UK	High-risk and 'all-comers' (lower risk) patients, sourced from observational studies of TYRX™	National Health Service (Payer). No indirect costs. Threshold of £30 000	TYRX™ adjunctive to SoC vs. SoC	12 months and lifetime	Infection rate: 3.3% (SoC) vs. 0.6% TYRX™ Mortality 1 year: 0.211 (infected), 0.064 (no infection) ICER: IPG £12 711, ICD £4348, CRT-P £11 248, CRT-D £6261. TYRX™ cost-effective at infection rates above 1.65% (CRT-D), 1.95% (CRT-P), 1.87% (IPG), 1.38% (ICD).
Burnhope *et al.* (2019)[22]	UK	All ICD and CRT procedures, from a single implanting centre ('all-comers')	National Health Service (Payer). No indirect costs.	TYRX™ adjunctive to SoC vs. SoC	12 months	Infection rate: 3.14% SoC vs. 1.02% TYRX™ cost savings estimated £184–£624 per patient QALYs and ICERs: not reported
Shariff *et al.* (2015)[50]	USA	All ICD and CRT procedures, from a single implanting centre ('all-comers')	Hospital costs only. No indirect costs.	TYRX™ adjunctive to SoC vs. SoC	6 months	Infection rates: 0% (TYRX™) vs. 1.71% (SoC) Mortality: 15.7% (infected) vs. 4.5% (not infected) Costs: $318 991 (TYRX™) vs. $342 854 (SoC) QALYs and ICERs: not reported Infection rate of 1.59% calculated as break-even

CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ICER, incremental cost-effectiveness ratio; PADIT, Prevention of Arrhythmia Device Infection Trial; QALY, quality-adjusted life-year; SoC, standard of care; WRAP-IT, Worldwide Randomized Antibiotic Envelope Infection Prevention Trial.

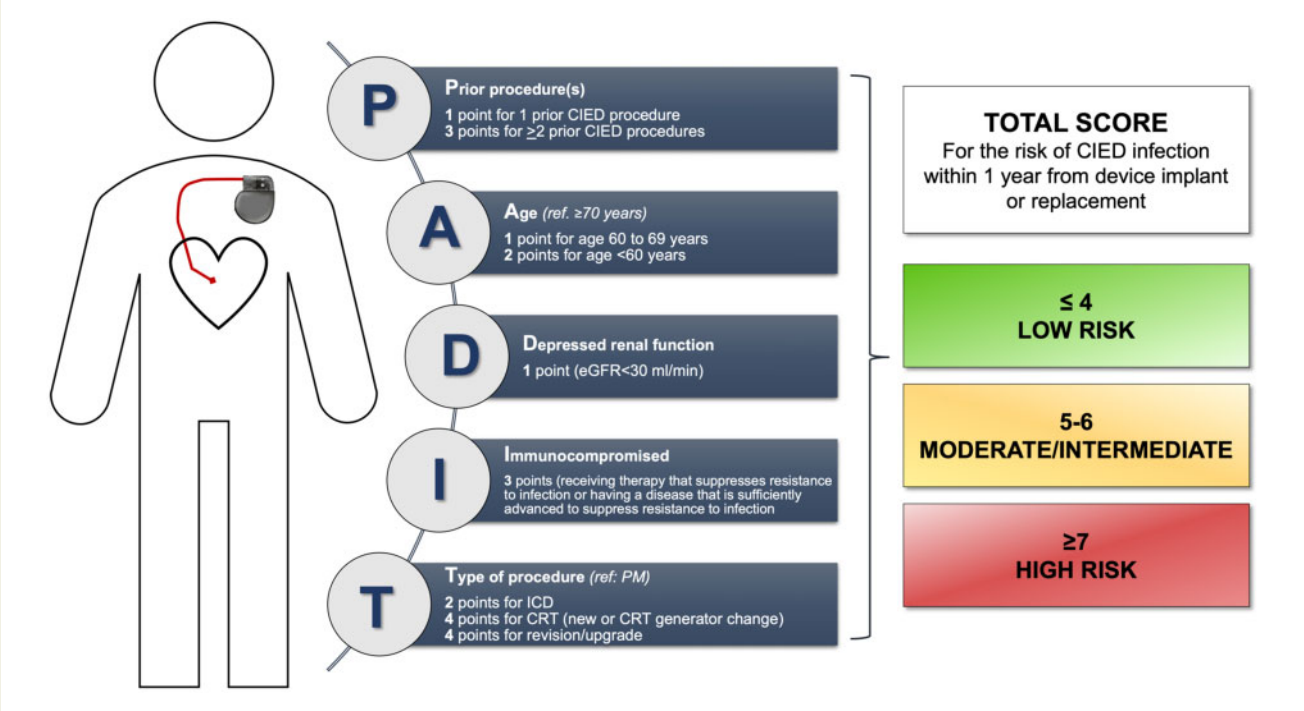

Figure 2 PADIT risk score. From Ref. 49. A correction was published to the original risk score (https://doi.org/10.1016/j.jacc.2020.06.001), the information above is based on the corrected version and the online calculator (https://padit-calculator.ca/). PADIT, Prevention of Arrhythmia Device Infection Trial.

patient subgroups; (iii) cost-effectiveness thresholds designated for each country; and (iv) resulting conclusions about cost-effectiveness.

A mortality analysis of the WRAP-IT trial compared the risk of death at 12 months and throughout all follow-up in patients with and without CIED major infections. Death occurred in 10 of the 67 patients in the infection group (12-month Kaplan–Meier estimate: 16%), and 345 of the 6836 patients in the no infection group (12-month Kaplan–Meier estimate: 5%).[46]

The risk-adjusted hazard ratio was 3.41 (95% CI, 1.81–6.41); $P < 0.001$ at 1 year, and through all follow-up it remained elevated at 2.30 (95% CI, 1.29–4.07); $P = 0.004$.[46]

Quality of life was collected using EQ-5D at baseline, infection diagnosis, 1, 3, and 6 months after diagnosis, and at 12 months after the index procedure. Utility scores calculated using the EQ-5D were significantly reduced at time of infection and did not normalize until 6 months later.[46]

For the USA, mean hospital costs were $55 547 per infection: costs varied from $16 592 for 5 infections treated without extraction, $45 694 for 12 infections treated with extraction and no replacement, and $67 586 for 26 infections treated with extraction and replacement. The ICER of the antibacterial envelope was considered to be cost effective in the overall WRAP-IT population: the ICER was estimated to be $112 603 per QALY gained, based on an overall baseline infection rate of 1.2% and a 40% reduction in major CIED infection with the antibacterial envelope in the trial.[46]

Subgroup analyses estimated the antibacterial envelope was cost-effective (ICER below $150 K threshold) for patients with a risk of infection ≥1.0%; is highly cost-effective (ICER below $50 K) when the risk of infection is ≥2.0%; and is cost-saving when the risk of infection is ≥4.0%. As examples, use in patients with prior CIED infection was cost-saving; use in immunocompromized patients was highly cost-effective; use in patients with renal dysfunction implanted with High Power devices was cost-effective; and use for initial CRT-D implants in patients without risk factors was not cost-effective.[46]

For Europe, resource use data (e.g. hospital length of stay) came from the WRAP-IT study, including specific resources like temporary pacing, wearable defibrillators, and leadless devices.[48] Significant differences in hospital length of stay were observed between patients at US and non-US sites, so the non-US data were used in the European analysis. Intensive care stays were 4.0 days and general ward stays were 23 days in the European analysis. Costs were estimated for each country based on various sources for each country, including Diagnostic Related Group (DRG) tariffs and national costing datasets.[48] As an example, the costs of complete extraction and replacement of an infected CRT-D device were estimated to be at €42 921 (Germany), €45 560 (Italy), and £37 633 (UK). The cost of the envelope was €945 in Germany and Italy, and £800 in UK. An additional analysis was included which builds into the analysis a risk-sharing agreement because the manufacturer provides a replacement device, leads, and envelope free-of-charge in case of occurrence of a CIED infection when the envelope was used.

Additional scenarios were performed in the European analysis to estimate the cost-effectiveness of the antibacterial envelope using risks of infection based on the Prevention of Arrhythmia Device Infection Trial (PADIT) risks score (*Figure 2*).[49] Three such subgroups were defined: PADIT score ≥5 points, ≥6 points, or ≥7 points.

Table 4 **TYRX™ incremental cost effectiveness ratios**

	Germany (€/QALY)	Italy (€/QALY)	UK (£/QALY)	UK* (£/QALY)
Replacement procedure				
CRT-D	€42 912	€39 094	£37 581	£24 972
ICD	€30,414	€26 421	£25 972	£18 264
CRT-P	N/A	N/A	N/A	N/A
PM	N/A	N/A	N/A	N/A
History of immunosuppressive therapy				
CRT-D	€5957	€2226	£6417	Cost saving
ICD	€4430	€522	£4067	Cost saving
CRT-P	€9898	€7005	£13 368	£9338
PM	€13 143	€8635	£16 502	£14 342
≥2 previous CIED procedures				
CRT-D	€18 181	€14 371	£16 680	£4071
ICD	€23 273	€19 299	£19 950	£12 304
CRT-P	€40 652	€37 705	£39 370	£35 227
PM	€43 112	€38 296	£41 957	£39 736
Previous CIED infection				
CRT-D	€6982	€3176	£7215	Cost saving
ICD	€5187	€1201	£4651	Cost saving
CRT-P	€11 149	€8198	£14 438	£10 261
PM	€13 209	€8313	£16 722	£14 483
Generator replacement with lead modification				
CRT-D	€23 080	€19 269	£20 821	£8211
ICD	€16 536	€22 818	£22 926	£15 218
CRT-P	€34 717	€31 777	£34 352	£30 224
PM	€24 322	€19 810	£25 950	£23 790

	Germany (€/QALY)	Italy (€/QALY)	UK (£/QALY)	UK* (£/QALY)
PADIT score ≥7				
CRT-D	€19 300	€15 521	£17 654	£5228
ICD	€13 821	€9864	£11 971	£4374
CRT-P	€5665	€2806	£9781	£5710
PM	€7641	€2896	£11 968	£9785
PADIT score ≥6				
CRT-D	€33 636	€29847	£29 765	£17 311
ICD	€23 889	€19 924	£20 476	£12 862
CRT-P	€18 803	€15 930	£20 887	£16 804
PM	€20 839	€16 075	£23 128	£20 939
PADIT score ≥5				
CRT-D	€66 179	€62 381	£57 270	£44 820
ICD	€46 738	€42 767	£39 788	£32 176
CRT-P	€43 417	€40 537	£41 690	£37 609
PM	€45 556	€40 785	£44 017	£41 829

Colour coding for ICER values:

Green: Germany < €50 000; Italy < €40 000; UK < £30 000

Orange: Germany > €50 000 to < €124 500; Italy > €40 000 to < €88 900; UK > £30 000 to < £99 400 based on WHO limit of 1–3 × GDP

CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; GDP, Gross Domestic Product; ICER, incremental cost-effectiveness ratio; ICD, implantable cardioverter-defibrillator; PM, pacemaker; PADIT, Prevention of Arrhythmia Device Infection Trial; QALY, quality-adjusted life-year; WHO, World Health Organization. *results for scenario with risk-sharing programme
From Ref. 48.

Furthermore, the infection rate for High Power Replacement procedures (2.9%) used in this analysis was sourced from a subgroup analysis of the Western European sites (n = 313) of the WRAP-IT study, as a significantly higher rate of infection was observed than in the overall study.

Incremental cost-effectiveness ratios from the European analysis are reproduced in *Table 4* (colour-coding added by the authors of this paper to aid interpretation)[48] Among the WRAP-IT subgroups, the Italian and German analyses indicate the envelope was cost-effective at thresholds of €40 000 and €50 000 per QALY, respectively, across all subgroups and device types. The results for UK showed the envelope also was cost-effective, with the following caveats: (i) for high power replacement when the risk-sharing program was included but not otherwise; (ii) for patients with ≥ 2 previous CIED procedures it was cost-effective for high power devices but not low power devices; and (iii) for generator replacements with lead modification it was cost-effective for all device types except cardiac resynchronization therapy-pacemaker (CRT-P).

Considering the analyses based on the PADIT risk score, for both low and high-power devices, the envelope was more cost-effective in patients with higher PADIT scores (i.e. at higher baseline risk of infection). This is indicated by lower ICER values for patients with higher PADIT scores. Incremental cost-effectiveness ratios for patients with PADIT scores ≥6 were below the cost-effectiveness thresholds used in the respective countries.

Sensitivity analyses are used in CEAs to identify what factors are most important to making the results positive or negative. This type of analysis indicated that the main drivers of the model in all three European countries were baseline rates of major CIED infections, the efficacy of the envelope, and the excess mortality associated with CIED infection.[48]

Economic analyses based on non-randomized trial data

A CEA of the TYRX™ absorbable antibacterial envelope, from the perspective of the English NHS, was performed based on a combination of two prospective and four retrospective observational studies of TYRX™.[47] The analysis modelled infection rates associated with 'high-risk' patients (3.3%) and an 'all-comers' category (1.9%) based on these observational studies and a relative risk associated with TYRX™ of 0.163 (84% risk reduction). The analyses suggested that over a 12-month time horizon, TYRX™ use in high-risk patients was cost-saving in patients with an ICD or CRT-D, and associated with ICERs of £46 548 and £21 768 per QALY gained in patients with an IPG or CRT-P, respectively. The structure of this model was the basis for the two analyses described above, which incorporated higher quality data inputs after the WRAP-IT study was completed.

A single-centre retrospective analysis in the UK reported data on the costs of CIED-related infections and estimated cost savings with TYRX™.[22] Five infections were identified within 12 months amongst 159 (3.14%) ICD/CRT procedures over a period spanning 2014–2017, without the use of TYRX™. An average cost of £41 820 was estimated to be directly attributable to CIED infection, based on patient-level costing data. A secondary analysis estimated the excess total healthcare costs for patients with CIED infection at £62 214. Modelling a potential reduction in the number of infections using TYRX™, by applying an odds ratio of 0.31 (based on a meta-analysis), a cost-saving of £624 per patient was estimated. The main limitations of this analysis were the small sample size and that the efficacy of TYRX™ was modelled based on non-randomized data. A large single-centre retrospective analysis in the USA reported a cost analysis based on CIED infections observed amongst patients treated with or without TYRX™.[50] A total of 1476 patients having CIED procedures were followed up: 1111 patients treated without TYRX™ and 365 patients treated with TYRX™. A propensity score matching analysis led to a comparison of 362 of the patients treated with TYRX™ matched to 362 patients with similar risk profiles who did not receive TYRX™. The infection rates in this analysis were 0% with TYRX™ compared to 1.9% without TYRX™. Costs were estimated from hospital length of stay, use of home intravenous antibiotics, and the LifeVest®: the average cost was $54 926 per CIED infection. The cost of treating CIED infections in patients treated without TYRX™ was reported to be similar to the cost of using TYRX™ and having no infections: $340 000 vs. $320 000, respectively.

The CEA results for TYRX™ are similar to those reported for other cardiovascular therapies. In NYHA Class III patients with wide QRS duration, ICERs of £24 875–£28 646 were estimated for CRT-D compared to CRT-P in a comprehensive analysis from the UK National Health Service perspective.[51] A recent analysis for Germany reported an ICER of €24 659 for CRT-D compared to CRT-P.[52] An analysis from a US Medicare perspective reported an ICER of $43 678 for CRT-D vs. CRT-P, based on the REVERSE trial.[53] The CardioMems implantable pulmonary artery pressure monitor was estimated to have an ICER of $71 K in NYHA Class III patients in the USA,[54] and ICER between £22 342–£25 464 per QALY gained (€28 709–32 721) from the UK National Health Service perspective.[55]

Conclusions

The occurrence of CIED infections and related adverse outcomes have an important financial impact on the healthcare system, with hospitalization length of stay (2–3 weeks on average) being the largest cost driver, including the cost of device system extraction and device replacement accounting for more than half of total costs. In a recent analysis, the economic profile of the TYRX™ absorbable antibacterial envelope was analysed taking into account both randomized and non-randomized trial data. Economic analysis found that the envelope is associated with cost-effectiveness ratios below US and European benchmarks in selected patients at increased risk of infection. Therefore, the TYRX™ envelope, by effectively reducing CIED infections, provides value according to the criteria of affordability currently adopted by US and European healthcare systems.

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