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ORIGINAL RESEARCH

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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

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ABSTRACT

Background and aims: Infection is a serious and expensive complication of Cardiac Implantable Electronic Device (CIED) procedures. A retrospective based cost analysis was performed to estimate Trust level savings of using the TYRX antibacterial envelope as a primary prevention measure against infection in a tertiary referral centre in South London, UK.

Methods: A retrospective cohort of heart failure patients with reduced ejection fraction undergoing Implantable Cardioverter Defibrillator (ICD) or Cardiac Resynchronization Therapy (CRT) procedures were evaluated. Decision-analytic modelling was performed to determine economic savings of using the envelope during CIED procedure vs CIED procedure alone.

Results: Over a 12 month follow-up period following CIED procedure, the observed infection rate was 3.14% ($n = 5/159$). The average cost of a CIED infection inpatient admission was £41,820 and, further to economic analysis, the additional costs attributable to infection was calculated at £62,213.94. A cost saving of £624 per patient by using TYRX during CIED procedure as a primary preventative measure against infection was estimated.

Conclusions: TYRX would be a cost-saving treatment option amongst heart failure patients undergoing ICD and CRT device procedures based on analysis in the local geographical area of South London. If upscaled to the UK population, we estimate potential cost savings for the National Health Service (NHS).

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Introduction

In recent decades, the number of Cardiac Implantable Electronic Device (CIED) procedures has increased substantially[1], consequent to growing indications for implantation based upon expanding evidence on improved morbidity and mortality[2–7], increased survival rates from ischaemic heart disease and an ageing population[8]. In accordance with this, the numbers of CIED related infections have climbed, with an estimated annual prevalence of 2–4%[9–11], despite best practise and vigilant infection-control standard operating protocols[12–15]. Certain risk factors have been observed in relation to CIED infections, including a medical history of diabetes, renal failure, heart failure and prior CIED infection, and use of anticoagulant or corticosteroid therapy. Additionally, Cardiac Resynchronization Therapy (CRT) implants, revision or upgrade procedures, and procedures involving three or more pacing leads have increased infection risk[16–19]. The risk of infection to any individual is most likely determined by the combination of risk factors that is present.

CIED infection is one of the most serious complications following the procedure, characterized by high levels of patient related morbidity and mortality. Infections are associated with prolonged hospital admissions, extended antibiotic therapy, and, if the patient is a suitable candidate, recommended complete device extraction followed by re-implantation, the former being a major procedure with non-insignificant risks of serious complications including fatality[12,14,20,21]. All-cause mortality rates over a 5 year follow-up period have been reported as high as 35%[14,19] and, in cases of CIED endocarditis without concomitant device extraction, mortality rates range from 31–66%[13]. Consequently, CIED infections contribute considerable financial burden to healthcare systems globally. Recent estimated costs attributable to a CIED infection related hospital admission were $146,000 and £30,958 in the US and UK, respectively[12,21].

Given the significant clinical and financial burden of infection complications, ongoing primary prevention at the time of device procedure is paramount. The TYRX Absorbable

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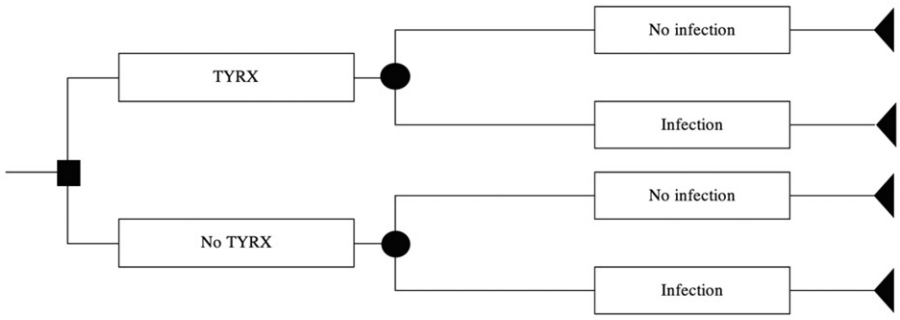

Figure 1. Decision analytic model developed to analyse the expected economic impact of introducing TYRX.

Antibacterial Envelope (Medtronic plc, Mounds View, Minnesota)[22], is a sterile, single use multifilament knitted mesh composed of a polymer made of glycolide, caprolactone, and trimethylene carbonate, that houses the CIED generator within the subcutaneous pocket which elutes two antibiotics (rifampicin and minocycline) over at least a 7 day period following device implantation and, thereby, provides a primary prophylaxis against infection. A non-absorbable version of the envelope was previously available and in several observational studies demonstrated an infection reduction rate between 69–100% with associated cost-effectiveness[11, 23,24]. A prospective randomized controlled trial determining the efficacy of the absorbable TYRX; the World-wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT)[25] is currently underway with highly anticipated results.

This paper describes an economic model developed to demonstrate the potential financial savings of using TYRX as a preventative measure against infection within a retrospective cohort of Heart Failure patients with reduced Ejection Fraction (HFrEF)[26] undergoing CIED procedures inclusive of an Implantable Cardioverter Defibrillator (ICD) or CRT, to a single National Health Service (NHS) Foundation Trust within South London, UK and its local Clinical Commissioning Group (CCG).

Methodology

Retrospective audit

A retrospective audit of all ICD and CRT procedures in patients with HFrEF within two local geographical residential areas of a single tertiary referral institution and high volume device implantation centre (Guy's and St Thomas' NHS Foundation Trust, London, UK) was registered, approved, and conducted between 1 January 2014 and 31 September 2017. St Thomas' Hospital is a large NHS teaching hospital in South London. It acts as a tertiary referral centre for cardiovascular disease, with services covering cardiology, cardiothoracic surgery, and congenital heart disease for both paediatric and adult populations. The estimated population of the two local geographical areas is ∼ 575,000 people. Both are socially deprived areas based on UK local authority data (40th and 44th most deprived areas, respectively). Approximately 60% of this population is Caucasian and 25–30% Black ethnic origin. Procedures were inclusive of new or de novo implant, generator change, and upgrades, and performed by appropriately skilled operators. Data collected was inclusive of those specific to the device procedure, in addition to patient demographics, co-morbidities, prescribed medications, and healthcare utilization to the Trust within a 24 month window; 12 months pre- and post-device procedure. CIED infection was defined by a hospital admission within the first 12 months following device procedure requiring a prolonged course of intravenous antibiotics with or without a device extraction procedure. Infections were identified through a combination of searching a purpose built Trust Extraction Database, which contributed to the European Lead Extraction Registry,[19,27] and using the 10th Edition of the World Health Organization (WHO) International Classification of Disease (ICD) discharge code for the admission relating to the CIED infection containing ICD-10 code T82.7 within the Trust's information systems.

Infection-control protocol

The Trust's infection-control protocol when performing CIED procedures throughout the period of January 2014–September 2017 is detailed in the Supplementary Appendix and we assume 100% compliance. The TYRX envelope was not in use during ICD and CRT related device procedures within the Trust during the time period analysed.

Economic analysis

We developed a decision-analytic model seeking to assess the expected economic impact of introducing the TYRX Absorbable Antibacterial Envelope whereby the primary aim is to reduce infection rates after CIED procedures. The perspective of the model is within a single NHS Foundation Trust. The time horizon captured in the analysis was set to 1 year to be consistent with the scope of the study. The model consists of two mutually exclusive pathways; CIED procedure with TYRX vs CIED procedure alone without TYRX (see Figure 1). Mortality was not included as there were no deaths observed within the CIED infection group during the first 12 months post-discharge. Costs of healthcare utilization in the 12 months post-CIED procedure were captured subsequent to the date of discharge following the CIED procedure, therefore the procedural costs relating to this were not included in the total cost estimation. The model was probabilistic to capture the joint impact of parameter uncertainty.

Table 1. Parameters of economic model.

Parameter	Value	Source
Infection cost	£61,585.76	GLM estimate
Mean cost of TYRX	£719.00	Reported market price
Probability of infection in the No TYRX group	3.205%	Retrospective data
Odds ratio of TYRX vs No TYRX	0.31	Koerber *et al.*
Probability of infection in the TRX group	1.0161%	Derived from Koerber *et al.* and retrospective data

A Monte Carlo simulation consisting in 999 iterations was conducted in Microsoft Excel. The model parameters were cost of infection, baseline infection risk, and odds ratio of infection with TYRX relative to current practice. We used an odds ratio of 69% based on a recent meta-analysis[28] to derive the probability of infection within the TYRX group. A Gamma distribution was assumed for Infection cost. A log normal distribution was selected for the odds ratio of infection with TYRX relative to current practice. For both groups, the procedural costs were assumed to be equivalent, therefore were not included in the model.

The probability of developing infection for the no-TYRX branch was defined as the proportion of procedures that resulted in an infection episode throughout the 12-month follow-up period in the 159 procedures cohort. In the absence of an experimental group, we assumed infection risk using TYRX reduced by the odds ratio obtained from a recent meta-analysis[28]. We derived the probability of infection in the TYRX-group by combining the odds ratio for infection with TYRX and the odds of infection without TYRX observed from the retrospective audit (please refer to the Supplementary Appendix for further detail). The parameters of the model are presented in Table 1.

Cost analysis

An estimated cost for each patient for the 12-month period following their device procedure was calculated. This was inclusive of inpatient admissions, outpatient department (OPD) and Accident and Emergency (A&E) department visits, and Community Heart Failure Nurse visits. As HFrEF patients are frequently associated with multiple co-morbidities, we felt it was vitally important to calculate and present the "total" expense of their 12-month post-device procedure journey rather than just the cardiac related costs. In addition to the "total" 12-month cost, we were able to scrutinize our cost data in great detail, enabling us to calculate costs related specifically to cardiac and non-cardiac healthcare utilization. Unlike previous published works, which used financial data derived from reference costs, our inpatient admission, A&E, and OPD department related financial data were derived from patient level costing and represent the actual cost to the Trust. Inpatient admission costs represented the entire outlay of the hospital stay, including device, staffing, overheads, and diagnostic testing. We also recorded hospital income for patient care, based on nationally and locally agreed reimbursement tariffs, but they have not been used further in our analysis or reported results. General Practise (GP) healthcare utilization was not reported and, because their costs are fixed, they have not been included in our analysis. Community Heart Failure Nurse visit costs are separately commissioned and available to the Trust drawn from reference costings. Overall, community related costs contribute less significantly to the overall 12-month care pathway post-device procedure in contrast to inpatient admissions. Missing costs data was observed for 9% of inpatient admissions, 6% of OPD visits, and 3% of A&E attendances. For missing inpatient costs we used the predicted values from a multi-variable linear regression model which included bed-days, critical care days, type of admission, and whether a CIED procedure was performed during the admission. We added some random noise to the imputed values (with a standard deviation equal to the root-mean-square error), to give some variability around the regression line. For the missing A&E data, we used HRG-level reference costs supplied by the trust. For the majority of the missing outpatient data we again used reference costs and, where this wasn't possible, we simply used median costs. A cost of £719 for the TYRX envelope was used for analysis purposes, which has been previously quoted and published in health economic literature[22].

Estimation of costs attributable to infection

We undertook regression analysis of total costs to allow adjustment for patient case-mix in the estimation of the cost attributable to infection. We applied Generalized Linear Modelling following recommendations by Mihaylova *et al.*[29] and used the Park test to select the distribution. Given the limitations of the sample size we considered a linear and a log link (additive and multiplicative model). We assessed the robustness of estimation of infection-attributable cost through two sensitivity analyses.

- We applied an ordinary least squares (OLS) model in place of the GLM model in combination with bootstrapping to quantify uncertainty.
- We estimated the cost of infection through attribution of resource use deemed to have arisen from infection for the five patients with an infection.

We also conducted a scenario analysis on the TYRX cost in order to determine the threshold of positive savings to the NHS. The reported market price of the device was varied ± 50%. We report the breakeven price of TYRX. All the statistical analyses were conducted on Stata SE 15. Further details on these methods are provided in the Supplementary Appendix.

Table 2. ICD and CRT device procedures in HFrEF patients between 1 January 2014 and 31 September 2017.

	ICD	CRT-P	CRT-D	Total
Generator change	4	11	29	44
Upgrade	—	16	10	26
New implant	28	19	42	89
Total	32	46	81	159

Abbreviations. CRT-D, Cardiac Resynchronization Therapy Defibrillator; CRT-P, Cardiac Resynchronization Therapy Pacemaker; ICD, Implantable Cardioverter Defibrillator.

Statistical analysis

The demographics, device procedural details, comorbidities, and other associated risk factors for CIED infection were compared among the two patient groups; with and without infections and presented using descriptive statistics with measures of frequency, central tendency, and variation.

Results

Device infection rate

One hundred and fifty-nine ICD and CRT device-related procedures occurred in 157 HFrEF patients between 1 January 2014 and 31 September 2017 within two specified catchment geographical areas for the Trust (see Table 2). Two patients underwent two separate procedures as a result of upgrade from ICD to CRT-D, each with separate 12-month follow-up periods that did not overlap within the 45-month time period, therefore accounting for 159 procedures. Five patients developed a CIED infection within 12 months of their device procedure, requiring prolonged inpatient admission and device extraction followed by re-implantation, resulting in an infection rate of 3.14%. All five patients had confirmed microbiology evidence of CIED infection with either positive blood cultures and/or pacing lead tip cultures for typical bacterial organisms; two Staphylococcus Aureus, two Staphylococcus Epidermis, and one Enterococcus Faecalis. All five patients underwent full CIED system extraction during the CIED infection related admission followed by re-implant procedures prior to discharge. The average length of stay for the CIED infection related admission was 43.6 days, with the largest contributors to the total admission cost being inpatient bed days (inclusive of critical care bed days; 27%), devices (17%), Trust overheads (16%), and finally medical staffing costs at 12%. Patient demographics, co-morbidities, and specifics of the device procedure for both groups (those with and without a CIED infection) are shown in Table 3.

Cost of infection

Using the raw cost data, excluding costs relating to the CIED procedural admission (as already detailed in our methodology), the average total 12-month post-device procedure healthcare cost was £13,326. The unadjusted difference between mean costs of non-infected and infected patients from the raw cost data was £59,048.82. The average cost of attributed individual resource use ($n = 5$) relating to a CIED infection was £41,820.40 (range = £28,377–£56,498). The distribution of total costs was strongly right-skewed (Figure 2). The modified Park test indicated the Gamma distribution best fit the data. Link tests indicated a linear link (additive model) was superior to a log link. Table 4 presents the results of alternative approaches to the estimation of "total" costs attributable to infection. Infection costs were highest when estimated using GLM and lowest when estimated using attribution of individual resource use. Additional costs attributable to infection costs were £62,213.94 [SE = £16,697.81] in the base case (GLM). When analysed for cardiac related costs only, the additional costs attributable to infection were £49,541.25 [SE = £10,707.48] in the base case (GLM).

Table 3. Baseline characteristics, comorbidities, and CIED risk factors in patients with and without CIED infections (*n*/%).

	Infection group ($n = 5$)	Non-infection group ($n = 152$)
Age (mean/range)	67 (54–82)	68 (22–92)
Gender: Male	4 (80%)	115 (76%)
Anaemia	1 (20%)	29 (19%)
Atrial Fibrillation	2 (40%)	79 (52%)
CAD	2 (40%)	79 (52%)
Malignancy	0 (0%)	22 (14%)
COPD	3 (60%)	47 (31%)
Dementia	0 (0%)	5 (3%)
Diabetes	2 (40%)	72 (47%)
Hypertension	4 (80%)	118 (78%)
Sleep Apnoea	0 (0%)	23 (15%)
CKD	2 (40%)	57 (38%)
Stroke	0 (0%)	5 (3%)
Valve Disease	4 (80%)	49 (32%)
Myocardial Infarction	3 (60%)	64 (42%)
Mood Disorder	0 (0%)	23 (15%)
Anticoagulation Therapy	2 (40%)	80 (53%)
Generator Change/Upgrade Procedure	2 (40%)	68 (45%)
Presence of Defibrillation Lead	5 (100%)	106 (70%)

Abbreviations. CAD, Coronary Artery Disease; CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease.

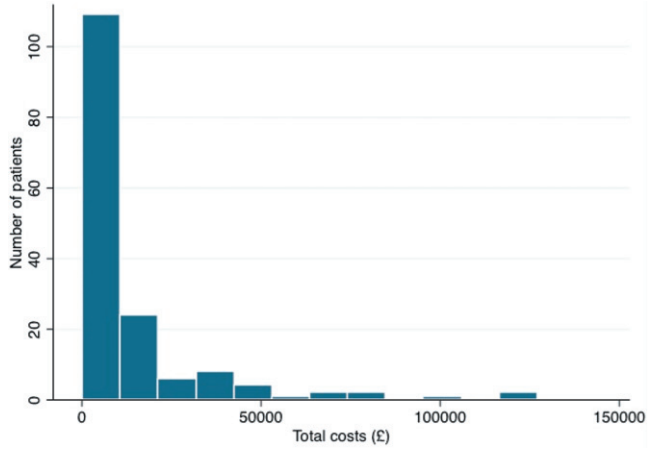

Figure 2. Histogram of total costs after 12-month follow-up ($n = 159$).

Economic analysis

Table 4 also summarizes the results of the economic impact assessment. Utilizing a base-case device price of £719 and infection costs estimated from GLM, TYRX generated savings

Table 4. Sensitivity analysis on cost estimation method.

Method of cost estimation	Total cost (SE)	Infection cost (SE)	Expected savings (95% CI)
GLM	13,193.64 (979.57)	62,213.94 (16,967.81)	624.09 (597.00–651.16)
OLS + Bootstrap	13,385.04 (54.06)	58,841.7 (644)	514.23 (484.74–543.71)
Attribution of resource use	13,425.61* (1,716.69)	41,820.4** (13,257.28)	184.67 (164.68–204.67)

*Average cohort total cost.
**Average cost of attribution of resource use in only infected patients.
Abbreviations. CI, Confidence Interval; GLM, Generalized Linear Model; OLS, Ordinary Least Squares; SE, standard error.

of £624 per procedure. In sensitivity analysis, savings were £514 and £184 per procedure using infection costs estimated from the OLS model and direct attribution of resource use, respectively. The breakeven price for the TYRX envelope was £1,361.

Discussion

We observed an infection rate of 3.14% ($n = 5/159$) amongst a HFrEF population undergoing ICD and CRT device-related procedures. The average cost of a CIED infection inpatient admission was £41,820 and, further to GLM analysis, the additional costs attributable to infection was calculated at £62,213.94 ("total" costs) and £46,770 (cardiac-related costs). Our economic analysis determined cost savings between £184 and £624 by using the TYRX absorbable envelope at the time of procedure as a primary preventative measure against CIED infection.

Accurate figures of the scale of CIED infection and their associated costs are not known within the UK, however predictions on continued growth in the number of CIED procedures, particularly within older and comorbid populations, mean that these figures are projected to increase. Definitions of what entails a CIED infection and during what timeframe of follow-up varies in the literature, making comparison challenging, however the observed rate of infection in our cohort within 12 months of the device procedure (3.14%) falls within the range published in current literature (2–4% annual prevalence). It is possibly not surprising, that our infection rate was nearer to the top end of this range, given that we specifically studied a "high risk" group; patients with HFrEF, of whom 80% had a CRT device, and 44% underwent a recurrent procedure (generator change or upgrade). As Table 2 demonstrated, significant comorbidities were substantially prevalent within our cohort, with traditional infection risk factors of diabetes, renal failure, and COPD featuring prominently.

To really understand the financial implications of CIED infections, the first key measures are to define a dedicated geographical area and utilize accurate and validated cost data. This project addresses these specifically; we created a purpose-built database able to capture both community and secondary care health utilization for patients with HFrEF and implanted ICD or CRT devices within a pre-defined local residential geographical location. Our cost data has been obtained directly from the Trust Finance department, and provides the actual cost incurred by the Trust at an extremely accurate and detailed level for any individual patient and any individual healthcare transaction. We have been able to provide a robust "total" cost estimate for any patient within our cohort, which more accurately represents the entire cost of their healthcare journey within 12 months of their device procedure, but are also able to interrogate our cost data by type of healthcare utilization (inpatient, A&E, etc.) or whether this is cardiac or non-cardiac related. Having reviewed the literature, we believe this is uniquely different to any previously published work in this area.

Previous estimates of the cost of CIED infection to healthcare systems globally within the last decade vary from $146,000 (US), £30,958 (UK), and €20,211–23,237 (France)[12,21,30]. Methodologies to determine cost estimates differed across these studies, all encompassed an estimated cost for a hospital admission relating to the CIED infection; however, the acquisition of cost data varied from a cost-to-charge ratio, diagnosis-related group (DRG) coding (similar to income reimbursements paid to NHS service providers) to the use of reference costings. Another important difference to highlight between our work and these studies is that they were all inclusive of single and dual chamber pacemakers for treatment of bradyarrhythmia, which incur a lower device tariff/cost compared to ICD or CRT-D for the replacement device procedure and one study included CIED infections that were medically managed without system extraction. All these factors in synergy may account for the higher comorbidity-adjusted estimate of cost attributable to CIED infection-related hospital admission in our cohort (£61,585). The fact that we also observed an inflated cost when adjusted to include only the cardiac related costs specifically (£49,541.25) reinforces our results and the strengths of our costing methodology. Discrepancies could also be explained by unobserved cofounders or due to a lack of earmarking of additional resource costs within the infection group to that of infection costs.

One of the main limitations of this report is the small sample size. In total, five patients from our limited cohort experienced a CIED infection within 12 months of their device procedure, therefore deriving definitive conclusions from this analysis should not be done without due care and attention. Alongside the small sample size, which had implications on the robustness and accuracy of our estimates, the fact that this was retrospective data with the lack of a control or placebo group necessitated making strong assumptions on similarities between groups to perform economic analysis to estimate cost savings from the intervention of using the TYRX envelope. Our first assumption was the probability of infection within the TYRX group, in the absence of results from the awaited randomized controlled WRAP-IT[25] trial on CIED infection rate reduction. We used a reduction of relative risk of 69% previously published in the literature[28] to

derive the probability of infection within the TYRX group. This calculation was made under the assumption of enough similarity amongst studies' population that enables reverse engineering combining primary and secondary data. Despite this, the structural sensitivity analysis on cost estimation demonstrated cost savings, although there is a marginal difference among approaches. Whilst our economic model analysis calculated a cost saving of ~ £600 per patient using TRYX as a preventative measure against infection, this was observed in a "high risk" studied group and, therefore, it cannot be assumed that, when applied to patients without heart failure or those undergoing bradyarrhythmia pacemaker procedures, the same savings effect would be observed.

However, using our methods of a fixed geography, unique costings; which provide full and accurate costs at a Trust level, and using our calculated cost saving of £624 per procedure, suggests that using the TYRX envelope would result in reductions in costs to the NHS. Based on national figures in 2015–2016[31], whereby 295 new or de novo ICD and CRT device implants per million population were performed In England, potential savings to the NHS could be estimated at over £9,700,000. This figure is under-estimated, as it is not inclusive of generator change and upgrade procedures or those from the Welsh, Scottish and Northern Ireland populations. Additionally, the use of the TYRX would have resulted in an estimated reduction in the infection rate to 1.02%, meaning three out of the five patients with CIED infection observed in our cohort would not have experienced an infection with a consequent reduction in the associated morbidity and mortality.

Conclusion

Overall, our study findings suggest that the TYRX envelope would be a cost-saving treatment option amongst HFrEF patients undergoing ICD and CRT device procedures within the local geographical area of the Trust.

Transparency

Declaration of funding

This work was funded by Medtronic.

Declaration of financial/other relationships

AR and RR have received research funding from Medtronic. MP has received consulting advisory fees from Merck. GCW has received research funding from Medtronic and Abbott. The remaining authors on this manuscript have no financial or other relationships to disclose. Peer reviewers on this manuscript have received an honorarium from JME for their review work, but have no other relevant financial relationships to disclose.

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