The Blister Score: A Novel, Externally Validated Tool for Predicting Cardiac Implantable Electronic Device Infections, and Its Cost-utility Implications for Antimicrobial Envelope Use

Running title: *Maclean et al.; The BLISTER risk score for CIED infection*

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Abstract:

Background - Antimicrobial envelopes reduce the incidence of cardiac implantable electronic device (CIED) infections, but their cost restricts routine use in the UK. Risk scoring could help identify which patients would most benefit from this technology.

Methods - A novel risk score (BLISTER) was derived from multivariate analysis of factors associated with CIED infection. Diagnostic utility was assessed against the existing PADIT score in both standard and high-risk external validation cohorts, and cost-utility models examined different BLISTER and PADIT score thresholds for TYRX™ antimicrobial envelope (AE) allocation.

Results - In a derivation cohort (n=7,383), CIED infection occurred in 59 individuals within 12 months of a procedure (event rate: 0.8%). In addition to the PADIT score constituents, lead extraction (HR 3.3 (1.9-6.1), p<0.0001), C-reactive protein >50mg/l (HR 3.0 (1.4-6.4), p=0.005), re-intervention within two years (HR 10.1 (5.6-17.9), p<0.0001), and top-quartile procedure duration (HR 2.6 (1.6-4.1), p=0.001) were independent predictors of infection. The BLISTER score demonstrated superior discriminative performance versus PADIT in the standard-risk (n=2,854, event rate: 0.8%, AUC 0.82 vs 0.71, p=0.001) and high-risk validation cohorts (n=1,961, event rate: 2.0%, AUC 0.77 vs 0.69, p=0.001), and in all patients (n=12,198, event rate: 1%, AUC 0.8 vs 0.75, p=0.002). In decision-analytic modelling, the optimum scenario assigned AEs to patients with BLISTER scores ≥ 6 (10.8%), delivering a significant reduction in infections (relative risk reduction: 30%, p=0.036) within the NICE cost-utility thresholds (ICER: £18,446).

Conclusions - The BLISTER score (https://qxmd.com/calculate/calculator_876/the-blister-score-for-cied-infection) was a valid predictor of CIED infection, and could facilitate cost-effective AE allocation to high-risk patients.

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Nonstandard Abbreviations and Acronyms

AE – Antimicrobial Envelope

AF – Atrial Fibrillation

CIED – Cardiac Implantable Electronic Device

CRT – Cardiac Resynchronisation Therapy

EHRA – European Heart Rhythm Association

ICD – Implantable Cardioverter-Defibrillator

NICE - National Institute for Health and Care Excellence

PPM – Permanent Pacemaker

QALY – Quality Adjusted Life Year

Introduction

Cardiac implantable electronic device (CIED) infection is a serious complication of device therapy, with significant ramifications for patient morbidity, mortality, quality of life, and healthcare costs[1,2]. The incidence of CIED infection is rising, attributed to the increasing use of complex devices, successive re-interventions on device pockets, and the proliferation of predisposing co-morbidities[3,4,5].

The WRAP-IT randomised controlled trial demonstrated how use of the TYRX™ antimicrobial envelope (AE) during CRT-D implant or device re-intervention reduced the risk of infection at 12 months, and this technology has since been adopted into the EHRA guidelines for high-risk patients[6,7]. However, the current EHRA definition of 'high-risk' incorporates a large proportion of the CIED population (including those with dual chamber devices, heart failure or diabetes) and, given the high cost of the AE, strict adherence with these recommendations may not conform with policymakers' cost-utility thresholds. In the UK, the National Institute for

Health and Care Excellence (NICE) technology appraisal of the AE was terminated in 2022 following withdrawal of data by the manufacturer[8]. However, decision-analytic modelling has suggested that the AE may be cost-effective in certain high-risk patient subgroups (e.g. ICD recipients), accounting for the current unit cost of £800 ($1,000)[9,10]. The existing PADIT risk score has been proposed as a gatekeeper strategy for AE use, however, whilst the discriminative power of this score has been validated in a large US registry, prognostic performance has been found inferior to other risk scores in European populations[11,12,13,14,15].

The present study investigated the factors associated with infection for all transvenous CIED patients with a view to, first, validating the PADIT risk score components in a large UK cohort and, subsequently, incorporating any additional, significant covariates into a novel risk score. The primary hypothesis was that this novel risk score may provide incremental prognostic data over and above those derived from PADIT, and hence could be used to direct more cost-effective AE use across the UK and broader CIED populations.

Methods

Data availability statement

The data that support the findings of this study are available upon reasonable request.

Patient populations

For all patient cohorts, consecutive patients undergoing de novo implants, generator changes, and lead interventions for transvenous pacemakers (PPM), implantable cardioverter defibrillators (ICD), and cardiac resynchronisation therapy (CRT) devices were identified from secured registries. Lead extractions performed for infected devices were excluded. No AEs were included in this analysis.

For the derivation cohort, consecutive procedures took place at St. Bartholomew's Hospital (SBH) from 2015-2019. For validation, additional data were extracted from two large tertiary UK cardiac centres. First, a standard-risk validation cohort combined consecutive patients at Royal Papworth Hospital (RPH) from 2018-2019 with distinct, consecutive patients at SBH (2019-2020).

Globally, as the prevalence of complex CIED implantation and reintervention has increased, so too has the incidence of infection[16]. As such, to examine the scores' performance under high-risk conditions, a second external validation cohort was composed with an event rate of 2%. For this high-risk group, consecutive patients with CIED infection from 2014-2018 at St. Thomas' Hospital (STH) were identified and combined with distinct, consecutive patients at SBH (2020-2021) with PADIT scores of ≥1. All included patients completed 12 months' follow-up.

Procedures

Device procedures were performed in either a catheter laboratory or, in cases of high-risk lead extraction warranting standby surgical cover, in a hybrid operating theatre. During the study period, patients anticoagulated for atrial fibrillation (AF) had their oral anticoagulation medications interrupted for 24 hours prior to the procedure. Those patients on vitamin K antagonists for a history of thromboembolism or mechanical heart valve underwent their procedures on uninterrupted anticoagulation, provided their INR was within therapeutic range (INR range 2-3.5). No heparin bridging was used, and those inpatients prescribed heparin for prophylaxis of venous thromboembolism had this treatment withheld the evening prior to the procedure. Antiplatelet therapy was withheld for five days unless prescribed within a year of percutaneous coronary intervention (PCI) or stroke. All patients received a bolus of intravenous

antibiotics within two hours of the procedure: at SBH, patients received gentamicin 5mg/kg (maximum dose 450mg) plus either flucloxacillin 1g or, in patients with penicillin allergy or a positive or unknown MRSA status, teicoplanin 6mg/kg rounded to the nearest 100mg. Patients with both penicillin and teicoplanin allergy received either a cephalosporin or vancomycin depending on the nature of the allergic reaction. At RPH, patients received gentamicin 2mg/kg (maximum dose 240mg) plus either flucloxacillin 1g or, in patients with penicillin allergy, teicoplanin 10mg/kg. At STH, patients received 2g of Flucloxacillin or 6mg/kg of Teicoplanin if allergic to penicillin. Double gloving was mandatory during draping, with the outer gloves removed prior to skin incision, and the skin was prepared with chlorhexidine scrub and a 3M Ioban™ antimicrobial skin barrier. Local anaesthetic was administered in the form of 1% lignocaine. For de novo implants, electrocautery was delivered via Pfizer's ValleyLab Force FX electrosurgical generator with cut and coagulation powers set at 40W. For re-interventions, Medtronic's AEX generator with PlasmaBlade™ was used on cut and coagulation setting 5-6. Pocket washing was not performed routinely, however, at the operators' discretion, intra-pocket Videne® antiseptic solution was administered during re-interventions with long procedure times. All lead collars were secured with Ethibond, and wounds were closed with layers of Polydioxanone (PDS), Vicryl, Monocryl, or a combination of these sutures. 3M Steri-Strips and a Softpore™ adhesive dressing were affixed to the skin surface, and a pressure dressing applied according to operator preference. No post-procedural oral antibiotics were prescribed in this study. Patients were advised to keep their wounds covered and dry for seven days; this was extended to 10 days in those with a history of diabetes. All patients received follow-up – including wound inspection – at one month post implant via a dedicated device clinic, and were reviewed subsequently at 12 months, or sooner if clinically indicated.

Outcomes

CIED infection was defined as hospital admission for device pocket or systemic infection within 12 months of a procedure.

Statistical analysis

Statistical analysis was performed using R. The Shapiro-Wilk test discerned whether data were normally distributed. Categorical group variables were compared using a Z-test for differences of proportion. Continuous variables were analysed using two-tailed unpaired t tests for normally distributed data or the Mann–Whitney U test for non-normally distributed data. Group outcomes were compared using Fisher's exact test. Univariate Cox proportional hazards analysis for the prediction of CIED infection was performed for patients' baseline characteristics, risk factors and procedural variables. The proportional hazards assumption was tested according to the relationship between scaled Schoenfeld residuals with time. Stepdown multivariate analysis (R package: My.stepwise) was performed subsequently including all univariate factors with $p < 0.25$; a variance inflating factor (VIF) was generated to assess for multicollinearity with a cut-off of 2.5 set for categorical variables and 10 for continuous variables. For parameters with multiple subcategories (e.g. age range), multivariate analyses were repeated with a fixed reference but different subcategories applied during each iteration, with the collective final results of these models presented. An expanded PADIT score (BLISTER) was calculated based on these results by assigning weighted points to beta coefficients as per Schneeweiss' method (see supplemental material)[17]. Missing data were accounted for using regression imputation (R package: MICE). Time-dependent receiver operating characteristics (ROC) curves (R package: timeROC) were calculated with prognostic performance at 12 months assessed according to differences in the area under the curve (AUC) by DeLong's test.

Cost-utility analysis was performed in Microsoft Excel. Expenses were calculated from the present study cohort, including the exact cost of replacement device components in the UK, NICE tariffs for extraction and hospital bed days, and antibiotic treatment according to the British National Formulary (BNF - see supplemental material). QALY data were taken from NICE TA 314, NICE TA 324, and other established economic analyses including post-hoc analysis of the WRAP-IT trial for UK patients[10,18,19]. A decision-analytic model (supplemental Figure 1) was constructed incorporating eight possible disease states for the 12 months following a CIED procedure, and the cost-utility of assigning AEs to patients according to different PADIT and BLISTER score thresholds was evaluated. The probability of device infection was based on the present study's derivation and standard-risk validation cohorts (n=10,237, all-comers probability of infection: 0.0081), and the estimated effect size of the AE was pooled from studies included in three meta-analyses (Mantel-Haenszel pooled OR: 0.41 (CI 0.28-0.6, $I^2 = 62\%$)[20,21,22]. Model branches were mutually exclusive, and whilst the initial probability of CIED infection was calculated from the present study cohort, to promote model generalizability all subsequent probabilities were imputed from consensus in the literature (e.g. probability of death if CIED infection managed without extraction: 0.422)[10,23,24,25,26,25,26,27,28]. Probability inputs are provided in the supplemental material. To account for a 12-month time-horizon in those patients undergoing CIED procedures without subsequent infection (disease state A), an annualised death rate of 5.9% was extrapolated from the standard-of-care arm in the WRAP-IT trial. Conservative management of device infection (disease state D) constituted an inpatient stay of 6 weeks for antibiotic treatment. A utility decrement of 0.1 was applied upon diagnosis of CIED infection for all device types[29]. A cost-per-QALY-gained was calculated at each risk score threshold according to whole-cohort QALY increment and the associated cost differences versus the

standard-of-care (i.e. pre-procedural antibiotics and an AE versus pre-procedural antibiotics only). For probabilistic sensitivity analysis, risk and transition probabilities varied according to a beta distribution, the AE efficacy varied according to a log-normal distribution, and costs varied according to a gamma distribution[30]. The model results presented are average values following 10,000 iterations at each risk score threshold.

Normally distributed data are presented as mean ± standard deviation and non-normally distributed data as median (interquartile range). Hazard ratios are provided with 95% confidence intervals.

Ethics

Following approval by the institutions' governance leads, a multi-centre collaboration was established on a secure online portal. As this was an analysis of registry data, the need for formal ethical approval was waived by each institution.

Results

Derivation Cohort

The derivation cohort included 7,383 consecutive procedures at SBH between 2015-2019. Referral pathways consisted of direct emergency admission via the London Ambulance Service, urgent or elective referral to the institution from 11 regional hospitals, or inpatients who had developed an indication for device therapy during an admission for a primary diagnosis not related to cardiac arrhythmia (for example, following aortic valve replacement). Patient characteristics are listed in table 1. 27 consultant physicians were listed as first operator in 36.2% of cases (n=2,675), and 79 trainees or fellows in the remaining 63.8% (n=4,708), performing these procedures under consultant supervision.

Within 12 months, CIED infection was diagnosed in 59 individuals (incidence: 0.8%). All 59 patients with CIED infection were admitted to SBH for complete device extraction; the median hospital stay was 18 days, and the average overall cost of treatment was £18,483 (±15,139). Complete device extraction was achieved in all cases, with no associated deaths within 30 days of the procedure.

Multivariate analysis (table 2) suggested that the components of the existing PADIT score were powerful independent predictors of infection, and four additional covariates (Lead extraction, raised C-reactive protein, re-intervention with two years, and top-quartile procedure duration) were incorporated into the proposed BLISTER score (table 3). The model C-statistic was 0.78 (0.71-0.85).

Validation cohorts

The standard-risk validation cohort included 2,854 consecutive procedures (2,509 from SBH (88%) and 345 (12%) from RPH). CIED infection within 12 months occurred in 24 patients (event rate: 0.8%). All 24 patients underwent complete CIED extraction. The average cost of treatment for CIED infection was £20,311 (±13,684). There were no associated deaths.

The high-risk validation cohort (PADIT score ≥1) included 1,935 consecutive procedures from SBH and 26 consecutive cases of CIED infection from STH, with 39 cases of infection overall (n=1,961, event rate: 2.0%). Two patients (5%) underwent conservative management of their CIED infection, and one patient (2.5%) died within 30 days of their extraction procedure. The average cost of treatment for CIED infection was £25,253 (±19,314).

For score validation, comparative time-dependent AUC analysis at 12 months demonstrated that BLISTER was superior to PADIT in the standard-risk (AUC 0.82 vs 0.71, p=0.001) and high-risk (AUC 0.77 vs 0.69, p=0.001) validation cohorts, and across all patients in

the derivation and validation cohorts combined (n=12,198, event rate: 1%, AUC 0.8 vs 0.75, p=0.002) (figure 1).

Cost-utility model results

Model outcomes are provided in table 4. For the PADIT score, assigning AEs to patients with scores ≥ 6 (13.5% of cohort) predicted a non-significant reduction in infection incidence (relative risk reduction: 26%, p=0.067) with a cost-per-QALY-gained of £23,444. For the BLISTER score, the optimum cut-off was again a score ≥ 6 (10.8% of cohort), predicting a significant reduction in infection (relative risk reduction: 30%, p=0.036) with a cost-per-QALY-gained of £18,446 (figure 2). Accordingly, when analysed as binary factors across all three cohorts, PADIT and BLISTER scores of ≥ 6 were powerful predictors of CIED infection (figure 3).

Discussion

In a large, multi-centre cohort including all subtypes of transvenous CIED implant, generator change and lead intervention, the incidence of CIED infection was significant, with considerable associated healthcare costs. Multivariate analysis further validates the constituents of the PADIT score for predicting infection, and the incorporation of four additional covariates into the novel BLISTER score – lead extraction, C-reactive protein ≥50mg/l, re-intervention within two years, and procedure duration ≥120 minutes – conferred additional prognostic utility. Cost-utility modeling suggests that both risk scores could be used to assign the TYRX™ antimicrobial envelope to high-risk patients within established willingness-to-pay thresholds. A model assigning AEs to patients with a BLISTER score of ≥ 6 delivered superior efficacy and cost-utility versus a comparable model using PADIT ≥ 6, despite the BLISTER model using 20% fewer AEs.

All four of the additional BLISTER score covariates have been associated with an increased risk of CIED infection in prior analyses[31]. By analysing lead interventions as distinct procedural subtypes, the present study found that lead extraction with lead upgrade or reimplantation confers the highest risk of infection amongst all procedures (adjusted HR versus pacemaker implant: 3.3 (1.9-6.1), p<0.0001). There were no infected devices included in this study's cohorts, hence all lead extractions were performed as part of device upgrade, or to address non-infective lead integrity or veno-occlusive complications. Whilst these data may therefore suggest that, where possible, abandoning leads may be preferable to extraction for mitigating the risk of infection within one year, there are compelling observational data demonstrating that this strategy significantly increases the risk of complications (including infection) in the long term. Although there are usually convincing indications for CIED extraction, this approach needs to be carefully considered in clinical risk-benefit decision making[32,33].

Long procedure duration (skin-to-skin time of ≥120 minutes) was associated with CIED infection independent of procedure type (adjusted HR 2.6 (1.6-4.1), p=0.001). This finding is in keeping with a meta-analysis of 60 studies by Polyzos et al. (2015), who found that procedure duration correlated with infection risk, and this relationship was also corroborated in post hoc analysis of the PADIT trial (procedure duration >1 hour: OR 1.91 (1.41-2.57), p<0.001), although this factor was not included in the final PADIT score[31]. Whilst including this variable in the BLISTER score introduces the possibility of a small number of patients crossing the risk threshold for antimicrobial envelope use during the procedure itself, the authors suggest that the logistical challenges of implanting an unanticipated AE are outweighed by the potential benefits of protection from serious CIED infection.

Raised CRP at the time of CIED implant has a known association with infection, and in the present study 510 patients (4.2%) underwent procedures with a CRP of >50mg/l measured within the previous 24 hours[34]. This biomarker was independently associated with subsequent CIED infection (adjusted HR 3.0 (1.4-6.4), p=0.005). The subgroup was comprised of a combination of post-surgical inpatients requiring urgent pacemaker insertion (in whom permanent pacing was preferred), or direct admissions via the London Ambulance Service in whom devices were implanted emergently prior to the availability of blood test results. These data suggest that, if available, CRP should be incorporated into patient risk assessment and, where possible, any source of infection should be identified and treated before a definitive CIED is implanted.

Previous procedures are well-established as a risk factor for infection; in addition, the present study demonstrated that a re-intervention performed within two years was a particularly powerful independent predictor of adverse outcomes (adjusted HR: 10.1 (5.6-17.9), p<0.0001). Evidence for the association between early re-intervention and CIED infection has been published previously, however, data vary on the definition and significance of the term 'early'. Klug et al. (2007) found a 15-fold increase in infection risk for patients undergoing re-intervention during their index admission (for example, to reposition an early lead displacement)[35]. By contrast, the PADIT investigators examined the impact of re-intervention within one month of a procedure, and found no association with infection, whereas re-intervention beyond one month predicted infection (OR 2.45 (1.76-3.43), but was not included in the final PADIT risk score. In the present study, other temporal relationships were explored, for example re-intervention within one year (adjusted HR: 6.9 (3.7-17.4, p<0.001) or within five years (adjusted HR 2.9 (0.8-10.7, p=0.09), however, a two-year cut-off was found to confer

maximum prognostic significance. As such, this parameter alone assigns seven risk points in the proposed BLISTER score, and our cost-utility analysis suggests that the AE would be warranted in all patients undergoing a re-intervention within two years of a prior procedure (n=409, 3.3%). The authors propose that this is a key factor driving the improved prognostic utility of BLISTER versus the PADIT score.

As the occurrence of haematoma cannot always be predicted prior to closure of the device pocket (and hence AE implantation), we did not include this factor in the BLISTER score. Nevertheless, the finding that haematomas conferred nearly a four-fold risk of infection emphasises the importance of good surgical technique, and measures to improve haemostasis in the CIED population are essential.

Several other economic analyses have modelled the cost-utility of the AE for preventing device infection, hospitalisation and patient mortality. In a high-risk cohort, Kay at al. (2018) estimated a number needed to treat of 36 to prevent CIED infection, which is similar to the present study findings. However, the authors also predicted a cost-per-QALY-gained of £46,548 for high-risk patients with pacemakers, with evidence of a cost-saving (i.e. dominant) effect in those with ICDs and CRT-Ds. Whilst the present study does suggest the AE to be a cost-effective treatment versus standard-of-care antibiotics in high-risk patients, it did not find the envelope to be dominant at any risk threshold. This may reflect the differences in AE effect size used between the two studies, with Kay et al. imputing a relative risk of 0.163 versus standard-of-care based on observational studies published prior to the WRAP-IT trial. Boriani et al. (2020) analysed the UK patients enrolled in the WRAP-IT study, predicting a cost-per-QALY-gained for the AE within the NICE cost-utility threshold (i.e. <£30,000) for all devices in patients with PADIT scores of ≥ 6, and again found that the envelope became dominant in certain subgroups

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(e.g. immunosuppressed patients with high-energy devices). Whilst the present analysis concurs with a PADIT score threshold of ≥ 6 to support cost-effective AE allocation, the more favourable results demonstrated in the Boriani analysis likely reflect the assumption that the benefits of the AE are sustained over a lifetime horizon.

Limitations

As a retrospective analysis, this study cannot demonstrate causation, and is subject to selection bias. Likewise, although consecutive patients were selected from three tertiary centres, the majority were from a single centre (SBH). Whilst this may limit generalizability to other populations, the SBH data include procedures from over 100 operators and an ethnically diverse catchment population of more than four million people, hence we suggest the cohort is sufficiently heterogeneous to confer external validity. Data completeness exceeded 90% for all parameters other than CRP (<50%); in this case, regression imputation was required, which generated a distribution of values with a strong positive skew, similar to that seen in patients with available CRP measurements. An alternative multivariate analysis performed imputing the median CRP yielded similar beta coefficients. External validation of the BLISTER score demonstrated superior discriminative performance versus PADIT, however, the PADIT score was derived from a randomised cohort with inherently different levels of risk, hence a divergence in the utility of the two scores may be an expected finding in a real-world population. Despite this, the fact that this divergence persisted in both standard and high-risk validation cohorts supports the generalizability of the novel score. A baseline infection rate of 0.8% was used to inform cost-utility analysis; this was calculated from an all-comers, real-world population, but nevertheless is lower than that reported in comparable registries. It is plausible that the AE is less effective in lower-risk populations and hence the present study's cost-utility

results may be overestimated. The pooled odds ratio for the antimicrobial envelope included studies with different follow-up durations, however, this calculation was heavily weighted towards the WRAP-IT trial data, which examined the same temporal endpoint as the BLISTER score (12 months). Although costs were summated from real-world expenses, the cost of CIED components varies broadly between manufacturers and implanting centres, hence the present study's cost-utility projections may not necessarily apply to other patient groups. Furthermore, the present study incorporates all costs associated with inpatient treatment of CIED infection, but does not include supplementary expenses incurred following hospital discharge (such as rehabilitation). The time-horizon used in this study's analysis was 12 months; it is possible that the benefits of an AE may extend to additional QALY gain beyond this time period, which may have further improved cost-utility estimates. Finally, additional co-morbidities that are known to influence CIED infection, such as chronic obstructive pulmonary disease, were not included in our analysed demographics[31].

Conclusions

This multi-centre analysis validates the PADIT score in a large, UK population, and presents and validates the novel BLISTER score as a useful tool for risk stratification in CIED patients. Economic modelling – informed by real-world costs and infection risk – suggests that risk score thresholds may facilitate individualized, cost-effective TYRX™ envelope (AE) allocation across large populations. A BLISTER score cut-off of ≥ 6 was a particularly useful prognostic marker, and incorporates key high-risk subgroups in their entirety, including patients undergoing CRT generator change, lead extraction, or re-intervention within two years. At this level of patient risk, the number needed to treat with an AE to prevent a CIED infection was estimated at 31.

Our institutions have adopted the BLISTER score into routine clinical practice; prospective validation is ongoing. A free online calculator is available to facilitate point-of-care decision-making (https://qxmd.com/calculate/calculator_876/the-blister-score-for-cied-infection)[36].

Disclosures: None

Supplemental Materials:
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Table 1: Baseline demographics

	Derivation cohort (n=7,383)			Standard-risk validation cohort (n=2,855)			High-risk validation cohort (n=1,935)		
	No infection (n=7,324)	Infection (n=59)	p value	No infection (n=2,831)	Infection (n=24)	p value	No infection (n=1896)	Infection (n=39)	p value
Demographics									
Age (years)	**76 (21)**	**71 (26)**	**0.008**	**74 (23)**	**67.5 (15.5)**	**0.038**	68 (25)	63 (22)	0.13
Male	62.7% (n=4,594)	55.9% (n=33)	0.28	61.8% (n=1,750)	66.7% (n=16)	0.67	**62.9% (n=1,192)**	**79.5% (n=31)**	**0.033**
Caucasian	61.3% (n=4,490)	61% (n=36)	0.96	59.8% (n=1,692)	62.5% (n=15)	0.77	64% (n=1,213)	58.9% (n=23)	0.52
Co-morbidities									
Ischaemic heart disease	19.9% (n=1,455)	20.3% (n=12)	0.93	20.7% (n=586)	16.7% (n=4)	0.76	**20.8% (n=394)**	**48.7% (n=19)**	**<0.0001**
Dilated cardiomyopathy	8.6% (n=630)	11.9% (n=7)	0.37	10.5% (n=297)	4.2% (n=1)	0.35	10.9% (n=207)	12.8% (n=5)	0.7
Hypertrophic cardiomyopathy	5.8% (n=426)	5.1% (n=3)	0.81	5.5% (n=156)	4.2% (n=1)	0.79	7.4% (n=140)	2.6% (n=1)	0.25
Congenital heart disease	1.7% (n=125)	1.7% (n=1)	0.94	3.3% (n=93%)	4.2% (n=1)	0.87	4.6% (n=88)	5.1% (n=2)	0.89
Atrial fibrillation	25.3% (n=1,853)	20.3% (n=12)	0.38	19.8% (n=561)	25% (n=6)	0.63	16.4% (n=310)	25.6% (n=10)	0.12
NYHA class	1 (1)	1 (1)	0.16	2 (1)	2 (2)	0.23	2 (1)	2 (2)	**0.038**
Severe LV systolic dysfunction	23.6% (n=1,727)	15.3% (n=9)	0.13	20.4% (n=577)	25% (n=6)	0.58	**21.8% (n=413)**	**46.1% (n=18)**	**0.0003**
Renal impairment (eGFR < 30ml/min/1.73m^2)	**4.6% (n=343)**	**11.9% (n=7)**	**0.024**	**3% (n=85)**	**12.5% (n=3)**	**0.007**	**9% (n=171)**	**20.5% (n=8)**	**0.014**
CRP > 50mg/l	5.6% (n=407)	13.6% (n=8)	**0.018**	**1.8% (n=50)**	**12.5% (n=3)**	**0.001**	**2.6% (n=39)**	**7.7% (n=3)**	**0.017**
Diabetes	19.9% (n=1,456)	25.4% (n=15)	0.29	17.7% (n=501)	16.7% (n=4)	0.51	21% (n=398)	12.8% (n=5)	0.21
HIV infection	0.12% (n=9)	0	0.79	**0.14% (n=4)**	**4.2% (n=1)**	**<0.0001**	0.2% (n=4)	0% (n=0)	0.77
Procedural variables									
Re-intervention within 2 years	**3.2% (n=232)**	**28.9% (n=17)**	**<0.0001**	**1.9% (n=54)**	**16.7% (n=4)**	**<0.0001**	**5% (n=95)**	**17.9% (n=7)**	**<0.0001**
Trainee first operator	63.8% (n=4,675)	55.9% (n=33)	0.28	65% (n=1840)	83.3% (n=20)	0.06	**52.8% (n=1,001)**	**33.3% (n=13)**	**0.016**
Fluoroscopy time (minutes)	6.8 (±12.3)	5.5 (±11.7)	0.41	3.1 (7)	11.1 (25)	0.05	**7.6 (14)**	**13.6 (14)**	**<0.0001**
Procedure time (minutes)	**60 (55)**	**75 (65)**	**0.006**	**74.5 (64)**	**150 (115)**	**0.001**	72 (64)	114 (54)	**<0.0001**
Subpectoral generator	2.4% (n=175)	0	0.23	2.2% (n=62)	4.2% (n=1)	0.51	**2.5% (n=47)**	**15.4% (n=6)**	**<0.0001**
Haematoma	**0.6% (n=44)**	**3.4% (n=2)**	**0.007**	**0.8% (n=24)**	**12.5% (n=3)**	**<0.0001**	**1.1% (n=21)**	**12.8% (n=5)**	**<0.0001**

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Procedure type									
New implant	**65.9%** **(n=4,824)**	**47.5%** **(n=28)**	**0.003**	**68.9%** **(n=1,951)**	**33%** **(n=8)**	**0.0002**	63.7% (n=1209)	51.3% (n=20)	0.11
Generator change	18.6% (n=1,361)	11.9% (n=7)	0.19	17.9% (n=507)	33% (n=8)	0.05	20.7% (n=393)	12.8% (n=5)	0.22
Lead intervention	**15.6%** **(n=1,139)**	**40.7%** **(n=24)**	**<0.0001**	**13.2%** **(n=373)**	**33%** **(n=8)**	**0.004**	**15.5%** **(n=294)**	**35.9%** **(n=14)**	**0.0006**
New lead inserted or existing lead revised	**9.7%** **(n=708)**	**22.0%** **(n=13)**	**0.001**	10.9% (n=309)	12.5% (n=3)	0.8	**14.1%** **(n=268)**	**23.1%** **(n=9)**	**0.11**
Lead extracted	**5.9%** **(n=431)**	**18.6%** **(n=11)**	**<0.0001**	**2.3%** **(n=64)**	**20.8%** **(n=5)**	**<0.0001**	**1.4%** **(n=26)**	**12.8%** **(n=5)**	**<0.0001**
Single chamber device	18.4% (n=1,349)	11.9% (n=7)	0.19	20.9% (n=592)	20.8% (n=5)	0.99	16% (n=303)	10.3% (n=4)	0.33
Device implanted or intervened on: Pacemaker (PPM)	**58.7%** **(n=4,302)**	**44.1%** **(n=26)**	**0.023**	**62.6%** **(n=1,772)**	**58.3%** **(n=14)**	**0.01**	**48.3%** **(n=917)**	**25.6%** **(n=10)**	**0.005**
Device implanted or intervened on: ICD	19.5% (n=1,426)	20.3% (n=12)	0.87	16.4% (463)	33.3% (n=8)	0.42	23.5% (n=445)	30.8% (n=12)	0.28
Device implanted or intervened on: CRT	**21.8%** **(n=1,596)**	**35.6%** **(n=21)**	**0.011**	**21.2%** **(n=596)**	**8.3%** **(n=2)**	**0.009**	**28.2%** **(n=534)**	**43.6%** **(n=17)**	**0.035**
Medications									
Insulin	9.8% (n=720)	5.1% (n=3)	0.69	6.3% (n=178)	8.3% (n=2)	0.68	8.5% (n=161)	7.7% (n=3)	0.86
Prednisolone	**3.1%** **(n=228)**	**13.6%** **(n=8)**	**<0.0001**	**2%** **(n=57)**	**8.3%** **(n=2)**	**0.03**	2.2% (n=41)	5.1% (n=2)	0.21
Methotrexate	0.5% (n=38)	0	0.58	0.1% (n=3)	0	0.87	**0**	**2.6%** **(n=1)**	**<0.0001**
Hydroxychloroquine	0.30% (n=22)	0	0.67	**0.2%** **(n=5)**	**4.2%** **(n=1)**	**<0.0001**	0.2% (n=3)	0	0.8
Mycophenolate mofetil	0.26% (n=19)	0	0.69	0.2% (n=6)	0	0.81	0.1% (n=2)	2.6% (n=1)	0.84
Tacrolimus	0	0		**1.4%** **(n=40)**	**20.8%** **(n=5)**	**<0.0001**	0.1% (n=1)	0	0.89
Immunosuppressed (by medication or co-morbidity)	**4.3%** **(n=316)**	**13.6%** **(n=8)**	**0.001**	**4.9%** **(n=140)**	**33.3%** **(n=8)**	**<0.0001**	**3.3%** **(n=62)**	**17.9%** **(n=7)**	**<0.0001**
Oral anticoagulant	25.3% (n=1,853)	20.3% (n=12)	0.38	24% (n=680)	16.6% (n=4)	0.4	20.2% (n=384)	23% (n=9)	0.66
Aspirin	18.8% (n=1,378)	27.1% (n=16)	0.1	13% (n=369)	16.7% (n=4)	0.59	18.3% (n=345)	20.5% (n=8)	0.71
Clopidogrel	9.4% (n=688)	8.5% (n=5)	0.81	7% (n=198)	8.3% (n=2)	0.79	10% (n=190)	7.7% (n=3)	0.63
Ticagrelor	1.4% (n=101)	0	0.36	0.7% (n=20)	0	0.68	2.1% (n=40)	2.6% (n=1)	0.84
Dual antiplatelet therapy	6.9% (n=507)	5.1% (n=3)	0.58	4.5% (n=127)	8.3% (n=2)	0.36	7.2% (n=137)	7.7% (n=3)	0.91

Table 2: Univariate and final multivariate analysis predicting CIED infection at 12 months

Covariate	Hazard ratio from univariate analysis (95% CI)	p value	Adjusted hazard ratio from multivariate analysis (95% CI)	p value
Age <60 years (ref: >69 years)	2.6 (1.6-4.5)	0.0003	2.4 (1.4-4.2)	0.002
Age 60-69 years (ref: >69 years)	1.6 (1.1-3.9)	0.017	1.5 (1.2-3.5)	0.04
1 previous procedure (ref: first procedure)	4.5 (3.2-6.9)	0.0001	3.5 (2.1-5.9)	<0.0001
2+ previous procedures (ref: first procedure)	6.1 (2.6-12.3)	<0.0001	6.2 (3-13)	<0.0001
Single chamber device (PPM/ICD) (ref: dual chamber device)	0.61 (0.28-1.3)	0.31		
New lead inserted or existing lead revised (ref: PPM)	2.3 (1.3-4.3)	0.008	2.1 (1.3-3.8)	0.004
Lead extracted (ref: PPM)	3.7 (1.9-7.1)	<0.0001	3.3 (1.9-6.1)	0.0001
Lead intervention (ref: PPM)	3.1 (1.8-6.1)	0.0001	2.6 (1.5-5.9)	0.0018
ICD (ref: PPM)	1.5 (0.95-2)	0.07	1.3 (0.9-2.1)	0.09
CRT (ref: PPM)	2 (1.2-3.4)	0.012	3.9 (2.1-7.3)	0.0001
Top quartile procedure time ($\geq$120 minutes)	2.5 (1.4-4.4)	0.005	2.6 (1.6-4.1)	0.001
eGFR < 30ml/min/1.73m^2	2.5 (1.1-5.8)	0.03	2.6 (1.1-6.5)	0.034
CRP > 50mg/l	2.5 (1.2-5.3)	0.016	3.0 (1.4-6.4)	0.005
Diabetes Mellitus	1.7 (0.95-3.1)	0.08	1.94 (0.9-3.3)	0.17
Immunosuppressed (by medication or co-morbidity)	2.2 (1.3-3.7)	0.005	1.83 (1-3.2)	0.035
Re-intervention within 2 years	11 (5.5-23)	<0.0001	10.1 (5.6-17.9)	<0.0001
Risk scores (multivariate analysis repeated with individual components of each score removed as covariates)				
PADIT score (0-13; per point increase)			1.36 (1.27-1.47)	<0.0001
BLISTER score (0-25; per point increase)			1.29 (1.24-1.35)	<0.0001

Table 3: Final proposed BLISTER score

BLISTER component	Criteria	Points
Blood results	eGFR < 30ml/min/1.73m² at time of procedure CRP ≥ 50mg/l within 24 hours of procedure	2 1
Long procedure time	Pocket open for ≥120 minutes during procedure	2
Immunosuppressed	Current steroid or immunosuppressant medication use, or immunocompromised by co-morbidity (e.g. HIV infection)	2
Sixty years old (or younger)	<60 years old 60-69 years old	2 1
Type of procedure	ICD implant or generator change CRT implant or generator change New lead inserted or existing lead revised without extraction Lead extracted	1 4 4 6
Early re-intervention	Intervention on the same pocket within 2 years of a previous procedure	7
Repeat procedure	1 previous procedure 2 or more previous procedures	2 4

Table 4: Results of cost-utility modelling

Threshold for TYRX™ envelope allocation	Proportion of patients receiving TYRX™ envelope (n=10,237)	Number needed to treat	Cost-per-QALY-gained (£)	Projected reduction in CIED infection incidence (whole cohort)	p value (infection reduction for whole cohort)
All patients	100% (n=10,237)	238	79,664	**51%**	**0.0002**
PADIT ≥ 3	40.4% (n=4133)	109	57,654	**31%**	**0.029**
PADIT ≥ 4	32.8% (n=3360)	96	40,022	**30%**	**0.036**
PADIT ≥ 5	16% (n=1643)	51	33,663	**29%**	**0.045**
PADIT ≥ 6	13.5% (n=1381)	46	23,444	26%	0.067
PADIT ≥ 7	7.2% (n=739)	44	20,123	14%	0.33
BLISTER ≥ 3	39.5% (n=4041)	103	49,876	**34%**	**0.018**
BLISTER ≥ 4	29.7% (n=3041)	79	37,112	**33%**	**0.023**
BLISTER ≥ 5	15.1% (n=1550)	45	29,766	**32%**	**0.023**
BLISTER ≥ 6	10.8% (n=1100)	31	18,446	**30%**	**0.036**
BLISTER ≥ 7	5.3% (n=547)	21	12,477	15%	0.38

Figure Legends:

Figure 1: Time-dependent receiver operating characteristic (ROC) curves for the PADIT and BLISTER scores in diagnosing CIED infection at 12 months (Panel A – Standard-risk validation cohort; Panel B: High-risk validation cohort; Panel C: All patients from both validation cohorts and the derivation cohort).
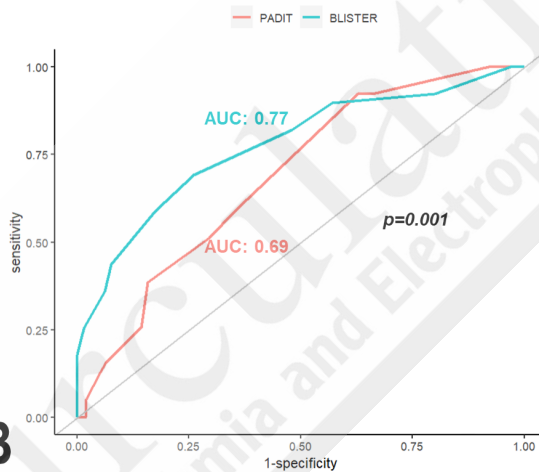
Figure 2: Trade-off plot demonstrating Cost-per-QALY-gained versus relative reduction in CIED infections (%) for the whole cohort, with TYRX^{TM} antimicrobial envelopes allocated according to different BLISTER and PADIT score thresholds.

Figure 3: Cumulative event plots for CIED infection according to high or low PADIT (panel A) and BLISTER scores (panel B).

Standard-risk validation cohort
(n=2,854, 24 events = 0.8% event rate)

— PADIT — BLISTER

AUC: 0.82

AUC: 0.71

p=0.001
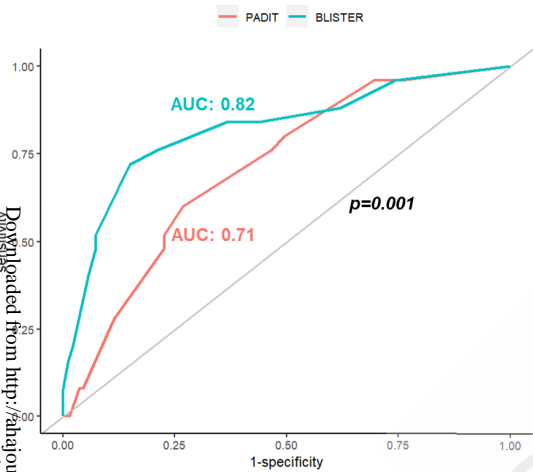
High-risk validation cohort
(n=1,961, 39 events = 2.0% event rate)

— PADIT — BLISTER

AUC: 0.77

AUC: 0.69

p=0.001

Whole cohort
(n=12,198, 123 events = 1.0% event rate)

— PADIT — BLISTER

AUC: 0.8

AUC: 0.75

p=0.002
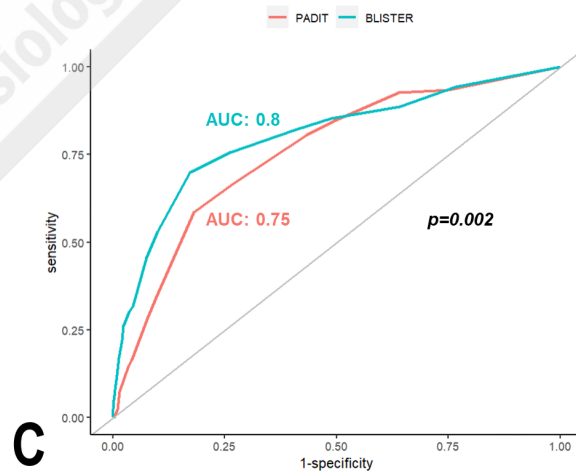
A   B   C

Cost-utility modelling: predicted impact of TYRX™ antimicrobial envelope allocation according to risk score threshold