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Risk Factors for CIED Infection After Secondary Procedures

Insights From the WRAP-IT Trial

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ABSTRACT

OBJECTIVES This study aimed to identify risk factors for infection after secondary cardiac implantable electronic device (CIED) procedures.

BACKGROUND Risk factors for CIED infection are not well defined and techniques to minimize infection lack supportive evidence. WRAP-IT (World-wide Randomized Antibiotic Envelope Infection Prevention trial), a large study that assessed the safety and efficacy of an antibacterial envelope for CIED infection reduction, offers insight into procedural details and infection prevention strategies.

METHODS This analysis included 2,803 control patients from the WRAP-IT trial who received standard preoperative antibiotics but not the envelope (44 patients with major infections through all follow-up). A multivariate least absolute shrinkage and selection operator machine learning model, controlling for patient characteristics and procedural variables, was used for risk factor selection and identification. Risk factors consistently retaining predictive value in the model (appeared >10 times) across 100 iterations of imputed data were deemed significant.

RESULTS Of the 81 variables screened, 17 were identified as risk factors with 6 being patient/device-related (nonmodifiable) and 11 begin procedure-related (potentially modifiable). Patient/device-related factors included higher number of previous CIED procedures, history of atrial arrhythmia, geography (outside North America and Europe), device type, and lower body mass index. Procedural factors associated with increased risk included longer procedure time, implant location (non–left pectoral subcutaneous), perioperative glycopeptide antibiotic versus nonglycopeptide, anticoagulant, and/or antiplatelet use, and capsulectomy. Factors associated with decreased risk of infection included chlorhexidine skin preparation and antibiotic pocket wash.

CONCLUSIONS In WRAP-IT patients, we observed that several procedural risk factors correlated with infection risk. These results can help guide infection prevention strategies to minimize infections associated with secondary CIED procedures. (J Am Coll Cardiol EP 2022;8:101-111) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CIED = cardiac implantable electronic device

CRF = case report forms

CRT-P/D = cardiac resynchronization therapy-pacemaker/defibrillator

DOAC = direct oral anticoagulants

ICD = implantable cardioverter-defibrillator

LASSO = least absolute shrinkage and selection operator

ML = machine learning

Cardiac implantable electronic device (CIED) infection is a major complication that affects 1% to 4% of all implantation procedures and leads to significant morbidity, mortality, and financial impact (1–5). Optimal management of major CIED infection often requires the removal or extraction of all hardware and disrupting CIED therapy, in addition to prolonged antibiotic treatment (6,7). A variety of risk factors for CIED infection and prophylactic measures to minimize incidence have been identified in the literature (1). However, many of the patient-related risk factors represent comorbidities that are nonmodifiable, whereas other modifiable risk factors that are related to the device or the procedure remain to be explored, or lack sufficient supportive evidence (1,8–10). Moreover, many studies investigating risk factors for CIED infection represent single-center reports or are retrospective in nature, rather than prospective, with variable definitions for CIED infection and follow-up durations (1). This has led to inconsistency in the findings reported and rendered the implementation of prophylactic measures and best practices a challenge.

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Recently, the development of the Prevention of Arrhythmia Device Infection Trial (PADIT) risk score identified 5 independent predictors for CIED infection including younger age, procedure type (implantable cardioverter-defibrillator [ICD], cardiac resynchronization therapy [CRT], or revision/upgrade procedure), depressed renal function, immunocompromised state, and the number of prior CIED procedures (11). However, given the nature of the trial design, detailed information on the procedural characteristics was not captured and all the predictive factors identified were nonmodifiable factors related to the patient or device rather than procedural techniques or practices. Therefore, although the PADIT score may be useful in identifying patients who require particular care and follow-up, there is still an opportunity to identify changes in practice patterns that can prevent infection, especially among patients presenting for secondary CIED procedures.

Notably, the WRAP-IT (World-wide Randomized Antibiotic Envelope Infection Prevention trial) trial presents a unique opportunity to study risk factors for infection in a large, detailed, and prospectively collected data set. WRAP-IT enrolled close to 7,000 patients undergoing secondary CIED procedures (replacement/revision/upgrade) or primary CRT-defibrillator (CRT-D) implants that were randomized to receive an absorbable antibiotic envelope or no envelope (conventional treatment). The procedures were performed by more than 700 implanters in 25 countries, and although the infection rate in patients who received conventional therapy (1.2%) was similar to that reported in PADIT and the expected range for CIED infection rates, the antibiotic envelope was shown to effectively reduce the rate of major CIED infection over 12 months of follow-up (12–15). Other than the required guideline-mandated perioperative prophylactic antibiotic therapy for all patients, WRAP-IT allowed operators to implement their local standard prophylactic measures. The variations in procedural approaches and infection prophylactic strategies provide a breadth of data on practice patterns not routinely collected in studies of this nature. The main objective of this analysis was to identify procedural and especially modifiable risk factors for CIED infection that could provide clinical insights about best prevention practices, which could ultimately lead to better patient outcomes.

METHODS

THE WRAP-IT TRIAL. WRAP-IT was a multicenter, randomized, single-blinded, interventional clinical trial in patients undergoing a CIED pocket revision, generator replacement or system upgrade, or an initial implantation of a CRT-D (NCT02277990). A steering committee designed and oversaw the conduct of the trial and data analyses in collaboration with the sponsor, Medtronic. The trial protocol was approved by the ethics committee at each participating institution and associated national and local regulatory agencies. All patients provided written informed consent. Further details on the trial design, prespecified endpoints, and primary and secondary outcomes have been reported previously (15–17). Patient inclusion/exclusion criteria are also detailed previously; exclusion criteria specific to WRAP-IT were treatment with chronic oral immunosuppressive agents or ≥20 mg daily of prednisone or its equivalent, hemodialysis or peritoneal dialysis, and requirement of long-term vascular access for any reason (15,16).

CIED infection was defined as superficial cellulitis in the region of the CIED pocket with wound dehiscence, erosion, or purulent drainage; deep incisional (pocket) surgical-site infection that met the Centers for Disease Control and Prevention criteria, independent of time from surgery; persistent bacteremia; or endocarditis (18). Major CIED infections through all follow-up (36 months), the endpoint used for this

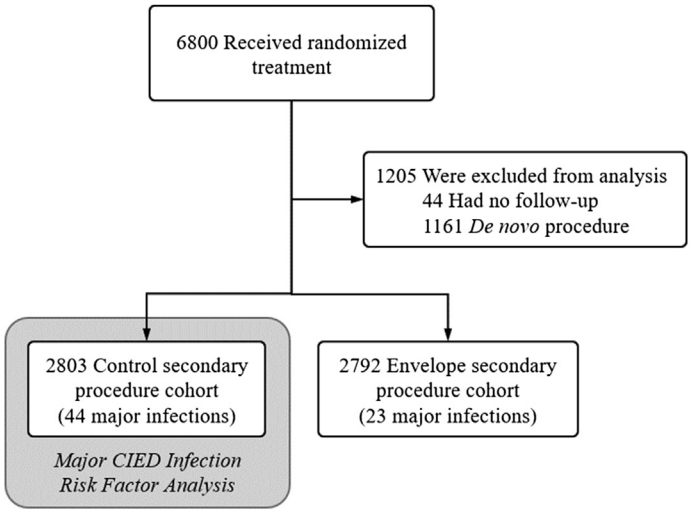
analysis, were defined as infections that resulted in CIED system removal, an invasive CIED procedure (eg, pocket revision without removal), treatment with long-term suppressive antibiotic therapy (if the patient was not a candidate for system removal) with infection recurrence after discontinuation of antibiotic therapy, or death. CIED infections that did not meet one or more of the criteria for major infection were classified as minor CIED infections, which were excluded from this analysis (15,16).

PATIENT COHORTS. Total patient cohorts. Enrollment, randomization, and follow-up of the trial patients have been reported previously (15–17). In total, 6,903 patients underwent CIED generator replacement or revision, upgrade, or initial CRT-D implant. Of these patients, 6,800 received their intended randomized treatment: 3,371 received an antibacterial envelope (TYRX Absorbable Antibacterial Envelope, Medtronic Inc) and 3,429 did not receive the envelope (control). Since de novo implants in general confer a lower risk of infection and have different procedural factors than secondary CIED procedures, we only targeted patients undergoing secondary CIED procedures. Patients undergoing an initial CRT-D implant in addition to patients with no recorded follow-up were excluded leaving 5,595 patients: 2,792 received the envelope and 2,803 did not receive the envelope.

Risk analysis: control cohort (secondary procedure). Because the goal of the current analysis was to identify procedural characteristics associated with an increase or decrease in infection risk within the WRAP-IT population, patients randomized to receive the envelope were excluded from the analysis cohort to avoid any potential interaction effects, which resulted in a total of 2,803 control group patients in our risk analysis cohort that underwent a secondary CIED procedure. There were 44 major infections among this cohort (**Figure 1**).

MACHINE LEARNING. Analysis strategy. Because of a low number of infections relative to the number of patients in the trial and the number of variables of interest in this large complex data set, we adopted a multivariate machine learning (ML) model that offers a robust approach, relative to conventional statistics, with least absolute shrinkage and selection operator (LASSO) regression to identify patient and procedural variables associated with risk of CIED infection. LASSO is a regression analysis method that simultaneously identifies important variables and estimates hazard ratios (HRs) through penalization to enhance analytical capability and maintain interpretability of the statistical model it produces (19–21). A summary

FIGURE 1 Patient Flow Diagram



CIED = cardiac implantable electronic device.

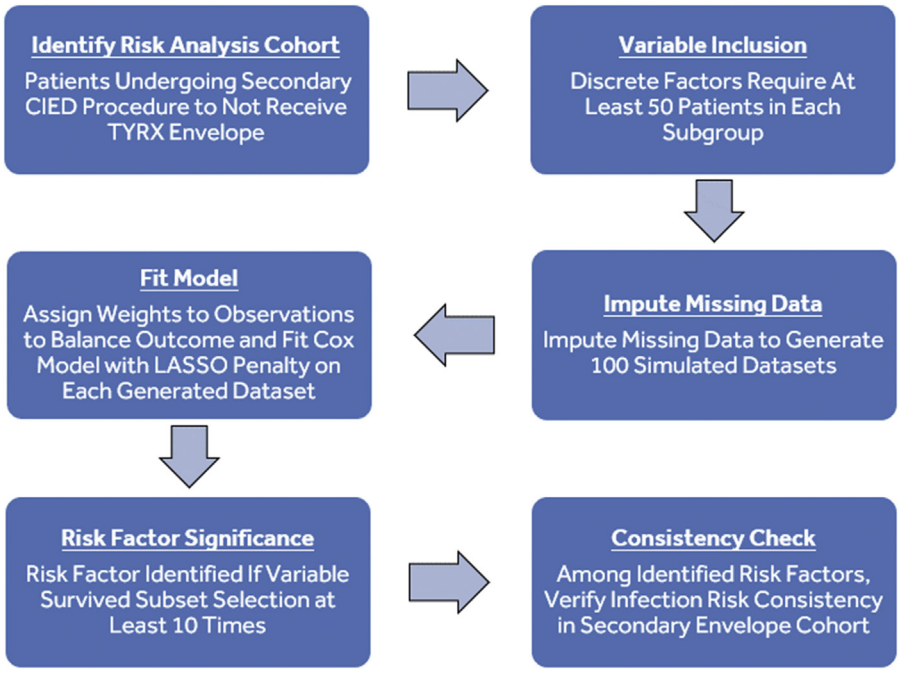
of our ML approach is provided in **Figure 2**, and an additional description of the methodology is provided in the Supplemental Appendix.

Variable inclusion. As the first step in our ML approach, we identified variables recorded on the case report forms (CRFs) either as part of the baseline visit or the day of the procedure that may have influenced infection risk (Supplemental Table 1). For variables to be included in the ML model, each option available on the CRF needed to be reported in at least 50 patients. If more than 2 options were available on the CRF and 1 option was reported in <50 patients but could be combined with another option on the CRF, subcategories were formed to allow for relevant comparisons. Relevant variables were then categorized as either patient/device-related variables that for the most part are nonmodifiable, or procedure-related variables that could be modifiable.

Risk factor significance. In our methodology, risk factor significance was determined based on a predefined level of importance due to the absence of *P* values with this type of ML approach. In total, 100 simulated datasets were generated accounting for missing data, and a variable was identified as a risk factor if it was selected by the LASSO model in at least 10 of the 100 simulated LASSO models. This measure of importance is analogous to the traditionally accepted $P < 0.05$ significance cutoff.

LASSO modeling. A weighted Cox regression model with a LASSO penalty was fit on each imputed dataset. Weights were assigned to balance major infection

FIGURE 2 Machine Learning Methodology



Flow chart describing the machine learning process used to identify risk factors and perform a consistency check. LASSO = least absolute shrinkage and selection operator; other abbreviation as in Figure 1.

versus no major infection as opposed to equal weights per patient. LASSO regression was chosen because of its ability to simultaneously estimate HRs, as well as to reduce HRs to 1 if a factor did not have a strong association with infection. A factor survived the LASSO penalty if the HR was not equal to 1. HRs were the consolidated mean of each time a factor survived the LASSO penalty.

Risk factor consistency check: envelope cohort (secondary procedure). The main risk analysis of the study targeted WRAP-IT control group patients (no envelope) who underwent secondary procedures. However, an additional consistency check was conducted using patients who received an envelope and underwent secondary procedures as a cohort (n = 2,792) to provide supplementary credence to the findings in the risk analysis cohort. As such, each factor identified in the risk analysis cohort was evaluated in the envelope cohort. Factors were considered consistent based on the directionality of the association with infection risk (ie, increased risk vs decreased risk).

STATISTICAL ANALYSIS. Summary statistics (mean ± SD, median [interquartile range], and frequency distribution) were generated for patient baseline characteristics and procedural details to characterize the study population. A chi square test was used to compare categorical variables and continuous variables were compared using the Student *t* test, as appropriate. All tests were 2-sided and a *P* value of <0.05 was considered statistically significant. Patients with no major CIED infections during study follow-up were censored at the last follow-up visit, which includes the date of exit or death.

All analyses were performed using the R statistical package (R Project for Statistical Computing) or SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS AND PROCEDURES. Baseline characteristics of all WRAP-IT patients who underwent secondary CIED procedures are presented in Table 1. The average age was 70.6 years, and 71.2% were male. As shown in Table 1, significant differences between the control group (nonenvelope) that represent the targeted cohort for the risk analysis and the group that received the envelope (which was used for consistency check) included the use of

immunosuppressants, antiplatelet use, postoperative antibiotic use, and capsulectomy.

ML. Risk factors. Of the 81 variables noted in the initial screening, 17 were identified as risk factors through LASSO selection in at least 10 of the 100 simulations (Table 2). Of these, 6 were patient/device-related factors (nonmodifiable) and 11 were procedure-related (potentially modifiable) (Central Illustration).

Patient/device-related risk factors (nonmodifiable). Patient/device-related risk factors comprised 6 of the 17 risk factors (Table 2). The 3 factors associated with increased risk of infection were a higher number of previous CIED procedures, history of atrial arrhythmia, and geography (outside of North America and Europe). Device type (CRT-D] vs pacemaker/ICD and CRT-pacemaker [CRT-P] vs pacemaker/ICD) was also identified as a risk factor with varying degrees of risk by device accounting for 2 risk factors in the model. Lower body mass index (BMI) was associated with increased infection risk.

Procedure-related risk factors (potentially modifiable). The remaining 11 risk factors were procedure-related (Table 2). Of these 11 procedural risk factors, 8 were associated with increased infection risk: increased procedure time, device implant location (non-left pectoral subcutaneous vs left pectoral subcutaneous), periprocedure glycopeptide use (vancomycin, vancocin, teicoplanin, etc, vs an alternative periprocedure antibiotic [primarily cephalosporin]), complete capsulectomy (vs partial or none), and 4 variables related to antithrombotic use. Specifically, antithrombotic use includes both anticoagulant use and antiplatelet use as separate risk factors with additional risk when taken concurrently. Anticoagulant use risk was further stratified by type of anticoagulant, with apixaban showing decreased risk both compared to vitamin K antagonists and the general population whereas other direct oral anticoagulants (DOACs) showed increased risk compared to vitamin K antagonists. Finally, there were 2 other procedural factors associated with decreased infection risk: chlorhexidine skin preparation (vs an alternative skin preparation [primarily povidone-iodine solution]), and an antibiotic pocket wash (vs a nonantibiotic pocket wash [iodine-based antiseptic, hemostatic agent, saline solution], or no pocket wash). Additional detailed characteristics of procedure time can be found in Supplemental Table 2 and Supplemental Figure 1.

Risk factor consistency check. Of the 17 identified risk factors, 9 (3 patient/device-related and 6 procedure-related) were directionally consistent between both the secondary control cohort and secondary envelope cohort. The 3 patient/device-related risk factors that maintained directional consistency were device type (CRT-P and CRT-D) and BMI. The 6 procedure-related risk factors that maintained directional consistency were procedure time, concurrent anticoagulant and antiplatelet use, use of apixaban, complete capsulectomy, periprocedure glycopeptide use, and chlorhexidine skin preparation (Table 3).

DISCUSSION

The risk for CIED infection after a device procedure in both PADIT and WRAP-IT was lower than expected and interestingly almost identical (between 1.2% and 1.3%) even among patients traditionally considered to be at higher risk (16,22). This lower rate of CIED infection in 2 of the largest trials in the field to date is a testament to the global commitment to minimize infection risk by adhering to proper surgical techniques and the use of perioperative antibiotic therapy per guidelines in the modern era. The fact that the antibiotic envelope used in WRAP-IT led to an even significantly lower infection rate is evidence of our ability to lower this infection rate even further in certain patient populations (7,16).

However, this low infection rate explains the variation in risk factors for CIED infection identified between different studies and highlights the challenges in demonstrating the efficacy of any additional infection prevention measures to minimize this risk further. A study designed to show a significant impact of any preventive measure would require the enrollment of thousands of patients who will need to be followed for an extended period.

In addition to its large size, prospective, and global nature, WRAP-IT collected detailed variables on the patients, devices, and procedural characteristics, which were not routinely collected in other trials of this size, and the data reflect the general practice globally. With the lower than expected event rate in the data set, ML offered a novel, more robust approach to identify risk factors for CIED infection. The analysis targeted WRAP-IT patients who underwent secondary CIED procedures (device replacements, revision, or upgrades) and who did not receive the antibiotic envelope to avoid any interaction effects. This is the group of patients who are usually at increased risk of infection compared to *de novo* primary device implantation procedures. Among this group, several patient/device-related risk factors for CIED infection were identified that are not

TABLE 1 Baseline Characteristics

	Total Patients Undergoing Secondary CIED Procedures (N = 5,595)	Control (n = 2,803)	Envelope (n = 2,792)	*P* value
Age, y	70.64 ± 12.65	70.61 ± 12.67	70.66 ± 12.62	0.89
Male	71.2 (3,984)	71.1 (1,992)	71.3 (1,992)	0.82
BMI, kg/m^2	29.11 ± 6.18	29.13 ± 6.28	29.09 ± 6.08	0.79
Medical history				
Atrial arrhythmia	38.8 (2,170)	39.1 (1,096)	38.5 (1,074)	0.63
Cardiomyopathy	64.2 (3,593)	63.9 (1,790)	64.6 (1,803)	0.58
Coronary artery disease	41.9 (2,347)	42.1 (1,180)	41.8 (1,167)	0.82
Myocardial infarction	27.6 (1,544)	26.5 (744)	28.7 (800)	0.08
COPD	12.2 (683)	11.6 (326)	12.8 (357)	0.19
Diabetes	30.4 (1,700)	30.0 (841)	30.8 (859)	0.54
Renal dysfunction	16.2 (905)	15.8 (442)	16.6 (463)	0.41
Cardiovascular surgical history				
CABG	21.2 (1,186)	21.4 (599)	21.0 (587)	0.75
Valve surgery	9.0 (501)	8.7 (245)	9.2 (256)	0.57
Baseline medications				
Antiplatelets	56.3 (3,152)	55.5 (1,557)	57.1 (1,595)	0.23
Anticoagulants	41.2 (2,307)	41.7 (1,168)	40.8 (1,139)	0.51
Antibiotics	0.9 (48)	0.9 (24)	0.9 (24)	0.99
Immunosuppressive	2.0 (112)	2.6 (74)	1.4 (38)	0.001
Insulin	9.8 (548)	9.9 (277)	9.7 (271)	0.82
Oral hypoglycemic agents	17.0 (950)	16.7 (467)	17.3 (483)	0.52
Number of prior CIEDs	1.46 ± 0.82	1.48 ± 0.87	1.45 ± 0.78	0.16
Number of prior CIED procedures	1.61 ± 0.99	1.63 ± 1.03	1.58 ± 0.93	0.12
Years since first CIED	9.07 ± 4.95	9.11 ± 5.03	9.02 ± 4.87	0.50
Implant reason				
Generator replacement only	75.7 (4,235)	74.7 (2,095)	76.6 (2,140)	0.18
System revision	9.2 (516)	9.8 (276)	8.6 (240)	
Upgrade	15.1 (844)	15.4 (432)	14.8 (412)	
CIED type received				
Pacemaker	24.7 (1,383)	24.5 (687)	24.9 (696)	0.06
CRT-P	5.1 (285)	5.9 (165)	4.3 (120)	
ICD	30.3 (1,696)	30.0 (841)	30.6 (855)	
CRT-D	39.9 (2,231)	39.6 (1,110)	40.2 (1,121)	
Location of CIED device				
Left subcutaneous	86.6 (4,846)	86.8 (2,434)	86.4 (2,412)	0.62
Antithrombotic use at time of procedure				
Anticoagulant use	35.2 (1,971)	35.6 (998)	34.8 (973)	0.55
Class of oral anticoagulant use				
Vitamin K antagonist	27.5 (1,541)	28.1 (789)	26.9 (752)	0.69
Apixaban	4.8 (266)	4.6 (130)	4.9 (136)	
Other DOAC	6.4 (359)	6.6 (184)	6.3 (175)	
Antiplatelet use	51.0 (2,854)	49.5 (1,387)	52.5 (1,467)	0.022
Aspirin	28.4 (1,589)	27.6 (774)	29.2 (815)	0.19
Clopidogrel	5.3 (298)	4.9 (138)	5.7 (160)	0.18
Dual anticoagulant/antiplatelet therapy	12.2 (682)	12.1 (339)	12.3 (343)	0.83
Infection management strategy				
Periprocedure antibiotic	98.6 (5,516)	98.7 (2,766)	98.5 (2,750)	0.56
Cephalosporin periprocedure	71.7 (4,014)	72.0 (2,017)	71.5 (1,997)	0.72
Glycopeptide periprocedure	26.0 (1,455)	25.9 (727)	26.1 (728)	0.91
Postprocedure antibiotic	26.8 (1,501)	28.1 (789)	25.5 (712)	0.025
Pocket wash	75.1 (4,202)	76.0 (2,131)	74.2 (2,071)	0.11
Capsulectomy				
None	51.5 (2,881)	53.5 (1,499)	49.5 (1,382)	0.012
Partial	42.4 (2,369)	40.2 (1,126)	44.5 (1,243)	
Complete	6.0 (335)	6.1 (172)	5.8 (163)	

Continued on the next page

TABLE 1 Continued

	Total Patients Undergoing Secondary CIED Procedures (N = 5,595)	Control (n = 2,803)	Envelope (n = 2,792)	*P* value
Skin preparation				
Chlorhexidine	77.4 (4,327)	77.4 (2,167)	77.4 (2,160)	0.98
Povidone-iodine solution	23.7 (1,327)	23.4 (656)	24.0 (671)	0.60
Alcohol	11.6 (646)	11.6 (325)	11.5 (321)	0.90
Procedure time, min	45.74 ± 40.66	45.00 ± 41.70	46.48 ± 39.58	0.18
Length of hospitalization, days	0.30 ± 2.05	0.26 ± 0.83	0.34 ± 2.78	0.11

Values are mean ± SD or % (n).

BMI = body mass index; CIED= cardiac implantable electronic device; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; CRT-D/P = cardiac resynchronization therapy defibrillator/pacemaker; DOAC= direct oral anticoagulant; ICD= implantable cardioverter-defibrillator.

possible to modify including a history of atrial arrhythmia, lower BMI, high-power devices (ICDs), and the number of prior CIED procedures. Many of these factors were previously highlighted in prior studies, but the non-modifiable nature of these factors leaves little room for changing practice (1,11). The association between the number of prior CIED procedures and infection is a reminder that the risk of infection from the patient's perspective is a lifetime risk and not just procedural risk (23). It is also a reminder that CIED infection prevention is a shared responsibility between clinicians and industry. Clinicians must adhere to best practices, use proper techniques, avoid complications that require additional procedures, and follow proper programming and upgrade decision-making processes, whereas industry must continue to work to improve lead performance and increase battery longevity (24). Some traditional patient-related risk factors including end-stage renal disease, immunocompromised state, and prior recent CIED infection (within 12 months), are well established; but these factors were exclusion criteria for WRAP-IT and therefore are not represented in this cohort (1,11,15).

PADIT and WRAP-IT showed similar 1-year CIED infection rates; however, in this analysis, we noted geographical variation where CIED infection rates were higher in centers from Asia compared to North America and Europe. These findings are important, and perhaps provide an opportunity for centers around the world to adhere to standard quality metrics established by these 2 large trials. Additionally, this analysis provides opportunities to modify certain procedure-related practices to minimize infection. The longer duration of the procedure was associated with a higher risk of infection. Clinical skills and expertise are important and every effort should be made to perform high-quality procedures efficiently and minimize the duration of an open pocket. Moreover, time itself likely reflects the complexity of the procedure, which may be burdened by multiple factors that are difficult to measure. Proper procedural surgical techniques and skills are therefore critical, and this is a process that starts from the initial implantation procedure.

The use of preoperative intravenous antibiotic has been shown to be effective in reducing CIED infection, but the choice of antibiotic prophylaxis differs widely (25,26). Staphylococcal species are the predominant organisms involved in CIED infection

TABLE 2 Risk Factor Results

	Times Appeared	Average HR
Patient or device-related factors		
Associated with increased infection risk		
Each increase in number of previous procedures	53	1.03
History of atrial arrhythmia	49	1.08
Device type (CRT-D vs pacemaker/ICD)	22	1.09
Geography (not North America or Europe)	13	1.30
Device type (CRT-P vs pacemaker/ICD)	10	1.21
Associated with decreased infection risk		
Increase in one BMI unit	16	0.99
Procedure-related factors		
Associated with increased infection risk		
Length of procedure time, hours	100	1.09
Anticoagulant use at time of procedure	66	1.08
Anticoagulant use (not warfarin or apixaban)	52	1.17
Device implant location (non-left pectoral subcutaneous)	36	1.10
Antiplatelet use at time of procedure	16	1.15
Antiplatelet + anticoagulant use at time of procedure	16	1.05
Complete capsulectomy vs partial or none	14	1.22
Periprocedural use of glycopeptide (vancomycin) vs alternative (primarily cephalosporin)	11	1.15
Associated with decreased infection risk		
Anticoagulant use (apixaban)	51	0.71
Chlorhexidine skin preparation vs alternative (primarily povidone-iodine)	38	0.87
Antibiotic pocket wash vs nonantibiotic pocket wash or no wash	15	0.94

HR = hazard ratio; other abbreviations as in Table 1.

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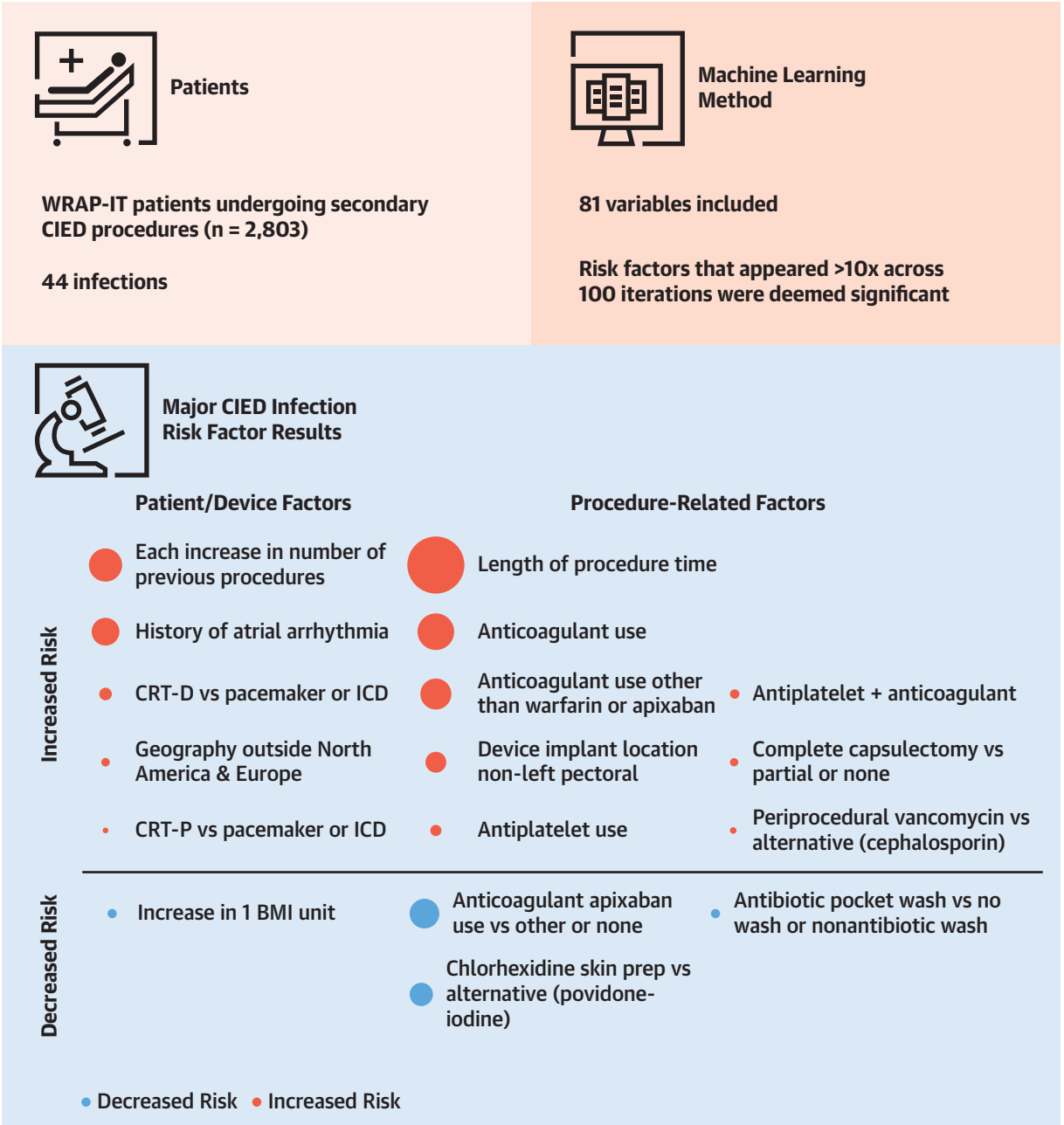
CENTRAL ILLUSTRATION **Risk Factors for Infection After Secondary Cardiac Implantable Electronic Device Procedures**



Tarakji, K.G. et al. J Am Coll Cardiol EP. 2022;8(1):101-111.

Size of dots is scaled to the number of times a factor appeared in the search. BMI = body mass index; CIED = cardiac implantable electronic device; CRT-D = cardiac resynchronization therapy-defibrillator; CRT-P = cardiac resynchronization therapy - pacemaker; ICD = implantable cardioverter-defibrillator; WRAP-IT= World-wide Randomized Antibiotic Envelope Infection Prevention trial.

TABLE 3 Consistency Check Results

	Secondary Procedure Control (n = 2,803)	Secondary Procedure Envelope (n = 2,792)	Consistency Check
Total major CIED infection	44 (1.57)	23 (0.82)	–
Associated with increased infection risk			
Length of procedure time >60 min[a]	14 (2.37)	8 (1.29)	✓
Anticoagulant use at time of procedure	22 (2.20)	7 (0.72)	
Anticoagulant use (not warfarin or apixaban)	7 (3.80)	0 (0.00)	
Device implant location (non-left pectoral subcutaneous)	10 (2.71)	2 (0.53)	
Antiplatelet use at time of procedure	15 (1.94)	5 (0.61)	
Antiplatelet + anticoagulant use at time of procedure	9 (2.65)	3(0.87)	✓
Complete capsulectomy vs partial or none	5 (2.91)	2 (1.23)	✓
Periprocedural use of glycopeptide (vancomycin) vs alternative (primarily cephalosporin)	13 (1.79)	9 (1.24)	✓
At least three previous CIED procedures[a]	13 (3.49)	3 (0.88)	
History of atrial arrhythmia	27 (1.90)	11 (0.75)	
Device type (CRT-D vs pacemaker/ICD)	23 (2.07)	12 (1.07)	✓
Geography (not North America or Europe)	3 (3.33)	0 (0.00)	
Device Type (CRT-P vs pacemaker/ICD)	4 (2.42)	1 (0.83)	✓
Associated with decreased infection risk			
Anticoagulant use (apixaban)	0 (0.00)	1 (0.74)	✓
Chlorhexidine skin preparation vs alternative (primarily povidone-iodine)	30 (1.38)	17 (0.79)	✓
Antibiotic pocket wash vs nonantibiotic wash vs no wash	26 (1.32)	16 (0.84)	
BMI ≥25 kg/m^2[a]	26 (1.25)	14 (0.67)	✓

Values are n (%). Additional consistency check was conducted using patients who received an envelope. Factors were considered consistent based on the directionality of the association with infection risk (increased or decreased risk). [a]Risk factor checked as a continuous variable in a cox regression and reported in table as a cutoff point with infection rates on either side.

Abbreviations as in Tables 1 and 2.

with some being methicillin-resistant and, in approximately 10% of cases, Gram-negative (27). Proponents of using cefazolin assert that it provides protection against methicillin-sensitive staphylococcal species in addition to many other species. Centers that advocate the use of glycopeptide (most commonly vancomycin) note the increased prevalence of methicillin-resistance among staphylococcal species. PADIT showed no significant benefit of preoperative antibiotics (cefazolin plus vancomycin) with an intraoperative wound pocket wash (bacitracin) and postoperative cefalexin/cefadroxil/clindamycin for 2 days compared to single-dose preoperative cefazolin (22). In our analysis, the use of glycopeptide (vancomycin) as the preoperative antibiotic of choice was associated with higher risk of infection compared to the use of cefazolin. On the other hand, the use of pocket wash with an antibiotic solution was associated with decreased risk of infection. These findings might suggest adhering to the guidelines by using a single dose of cefazolin as the antibiotic of choice for preoperative prophylaxis when feasible.

Surgical literature shows that the use of chlorhexidine alcohol is more effective than povidone-iodine-based skin preparation in preventing surgical site infection (28). Although there are no randomized CIED trials to address this issue, 2 electrophysiology studies showed no difference between the 2 agents in reducing CIED infection (29,30). In our dataset, the use of chlorhexidine was associated with a decreased risk of infection.

Another subject of debate is whether to perform capsulectomy at the time of secondary CIED procedures. Proponents believe the capsule represents an avascular tissue that could be colonized and hence provides the nidus for future infection (31,32), whereas opponents raise concerns about extending the length of the procedure and increasing the risk of lead and pocket complications, especially hematomas, which might lead to a higher risk of infection (33). In our analysis, a complete capsulectomy was associated with an increased risk of major infection compared to a partial capsulectomy or no capsulectomy. Procedure time was also longer in patients who had a complete capsulectomy, although the influence of procedure time on infection risk was already captured in our analysis model.

Antiplatelets are rarely discontinued at time of CIED procedure and warfarin is usually continued as it leads to fewer hematomas compared to bridging with heparin products, which significantly increases the risk of infection (10,34). Managing patients on

DOACs is less clear (35). The variety and differential use of different types of DOACs in combination with a low number of infections limit our ability to make any meaningful inference on the relationship of DOAC use and infection risk. In our analysis, the use of antiplatelets or anticoagulants or both were associated with an increased risk of infection. However, it was interesting to observe that apixaban was associated with a lower risk of infection. Understanding the correlation between antiplatelet use, anticoagulant use, and infection requires a complex analysis that includes the type of the agent used, the dose, the timing of the last dose, the incidence of hematoma formation, and infection. Such detailed analysis is beyond the scope of this paper.

STUDY LIMITATIONS. To contextualize the current findings, we must take into consideration the limitations that are inherent to these types of analyses. First, this is a *post hoc* analysis with results implying association but not causality. Regarding the consistency check, it may have limited value to corroborate primary results for some risk factors. One possible reason is that the envelope cohort is known to significantly reduce major infections leaving even fewer infections to detect a pattern (16). Furthermore, the antibacterial envelope was found to significantly reduce pocket infections, specifically, as compared to systemic infections leading to a proportionally higher number of major infections that remain due to endocarditis/severe bacteremia, which may have a different risk profile (16). Finally, the antibacterial envelope may be specifically intervening with the biological process for certain risk factors and not for others. As such, the value of the consistency check is to provide additional credence to the findings for the ML analysis but should be interpreted with caution when a risk factor is not corroborated. Another limitation is the combination of the low event rate and the sporadic distribution of these events per site and operator. With more data, site and/or operator effects could be added to the model because practice patterns would tend to be similar. However, at most, 2 infections within 1 site were observed and there were variations among operators even within the same sites. Because of the low number of per-site infections and the WRAP-IT trial's extensive baseline and procedural information collected, modeling based on procedural characteristics was used. We are also limited to looking only at main effects and cannot investigate interactions without more data.

CONCLUSIONS

Using an ML approach, several procedural risk factors correlating with infection risk were identified and validated using the WRAP-IT data. The findings can help guide our infection prevention strategies and procedural techniques that could ultimately lead to better patient outcomes, lower costs of care, improved quality of life, and potential survival by preventing CIED infection.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The results from this analysis identified several opportunities to modify CIED procedural practices to further decrease the risk of CIED infection.

TRANSLATIONAL OUTLOOK: This analysis identified both known and novel CIED infection risk factors. By optimizing implant procedures per the identified procedure-related infection risk factors identified here, this risk may be even further mitigated beyond already existing measures. To further validate these findings, large, prospective studies will be required.

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APPENDIX For supplemental figures and tables, please see the online version of this paper.