JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2019 PUBLISHED BY ELSEVIER ON BEHALF OF THE
AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 74, NO. 23, 2019

Risk Factors for Infections Involving Cardiac Implanted Electronic Devices

David H. Birnie, MD,[a] Jia Wang, MSc,[b] Marco Alings, MD, PhD,[c] François Philippon, MD,[d] Ratika Parkash, MD,[e] Jaimie Manlucu, MD,[f] Paul Angaran, MD,[g] Claus Rinne, MD,[h] Benoit Coutu, MD,[i] R. Aaron Low, MD,[j] Vidal Essebag, MD, PhD,[k] Carlos Morillo, MD,[l] Damian Redfearn, MD,[m] Satish Toal, MD,[n] Giuliano Becker, MD,[o] Michel Degrâce, MD,[p] Bernard Thibault, MD,[q] Eugene Crystal, MD,[r] Stanley Tung, MD,[s] John LeMaitre, MD,[t] Omar Sultan, MD,[u] Matthew Bennett, MD,[u,v] Jamil Bashir, MD,[w] Felix Ayala-Paredes, MD, PhD,[x] Philippe Gervais, MD,[d] Leon Rioux, MD,[y] Martin E.W. Hemels, MD, PhD,[z,aa] Leon H.R. Bouwels, MD,[bb] Derek V. Exner, MD,[l] Paul Dorian, MD,[g] Stuart J. Connolly, MD,[b] Yves Longtin, MD,[cc] Andrew D. Krahn, MD[w]

ABSTRACT

BACKGROUND Cardiac implantable electronic device infection is a major complication that usually requires device removal. PADIT (Prevention of Arrhythmia Device Infection Trial) was a large cluster crossover trial of conventional versus incremental antibiotics.

OBJECTIVES This study sought to investigate independent predictors of device infection in PADIT and develop a novel infection risk score.

METHODS In brief, over 4 6-month periods, 28 centers used either conventional or incremental prophylactic antibiotic treatment in all patients. The primary outcome was hospitalization for device infection within 1 year (blinded endpoint adjudication). Multivariable logistic prediction modeling was used to identify the independent predictors and develop a risk score for device infection. The prediction models were internally validated with bootstrap methods.

RESULTS Device procedures were performed in 19,603 patients, and hospitalization for infection occurred in 177 (0.90%) within 1 year of follow-up. The final prediction model identified 5 independent predictors of device infection (prior procedures [P], age [A], depressed renal function [D], immunocompromised [I], and procedure type [T]) with an optimism-corrected C-statistic of 0.704 (95% confidence interval: 0.660 to 0.744). A PADIT risk score ranging from 0 to 15 points classified patients into low (0 to 4), intermediate (5 to 6) and high (≥7) risk groups with rates of hospitalization for infection of 0.51%, 1.42%, and 3.41%, respectively.

CONCLUSIONS This study identified 5 independent predictors of device infection and developed a novel infection risk score in the largest cardiac implantable electronic device trial to date, warranting validation in an independent cohort. The 5 independent predictors in the PADIT score are readily adopted into clinical practice. (Prevention of Arrhythmia Device Infection Trial [PADIT Pilot]; NCT01002911) (J Am Coll Cardiol 2019;74:2845-54) © 2019 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]University of Ottawa Heart Institute, Ottawa, Ontario, Canada; [b]Population Health Research Institute, Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada; [c]Amphia Ziekenhuis and Working Group on Cardiovascular Research the Netherlands, Breda, the Netherlands; [d]Institut universitaire de cardiologie et de pneumologie de Québec, Laval University, Quebec City, Quebec, Canada; [e]Queen Elizabeth II Health Sciences Center, Halifax, Nova Scotia, Canada; [f]Lawson Health Research Institute, London Health Sciences, Western University, London, Ontario, Canada; [g]Department of Medicine, University of Toronto, Division of Cardiology, St. Michael Hospital, Toronto, Ontario, Canada; [h]St. Mary's General Hospital, Kitchener, Ontario, Canada; [i]Centre hospitalier de l'Université de Montréal, University of Montreal, Montreal, Quebec, Canada; [j]Chinook Regional Hospital, Lethbridge, Alberta, Canada; [k]McGill University Health Center, Montreal, Quebec, Canada; [l]Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Alberta, Canada; [m]Kingston General Hospital, Queen's University, Kingston, Ontario, Canada; [n]Horizon Health Network, Saint John, New Brunswick, Canada; [o]Hôpital du Sacré-Coeur de Montréal, University of Montreal, Montreal, Quebec, Canada; [p]Hôtel-Dieu de Lévis, Lévis, Quebec, Canada; [q]Montreal Heart Institute, Montreal, Quebec, Canada; [r]Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; [s]St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; [t]Royal Columbian Hospital, New Westminster, British Columbia, Canada; [u]Regina General Hospital, Saskatchewan Health Authority, Regina, Saskatchewan, Canada; [v]Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada; [w]University of British Columbia, Vancouver, British Columbia, Canada; [x]Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Quebec, Canada; [y]Centre de santé et de services sociaux de

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2019.09.060

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CIED = cardiac implantable electronic device

CRT = cardiac resynchronization therapy

ICD = implantable cardioverter defibrillator

PADIT = Prevention of Arrhythmia Device Infection Trial

Cardiac implantable electronic device (CIED) infection is reported in ≤2% of cases (1-5). Device infection usually requires complete system removal, is costly (6), leads to prolonged hospitalization (7), and is associated with a short-term mortality rate of ≤18% (2,8,9). Therefore, developing strategies to reduce infection and defining predictors of increased infection risk are important goals. PADIT (Prevention of Arrhythmia Device Infection Trial) recently reported on a comparison between conventional (pre-procedural cefazolin) and incremental (pre-procedural cefazolin plus vancomycin, intraprocedural bacitracin pocket wash, and 2-day post-procedural oral cephalexin) antibiotics. Hospitalization for infection was reduced by incremental therapy (23% reduction, nonsignificant); the nonsignificance was in part attributable to the unexpectedly low infection rate (1).

SEE PAGE 2855

More than 60 studies have examined risk factors for device infection (4). The studies are of variable quality, with many being retrospective and/or single-center studies, with inconsistent definitions of device infection, and few having independent endpoint adjudication (4). In addition, the studies examined variable numbers of potential predictors of infection, with no standardized definitions. Host-related (including diabetes, corticosteroid use, renal failure, and preoperative fever), procedure/device-related (including device type, procedure type, and hematoma), and operator-related factors (operator experience) have all been implicated (4). The most recent American Heart Association scientific statement on CIED infection commented that "although the existing published data provides some insight into CIED infection risk factors, larger, more representative studies would be useful in identifying and addressing the most important factors that are responsible for the development of CIED infection" (10).

Using the PADIT database of >19,000 patients, which enrolled all patients across a representative international sample, with independent adjudication of potential device infection, we sought to investigate independent predictors of device infection and develop a novel infection risk score.

METHODS

TRIAL DESIGN. The design of PADIT has previously been described (11), and the primary results have been published (1). In brief, the primary hypothesis of PADIT was that incremental antimicrobial prophylaxis would reduce the risk of hospitalization for device infection compared with a conventional strategy of a single dose of a pre-procedural antibiotic. Each therapy period lasted for 6 months at the Canadian sites. The Netherlands sites, which joined the trial later, were permitted to shorten the enrollment and transition periods once 35 patients and at least 3 months of enrollment were complete in each period. All centers collected data on patients at high risk, and 6 centers collected data on patients at both high and low risk (1,11).

OUTCOME. The primary outcome of the trial was admission to the hospital for proven CIED or pocket infection within 1 year of the procedure (1,11). Blinded adjudication was performed by 2 investigators (Y.L. and P.G.) blinded to treatment received, with all discrepancies resolved by the adjudication committee.

VARIABLE DEFINITIONS. Immunocompromised was defined as receiving therapy that suppresses resistance to infection (e.g., immunosuppression, chemotherapy, radiation, long-term or recent high-dose steroids) or having a disease that is sufficiently advanced to suppress resistance to infection (e.g., leukemia, lymphoma, HIV infection). Renal insufficiency was defined as estimated glomerular filtration rate <30 ml/min.

Procedure type definitions. The following procedure types were defined.

- Pacemaker: a new pacemaker or pacemaker generator change.
- Implantable cardioverter defibrillator (ICD): a new ICD or ICD generator change.

Rimouski-Neigette, Rimouski, Quebec, Canada; [z]Rijnstate Hospital, Arnhem, the Netherlands; [aa]Radboud University Medical Centre, Nijmegen, the Netherlands; [bb]Canisius Wilhelmina Ziekenhuis, Nijmegen, the Netherlands; and the [cc]Jewish General Hospital Sir Mortimer B. Davis, McGill University, Montreal, Quebec, Canada. Dr. Krahn has received support from the Heart and Stroke Foundation of Canada, the Sauder Family, and the Heart and Stroke Foundation Chair in Cardiology and the Paul Brunes Chair in Heart Rhythm Disorders. The study was supported by the CANNeCTIN (Canadian Network and Centre for Trials INternationally) network (Canadian Institute of Health Research grant 88370) and a clinical trial grant (Canadian Institute of Health Research grant 119442).

Manuscript received June 4, 2019; revised manuscript received September 18, 2019, accepted September 23, 2019.

- Cardiac resynchronization therapy (CRT): a new CRT pacemaker or defibrillator or CRT generator change.
- Revision/upgrade: A pocket and/or lead revision and/or system upgrade, that is, adding new lead(s).

These 4 groups within procedure type are mutually exclusive. For example, if a patient is undergoing upgrade to CRT, then he or she is counted in the revision/upgrade group.

STATISTICAL ANALYSIS. Continuous variables and categorical variables were summarized as mean ± SD and frequency (%), respectively. Baseline characteristics were compared between patients with and without hospitalization for device infection by using the 2-sample Student's *t*-test for continuous variables and chi-square or Fisher exact test for categorical variables, as appropriate.

For the development of the risk prediction model, we selected the following candidate predictors based on prior published data (4): 1) patient characteristics: age, sex, history of diabetes, heart failure, renal insufficiency, and immunocompromised; 2) procedure characteristics: procedure type, duration of procedure, and number and timing of previous procedure; and 3) center characteristics: tertiary care, surgery location, and use of skin barrier.

Hospitalization for device infection was treated as a binary outcome. According to the PADIT main publication (1), both intraclass correlation and interperiod correlation were extremely low (<0.001) and, therefore, were ignored in this analysis. A univariate logistic regression model was used to evaluate the association between each candidate predictor and primary outcome. In multivariable logistic regression analysis, all potential predictors identified in univariate analysis with $p < 0.25$ were tested for inclusion with a backward-elimination approach. Covariates with p values >0.1 in the multivariable model were individually removed in a stepwise fashion, starting with the one with the highest p value. Finally, to identify other remaining potential confounders, all the dropped variables were individually added to the multivariable model and kept in the model if the effect size of any of other predictors changed by >10%. Collinearity was assessed with the variance inflation factor. Age was fractional polynomial transformed to capture its nonlinear relationship with the primary outcome. A risk score for hospitalization for device infection was derived from the full prediction model by assigning weighted points to beta coefficients in the model by using the coefficient-based scoring system described by Schneeweiss et al. (12). To make the score more clinically interpretable, age was categorized into <60, 60 to 69, and ≥70 years. The age cutoffs were selected based on the nonlinear relationship illustrated by a restricted cubic spline approach.

Performances of the full prediction model and risk score model were assessed in terms of calibration-in-the-large, calibration slope, and the C-statistic. Internal validation was conducted by bootstrapping 200 samples of the original study group to correct for optimism.

The discriminative capacity and the agreement between the observed and predicted probability of the primary outcome for the full prediction and risk score models were illustrated with a receiver operating characteristic curve and a calibration plot, respectively. Statistical analyses were performed with SAS, version 9.4 software (SAS Institute, Cary, North Carolina) and closely followed the Transparent

TABLE 1 Baseline Characteristics in Patients With and Without Hospitalization for Device Infection

	Infection (n = 177)	No Infection (n = 19,382)	p Value*
Age, yrs	68.7 ± 12.7	72.1 ± 13.1	<0.001
Female	45 (25.4)	6,592 (34.0)	0.016
Diabetes	55 (31.1)	5,076 (26.2)	0.14
History of heart failure	94 (53.1)	7,740 (39.9)	<0.001
Renal insufficiency (eGFR <30 ml/min)	41 (23.2)	3,225 (16.6)	0.021
Penicillin allergy	28 (15.8)	1,969 (10.2)	0.013
Immunocompromised	7 (4.0)	314 (1.6)	0.027
Type of procedure			
New pacemaker	16 (9.0)	4,608 (23.8)	<0.001
New ICD	18 (10.2)	2,091 (10.8)	0.79
New CRT pacemaker	3 (1.7)	504 (2.6)	0.63
New CRT defibrillator	20 (11.3)	1,819 (9.4)	0.39
Pacemaker generator replacement	24 (13.6)	4,924 (25.4)	<0.001
ICD generator replacement	22 (12.4)	2,103 (10.9)	0.50
CRT generator replacement	21 (11.9)	810 (4.2)	<0.001
Revision or upgrade†	63 (35.6)	2,930 (15.1)	<0.001
Duration of procedure, h			<0.001
<1	98 (55.4)	13,629 (70.3)	
1–1.5	45 (25.4)	3,233 (16.7)	
>1.5–2	16 (9.0)	1,248 (6.4)	
>2	17 (9.6)	1,211 (6.2)	
Previous procedure on pocket	49 (27.7)	2,611 (13.5)	<0.001
Number of previous procedures			<0.001
1	27 (15.3)	1,939 (10.0)	
2	17 (9.6)	502 (2.6)	
>2	5 (2.8)	170 (0.9)	
Previous procedure performed within last month	1 (0.6)	50 (0.3)	0.37

Values are mean ± SD or n (%). *The p values are from chi-square test or Fisher exact test for categorical variables and 2-sample Student's *t*-test for continuous variables. †Revision or upgrade: pocket and/or lead revision and/or system upgrade (i.e., adding new lead[s]).

CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter defibrillator.

TABLE 2 Univariate Analysis of Predictors for Hospitalization Due to Device Infection

	Infection Rate	Odds Ratio (95% CI)	β Coefficient	p Value
Age*	–	–	-0.0411	<0.001
1/age^2*	–	–	-2120.682	0.047
Sex				
Female	0.7	Ref		
Male	1.0	1.51 (1.08-2.12)	0.4133	0.017
Procedure type				
PM	0.4	Ref		
ICD	0.9	2.14 (1.35-3.39)	0.7611	0.001
CRT	1.3	3.29 (2.11-5.12)	1.1908	<0.001
Revision/upgrade†	2.1	5.29 (3.53-7.94)	1.6667	<0.001
Diabetes				
No	0.8	Ref		
Yes	1.1	1.27 (0.92-1.74)	0.2365	0.147
Heart failure				
No	0.7	Ref		
Yes	1.2	1.70 (1.26-2.28)	0.5280	<0.001
Renal insufficiency				
No	0.8	Ref		
Yes	1.3	1.50 (1.05-2.13)	0.4044	0.024
Immunocompromised				
No	0.9	Ref		
Yes	2.2	2.49 (1.16-5.35)	0.9136	0.019
Procedure duration, h				
<1	0.7	Ref		
≥1	1.4	1.91 (1.41-2.57)	0.6449	<0.001
Number of previous procedures				
0	0.8	Ref		
1	1.4	1.82 (1.20-2.77)	0.5996	0.005
≥2	3.2	4.28 (2.71-6.78)	1.4545	<0.001
Timing of previous procedure				
None	0.8	Ref		
Beyond 1 month	1.8	2.45 (1.76-3.43)	0.8971	<0.001
Within 1 month	2.0	2.62 (0.36-19.1)	0.9617	0.343
Tertiary care				
No	0.8	Ref		
Yes	0.9	1.19 (0.59-2.43)	0.1774	0.625
Surgery location				
Operating room	0.8	Ref		
Electrophysiology laboratory	0.9	1.14 (0.72-1.82)	0.1335	0.576
Skin barrier used				
No	0.8	Ref		
Yes	1.0	1.32 (0.97-1.79)	0.2770	0.076

Values are % unless otherwise indicated. *Age was fractional polynomial transformed. †Revision or upgrade: pocket and/or lead revision and/or system upgrade (i.e., adding new lead[s]).

PM = pacemaker; Ref = reference; other abbreviations as in Table 1.

Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement (13).

RESULTS

PATIENTS. The study was performed between December 2012 and September 2016. A total of 19,603 patients across 28 centers underwent device procedures, of whom 19,559 patients completed their follow-up visit. Within 1 year of follow-up, hospitalization for device infection occurred in 177 (0.9%) patients. Baseline characteristics of patients with or without hospitalization for device infection are compared in Table 1. Patients with device infection were younger, more likely to be male, have a history of heart failure or renal insufficiency, or be immunocompromised. The duration of the procedure was longer in patients with device infection than those without. Compared with patients without infection, those with infection were more likely to have had a previous procedure on the pocket.

PREDICTORS OF INFECTION AND FULL PREDICTION MODEL. Univariate associations between risk factors and hospitalization for device infection are shown in Table 2. All variables except for the cluster-level variables of tertiary care institution and electrophysiology laboratory implant site met the selection criterion ($p < 0.25$) and were entered into the multivariable model for testing of inclusion. In the multivariable analysis (Table 3), age (as a fractional polynomial), procedure type, renal insufficiency, immunocompromised, and number of previous procedures remained independent significant predictors of device infection at a significance level of $p < 0.1$. We considered this model with 5 predictors as the full prediction model.

PADIT INFECTION RISK SCORE. The PADIT infection risk score was developed based on the full prediction model (P: prior procedure[s]; A: age; D: depressed estimated glomerular filtration rate; I: immunocompromised; and T: type of procedure), where age was categorized into <60, 60 to 69, and ≥70 years to facilitate the clinical application (Central Illustration, Table 4). The risk score was calculated for each patient by summing the points assigned to each predictor: number of previous procedures (1 point for 1, 4 points for ≥2), age (1 point for age 60 to 69 years, 2 points for age <60 years; we chose age ≥70 years as the reference group because it had the lowest risk), depressed renal function (1 point), immunocompromised (3 points), and procedure type (2 points for ICD, 4 points for CRT, and 5 points for revision/upgrade). The minimum risk score was 0 for patients without any risk factors, and the maximum risk score was 15. The rate of hospitalization for device infection increased monotonically with higher level of risk score (p value for trend: <0.001 from Cochran-Armitage test) (Central Illustration, Table 4). The predicted probability of having hospitalization due to device infection for an individual patient can be calculated by using the following risk score model,

where -5.776 and 0.288 are the intercept and slope coefficient, respectively:

$$\text{p (infection)} = \frac{1}{1 + e^{-(-5.776 + 0.288 \times \text{score})}}$$

We classified the risk scores into 3 risk groups according to the infection event rate: low risk (<1%), intermediate risk (1%–3%) and high risk (>3%). Based on this classification, 13,828 patients were at low risk (score: 0 to 4), 4,151 patients were at intermediate risk (score: 5 or 6), and 1,406 patients were at high risk (score: ≥7), with rates of hospitalization for infection of 0.51%, 1.42%, and 3.41%, respectively.

INTERNAL VALIDATION OF THE FULL PREDICTION AND RISK SCORE MODELS. We internally validated the performances of the full prediction and risk score models using a bootstrapping method. After correction for optimism, for both models, calibration-in-the-large was close to 0 and calibration slope was close to 1, indicating good agreement between observed and predicted risk (Table 5, Figure 1). The full prediction model was able to discriminate patients with and without hospitalization for device infection with an optimism-corrected C-statistic of 0.704 (95% confidence interval [CI]: 0.660 to 0.744). The discriminative capacity of the risk score model was similar to the original prediction model (optimism-corrected C-statistic: 0.702; 95% CI: 0.661 to 0.741) (Table 5, Figure 2).

TREATMENT EFFECT BY PADIT INFECTION RISK SCORE. Subgroup analysis by PADIT infection risk score of the 2 antibiotic regimens showed no treatment effect ($p_{\text{interaction}} = 0.37$) (Table 6).

DISCUSSION

MAJOR FINDINGS. Device infection is a major complication, usually requiring device removal, with associated significant morbidity and mortality. Using the PADIT dataset, we sought to investigate independent predictors of device infection and develop a novel infection risk score. Although overall infection rates were low, we were able to develop a final prediction model that identified 5 independent predictors of device infection. These 5 independent predictors in the PADIT score are routinely measured and can be readily adopted into clinical practice.

PRIOR STUDIES. More than 60 studies have examined risk factors for device infection. The studies are of variable quality (4), and experts have called for larger, more representative studies (10). Polyzos et al. (4) performed a meta-analysis and systematic review to synthesize the data. In their final analysis, they included only factors that were found to be positive in at least 5 studies. Consistent with our data, they found procedure type, renal insufficiency, immunocompromised, and previous procedures to be associated with infection. Additional patient-specific variables associated with infection were diabetes, chronic obstructive pulmonary disease, heart failure, malignancy, and oral anticoagulation. Procedure- and device-related factors were procedure duration, postoperative hematoma, and temporary pacing (4).

Age has been shown to be associated with device infection in at least 2 studies (5,14). In the Danish prospective pacemaker registry of >46,000 patients, there was a very clear and progressively decreasing risk of infection with advancing age. For example, the multivariate hazard ratio for patients ages 80 to 89 years was 0.29 (95% CI: 0.21 to 0.39) compared with patients ages 20 to 49 years (5). In another study of 3,105 patients, the mean age of patients with infection was 63.1 years compared with 67.5 years in those without infection, and this association remained significant after adjusting for other important variables (14). The biological explanation for this association is not clear. It has been suggested that perhaps a lesser immune response in older patients against low-virulence bacteria might be a factor, along with the presence of less firm subcutaneous tissue in older patients (5). The clinical implications of the observation are clear, however, as young patients with CIEDs face a lifetime of repeated device surgeries.

CLINICAL UTILITY OF A DEVICE INFECTION RISK SCORE. To our knowledge, this is the first prospective, internally validated CIED infection risk score. There are, however, published infection risk scores

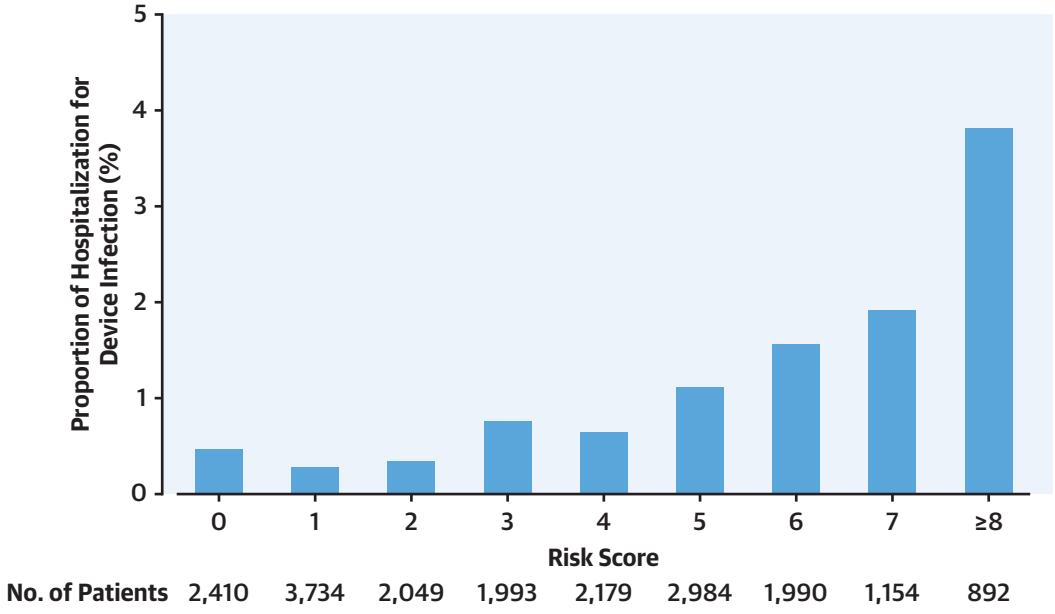
TABLE 3 Full Prediction Model for Hospitalization due to Device Infection

	OR (95% CI)	β Coefficient	p Value
Age*	–	-0.0274	0.018
1/age^2*	–	-1441.798	0.127
Procedure type (reference: pacemaker)			
ICD	1.77 (1.09–2.87)	0.5717	0.020
CRT	2.73 (1.72–4.31)	1.0026	<0.001
Revision/upgrade†	4.01 (2.62–6.13)	1.3881	<0.001
Renal insufficiency	1.45 (1.00–2.09)	0.3697	0.047
Immunocompromised	2.28 (1.05–4.96)	0.8261	0.037
Number of previous procedure (reference: 0)			
1	1.51 (0.99–2.32)	0.4146	0.058
≥2	3.43 (2.14–5.48)	1.2321	<0.001
Intercept	–	-3.3207	0.001

All variables identified in univariate analysis with $p < 0.25$ were tested for inclusion with a backward elimination approach. Covariates with p values of >0.1 in the multivariable model were individually removed in a stepwise fashion, starting with the one with the highest p value. Finally, to identify other remaining potential confounders, all dropped variables were individually added to the multivariable model and kept in the model if the effect size of any of other predictors changed by >10%. *Age was fractional polynomial transformed. †Revision or upgrade: pocket and/or lead revision and/or system upgrade (i.e., with adding new lead[s]).

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

CENTRAL ILLUSTRATION **Rate of Device Infection Stratified by PADIT Infection Risk Score**



Birnie, D.H. et al. J Am Coll Cardiol. 2019;74(23):2845-54.

This figure illustrates how the PADIT score might be used in clinical practice, with the graph showing the estimated risk of infection based on the calculated score.

for other forms of surgery. These include many risk scores for infection after joint arthroplasty (although none are considered valid for clinical use [15]) and 1 for infection after prosthetic breast reconstruction (16). The PADIT infection risk score is likely to be helpful to physicians and patients in shared decision making about device therapy. One example is patients reaching ICD elective replacement time. Many patients and families are not aware of the risks and benefits of ICD generator replacement (17-19). Also, it has been shown that patients often overestimate the lifesaving benefits and underestimate the risks of ICD generator change, in part because of the apparently routine nature of the surgery itself

TABLE 4 **PADIT Score in Clinical Practice**

	OR (95% CI)	β Coefficient	p Value	PADIT Risk Score Points
Age, yrs (Ref: 70 yrs)				
<60	1.63 (1.10-2.41)	0.4872	0.015	2
60-69	1.43 (0.99-2.05)	0.3552	0.054	1
Procedure type (Ref: pacemaker)				
Implantable cardioverter defibrillator	1.83 (1.14-2.93)	0.6016	0.013	2
Cardiac resynchronization therapy	2.87 (1.83-4.51)	1.0547	<0.001	4
Revision/upgrade	4.16 (2.74-6.32)	1.4254	<0.001	5
Renal insufficiency	1.48 (1.02-2.13)	0.3890	0.037	1
Immunocompromised	2.24 (1.03-4.86)	0.8051	0.042	3
No. of previous procedures (Ref: none)				
1	1.51 (0.98-2.31)	0.4114	0.059	1
≥2	3.37 (2.11-5.39)	1.2161	<0.001	4

The table shows the points for each of the 5 independent predictors (P: prior procedures; A: age; D: depressed estimated glomerular filtration rate; I: immunocompromised; and T: type of procedure).

Abbreviations as in Tables 2 and 3.

TABLE 5 Internal Validation of the Full Prediction Model and Risk Score Model*

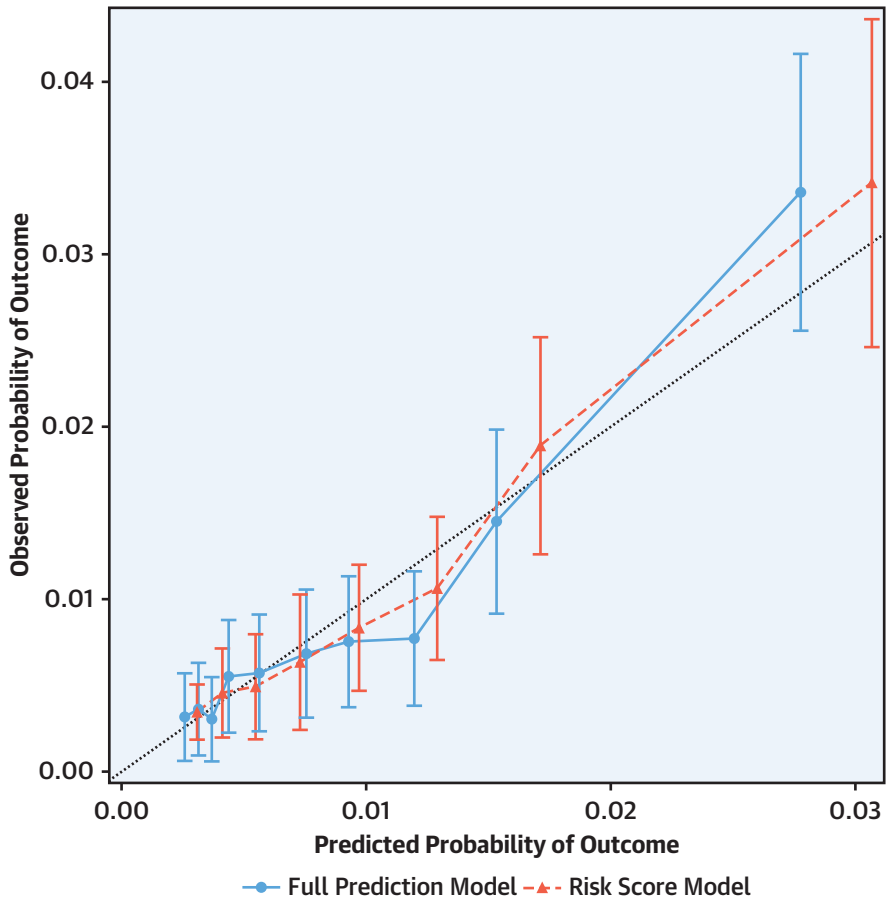
	Full Prediction Model			Risk Score Model		
	Apparent Performance	Average Optimism	Optimism Corrected	Apparent Performance	Average Optimism	Optimism Corrected
Calibration-in-the-large	0.000 (0.149 to 0.149)	0.001	-0.001 (-0.150 to 0.147)	0.000 (-0.149 to 0.149)	0	0.000 (-0.149 to 0.149)
Calibration slope	1.000 (0.814 to 1.186)	0.064	0.936 (0.750 to 1.122)	1.000 (0.813 to 1.187)	-0.01	1.010 (0.823 to 1.197)
C-statistic	0.715 (0.671 to 0.755)	0.011	0.704 (0.660 to 0.744)	0.710 (0.669 to 0.750)	0.008	0.702 (0.661 to 0.741)

*The performances of the full prediction model and risk score model were assessed by calibration and discrimination. All the measures were corrected for optimism by bootstrapping 200 samples from the original data.

(18). In particular, many patients are not aware of the substantial risk and clinical significance of infection (18). It can be estimated that an 85-year-old man with renal dysfunction who has reached elective replacement of his second primary prevention ICD has a PADIT infection risk score of 7 and, therefore, a device infection risk of 4.33% with conventional antibiotics.

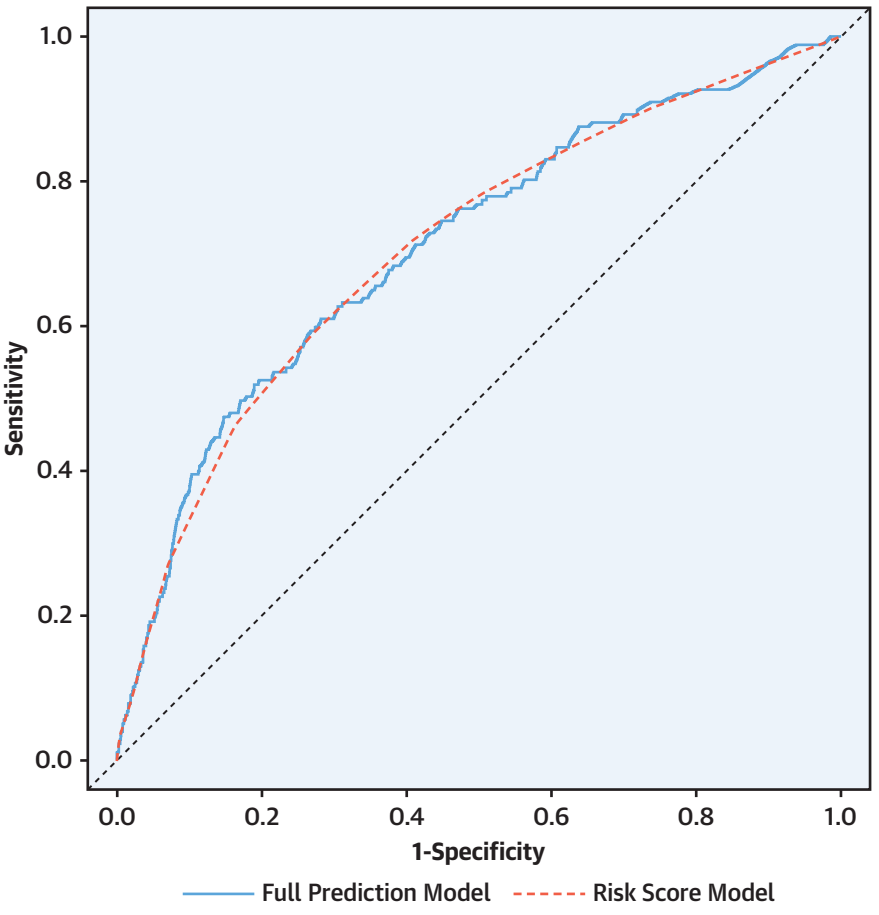
Subgroup analysis of the primary outcome according to PADIT infection risk score shows a largely

FIGURE 1 Calibration Plot of Predicted Probability Versus Observed Probability of Hospitalization for Device Infection for the Full Prediction and Risk Score Models



We internally validated the performance of the full prediction model and risk score model using a bootstrapping method. After correction for optimism, calibration-in-the-large was close to 0 and calibration slope was close to 1, indicating good agreement between observed and predicted risk.

FIGURE 2 Receiver Operating Characteristic Curve for Hospitalization for Device Infection for the Full Prediction and Risk Score Models



The full prediction model was able to discriminate patients with and without hospitalization for device infection with an optimism-corrected C-statistic of 0.704 (95% confidence interval: 0.660 to 0.744). The risk score model showed similar discriminative capacity (optimism-corrected C-statistic: 0.702; 95% confidence interval: 0.661 to 0.741).

TABLE 6 Subgroup Analysis of Adjudicated Primary Outcome According to PADIT Infection Risk Score

PADIT* Risk Score	All		Conventional		Incremental		Incremental vs. Conventional
	n/N	%	n/N	%	n/N	%	OR (95% CI)†
0	18/5,203	0.35	12/2,612	0.46	6/2,591	0.23	0.51 (0.19-1.37)
1	12/2,626	0.46	6/1,266	0.47	6/1,360	0.44	0.95 (0.30-2.96)
2	10/2,030	0.49	6/992	0.60	4/1,038	0.39	0.63 (0.18-2.26)
3	10/1,573	0.64	3/734	0.41	7/839	0.83	2.08 (0.53-8.09)
4	20/2,396	0.83	14/1,197	1.17	6/1,199	0.50	0.43 (0.16-1.12)
5	25/2,352	1.06	10/1,125	0.89	15/1,227	1.22	1.39 (0.62-3.12)
6	34/1,799	1.89	18/896	2.01	16/903	1.77	0.89 (0.45-1.77)
≥7	48/1,406	3.41	30/693	4.33	18/713	2.52	0.57 (0.31-1.04)

p for interaction = 0.37. (The p value for interaction is from the likelihood ratio test of the interaction term.)
*P: prior procedures; A: age; D: depressed eGFR; I: immunocompromised; T: type of procedure. †Odds ratio (OR) was estimated via a generalized linear mixed model with random cluster effects and random cluster-period effects.
Abbreviations as in Tables 1 and 3.

consistent effect of incremental antibiotic therapy, although there was no statistically significant difference between treatments. With higher event rates, the absolute risk reduction with incremental antibiotics increases. For example, the number needed to treat to prevent 1 infection in patients with a PADIT infection risk score ≥7 can be calculated to be 56. Hence, some physicians may consider incremental antibiotics for these high-risk patients. This would be consistent with expert guidelines that state that vancomycin should be considered for patients at increased risk for surgical site infection (20). However, there was no statistically significant benefit of incremental antibiotics in any risk score subgroup (Table 6). Very recently, the Worldwide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT) found a 40% relative risk reduction when

using an antibiotic envelope, and this could also be an option for patients at higher risk (21).

Another potential use of the PADIT infection risk score is in the inclusion criteria of future device infection prevention trials. For example, if only patients with a score of >7 were included, then it can be estimated that the event rate in the control arm (using standard antibiotics) would be 4.33%. Hence, a sample size of 4,820 would be required to detect a 35% relative risk reduction with the experimental arm.

STUDY LIMITATIONS. The primary limitation of the PADIT infection risk score is potentially missing predictors. Perhaps most importantly, we did not collect data on perioperative management of oral anticoagulation and antiplatelet therapy. Both of these have been shown to increase the risk of pocket hematoma, which, in turn, has been shown to increase the risk of subsequent device infection (4,7). The association with subsequent device infection seems to be related to large hematomas (7), and these are much less common than they were when heparin bridging was used (22,23). Additional potentially important missing predictors include history of previous device infection, presence of a temporary pacemaker at the time of surgery, other comorbidities (e.g., cancer), and so on. (4). Some device infections happen later than 1 year after the index surgery, and we have no data for these patients. Finally, the lack of validation in an independent dataset is another limitation.

CONCLUSIONS

We identified 5 independent predictors of device infection and developed a user-friendly infection risk score. These observations are largely consistent with a meta-analysis of findings from many smaller studies (4). We believe it will be helpful for shared decision making around CIED therapy and for clinical researchers. Further validation and modification with future high-quality datasets are warranted.

ACKNOWLEDGMENTS The authors are indebted to the tireless work of the study coordinators and to our patients

ADDRESS FOR CORRESPONDENCE: Dr. Andrew D. Krahn, Heart Rhythm Vancouver, 211-1033 Davie Street, Vancouver, British Columbia V6E 1M7, Canada. E-mail: akrahn@mail.ubc.ca. Twitter: @ccsprez.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In a large cohort of patients with implanted electronic cardiac devices, hospitalization for infection occurred in 0.90% within 1 year of follow-up. Prior procedures, older patient age, reduced renal function, immunocompromised, and procedure type were significant predictors of device infection.

TRANSLATIONAL OUTLOOK: The predictive value risk of this model should be validated in other study groups.

REFERENCES

1. Krahn AD, Longtin Y, Philippon F, et al. Prevention of Arrhythmia Device Infection Trial: the PADIT trial. J Am Coll Cardiol 2018;72:3098–109.

2. Sohail MR, Uslan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. J Am Coll Cardiol 2007;49:1851–9.

3. Klug D, Balde M, Pavin D, et al. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. Circulation 2007;116:1349–55.

4. Polyzos KA, Konstantelias AA, Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. Europace 2015;17:767–77.

5. Johansen JB, Jorgensen OD, Moller M, Arnsbo P, Mortensen PT, Nielsen JC. Infection after pacemaker implantation: infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients. Eur Heart J 2011;32:991–8.

6. Sohail MR, Henrikson CA, Braid-Forbes MJ, Forbes KF, Lerner DJ. Mortality and cost associated with cardiovascular implantable electronic device infections. Arch Intern Med 2011;171:1821–8.

7. Essebag V, Verma A, Healey JS, et al. Clinically significant pocket hematoma increases long-term risk of device infection: BRUISE CONTROL INFECTION Study. J Am Coll Cardiol 2016;67:1300–8.

8. Baman TS, Gupta SK, Valle JA, Yamada E. Risk factors for mortality in patients with cardiac device-related infection. Circ Arrhythm Electrophysiol 2009;2:129–34.

9. Tarakji KG, Chan EJ, Cantillon DJ, et al. Cardiac implantable electronic device infections: presentation, management, and patient outcomes. Heart Rhythm 2010;7:1043–7.

10. Baddour LM, Epstein AE, Erickson CC, et al. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. Circulation 2010;121:458–77.

11. Connolly SJ, Philippon F, Longtin Y, et al. Randomized cluster crossover trials for reliable, efficient, comparative effectiveness testing: design of the Prevention of Arrhythmia Device Infection Trial (PADIT). Can J Cardiol 2013;29:652–8.

12. Schneeweiss S, Wang PS, Avorn J, Glynn RJ. Improved comorbidity adjustment for predicting mortality in Medicare populations. Health Serv Res 2003;38:1103–20.

13. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015;162:W1–73.

14. Margey R, McCann H, Blake G, et al. Contemporary management of and outcomes from cardiac device related infections. Europace 2010;12:64–70.

15. Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD. Systematic review of risk prediction scores for surgical site infection or periprosthetic joint infection following joint arthroplasty. Epidemiol Infect 2017;145:1738–49.

16. Blough JT, Vu MM, Qiu CS, et al. Beyond 30 days: a risk calculator for longer term

outcomes of prosthetic breast reconstruction. Plast Reconstr Surg Glob Open 2018;6:e2065.

17. Diaconis P. I wish someone had told us the risks and benefits of replacing my father's defibrillator. JAMA Intern Med 2016;176:885.

18. Lewis KB, Nery PB, Birnie DH. Decision making at the time of ICD generator change: patients' perspectives. JAMA Intern Med 2014;174:1508–11.

19. Kramer DB, Buxton AE, Zimetbaum PJ. Time for a change—a new approach to ICD replacement. N Engl J Med 2012;366:291–3.

20. Anderson DJ, Kaye KS, Classen D, et al. Strategies to prevent surgical site infections in acute care hospitals. Infect Control Hosp Epidemiol 2008;29 Suppl 1: S51–61.

21. Tarakji KG, Mittal S, Kennergren C, et al. Antibacterial envelope to prevent cardiac implantable device infection. N Engl J Med 2019; 380:1895–905.

22. Birnie DH, Healey JS, Essebag V. Device surgery without interruption of anticoagulation. N Engl J Med 2013;369:1571–2.

23. Birnie DH, Healey JS, Wells GA, et al. Continued vs. interrupted direct oral anticoagulants at the time of device surgery, in patients with moderate to high risk of arterial thrombo-embolic events (BRUISE CONTROL-2). Eur Heart J 2018; 39:3973–9.

KEY WORDS antibiotics, cardiac implantable electronic device, implantable cardioverter defibrillator, infection, pacemaker