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Prevention of Arrhythmia Device Infection Trial

The PADIT Trial

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ABSTRACT

BACKGROUND Infection of implanted medical devices has catastrophic consequences. For cardiac rhythm devices, pre-procedural cefazolin is standard prophylaxis but does not protect against methicillin-resistant gram-positive organisms, which are common pathogens in device infections.

OBJECTIVE This study tested the clinical effectiveness of incremental perioperative antibiotics to reduce device infection.

METHODS The authors performed a cluster randomized crossover trial with 4 randomly assigned 6-month periods, during which centers used either conventional or incremental periprocedural antibiotics for all cardiac implantable electronic device procedures as standard procedure. Conventional treatment was pre-procedural cefazolin infusion. Incremental treatment was pre-procedural cefazolin plus vancomycin, intraprocedural bacitracin pocket wash, and 2-day post-procedural oral cephalexin. The primary outcome was 1-year hospitalization for device infection in the high-risk group, analyzed by hierarchical logistic regression modeling, adjusting for random cluster and cluster-period effects.

RESULTS Device procedures were performed in 28 centers in 19,603 patients, of whom 12,842 were high risk. Infection occurred in 99 patients (1.03%) receiving conventional treatment, and in 78 (0.78%) receiving incremental treatment (odds ratio: 0.77; 95% confidence interval: 0.56 to 1.05; $p = 0.10$). In high-risk patients, hospitalization for infection occurred in 77 patients (1.23%) receiving conventional antibiotics and in 66 (1.01%) receiving incremental antibiotics (odds ratio: 0.82; 95% confidence interval: 0.59 to 1.15; $p = 0.26$). Subgroup analysis did not identify relevant patient or site characteristics with significant benefit from incremental therapy.

CONCLUSIONS The cluster crossover design efficiently tested clinical effectiveness of incremental antibiotics to reduce device infection. Device infection rates were low. The observed difference in infection rates was not statistically significant. (Prevention of Arrhythmia Device Infection Trial [PADIT Pilot] [PADIT]; NCT01002911) (J Am Coll Cardiol 2018;72:3098–109) © 2018 by the American College of Cardiology Foundation.

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With the increased use of implantable medical devices in orthopedic, cardiovascular, and other areas of medicine, device infection has become a major problem. *Staphylococcus aureus* and *S. epidermidis* have emerged as the most common pathogens in patients receiving medical devices, which can be difficult to treat or prevent due to antibiotic resistance (1-3). Cardiac implantable electronic device (CIED) infection has been reported to occur in ~2% of all cases, and the risk is 2% to 4% in high-risk patients (2-7). The treatment cost of device infection is high, with case costs of US$146,000 attributed to hospitalization, long courses of intravenous (IV) antibiotics and frequent need for system removal (4-9). Prevention of infection is a major concern for device implant centers, which use standard policies to optimize outcomes.

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The conventional approach to prevention of device infection, based on several small randomized trials, is single pre-operative infusion of cefazolin, which is supported by guidelines (10). Incremental antibiotic measures are not supported by evidence from randomized trials (11).

However, even though cefazolin is active against most gram-positive bacteria and some gram-negative bacteria, approximately 20% of device infections are due to organisms that are resistant to cefazolin (also referred to as "methicillin-resistant" organisms) (12). Because virtually all gram-positive organisms that are implicated in CIED infection are sensitive to vancomycin, and the majority are sensitive to bacitracin (13), we hypothesized that an incremental antibiotic policy that included preprocedural infusion of both cefazolin and vancomycin, plus intraprocedural bacitracin wash followed by a 2-day course of postoperative antibiotics would reduce the 1-year risk of hospitalization for device infection as compared with conventional cefazolin alone.

Because device procedures are most frequently performed in larger centers using standard operating procedures, we considered that a cluster randomized crossover trial would be an optimal design to test whether an institutional standard policy of incremental antibiotics would reduce device infection. In this design, each institution is randomized to 1 of 2 antibiotic prophylaxis regimens, with randomized crossover between these regimens, such that institutions would switch randomly between the 2 antibiotic regimens every 6 months. We calculated that the crossover would substantially reduce the loss of power due to the cluster approach and result in substantial trial efficiency.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CIED = cardiac implantable electronic device

CRT = cardiac resynchronization therapy

ICC = intra-class correlation

ICD = implantable cardioverter-defibrillator

IPC = interperiod correlation

IV = intravenous

OR = odds ratio

METHODS

TRIAL DESIGN. The design of the PADIT (Prevention of Arrhythmia Device Infection Trial) has previously been described (14). The primary hypothesis of the PADIT trial was that an institutional policy of incremental antimicrobial prophylaxis would reduce the

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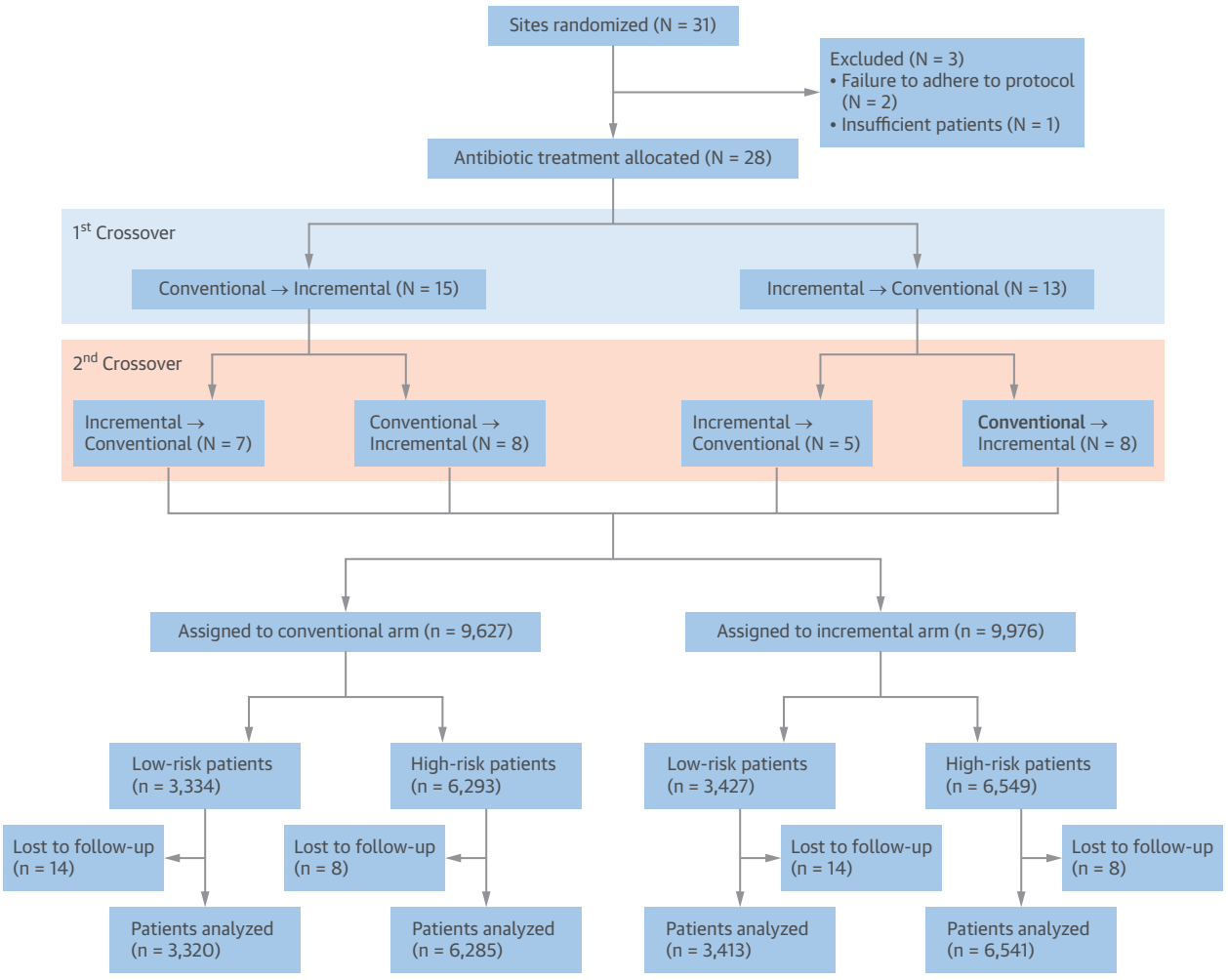
FIGURE 1 Consort Diagram of Center and Patient Participation in the PADIT Trial



Sites were randomized to 6-month periods of antibiotic prevention regimens with ascertainment of subsequent hospital admission for device infection.
PADIT = Prevention of Arrhythmia Device Infection Trial.

risk of hospitalization for device infection, compared with a conventional strategy of a single dose of pre-procedural antibiotic, in high-risk patients undergoing device procedures. A cluster randomized 4-period crossover design was employed, with center involvement and participant involvement summarized in Figure 1. Each participating hospital was randomized to any of 4 sequences of incremental (I) and conventional (C) strategies (i.e., ICIC, ICCI, CICI, CIIC). Sites were not informed of their sequence or of what regimen would be used until the end of each period. Each therapy period lasted for 6 months for the 27 Canadian sites. The Netherlands sites, which joined the trial later, were permitted to shorten enrollment and transition periods once 35 patients and at least 3 months of enrollment were complete in each period. There was a 2- to 4-week transition phase between each of the 4 study periods.

All patients at each center received the antibiotic strategy to which the center was randomized at the time, as standard procedure during each study period. Three sites were excluded from the trial early in the first period of participation because of failure to adhere to the randomized protocol (n = 2) and because of insufficient patients (n = 1). These exclusions were made without any knowledge by the steering committee of the treatment allocation or the number of infections at the site. One site restarted the first period after compliance with the protocol was corrected.

PATIENTS. All centers collected data on high-risk patients, and 6 centers collected data on both high-risk and low-risk patients. The high-risk patients were defined as those with: 1) any repeat procedure on an existing pocket (generator replacement, system revision or upgrade including any lead procedure); or 2) any cardiac resynchronization therapy (CRT) procedure (15-18). Low-risk patients were all other patients undergoing implantation, primarily new pacemaker and implantable cardioverter-defibrillator (ICD) implants.

ANTIBIOTIC TREATMENT REGIMENS. As per current guidelines (10), the conventional antibiotic strategy was a single dose of pre-operative antibiotics: cefazolin 1 to 2 g IV 60 min before skin incision or vancomycin 1 to 1.5 g IV administered within 120 min before skin incision in penicillin-allergic patients. In the incremental antibiotic strategy, patients received IV cefazolin as well as pre-operative vancomycin as outlined in the preceding text. Penicillin-allergic patients only received vancomycin. The incremental antibiotic strategy also included intraoperative wound pocket wash before skin closure (bacitracin 50,000 U diluted in 50 ml of saline) and post-operative oral cephalexin 500 mg 4 times/day, or cephadroxil 1,000 mg twice daily for 2 days. Penicillin-allergic patients received clindamycin 150 to 300 mg at 3 times/day. At all sites in the Netherlands and at 1 site in Canada, bacitracin was not available, and a saline or cefazolin pocket wash was used.

OUTCOMES. The primary outcome of the trial was admission to hospital for proven CIED or pocket infection within 1 year of the procedure. The definition of infection was adapted from standard definitions at the start of the trial, and categorized into pocket infection, bloodstream infection, and endocarditis (detailed definitions are in the Online Appendix). Blinded adjudication was performed by 2 investigators (Y.L. and P.G.) blinded to treatment received, with all discrepancies resolved by the adjudication committee. Adjudication materials included clinical records including culture and sensitivities of any organisms from blood or wound cultures. Outcomes were identified by sites with collection of source data regarding the hospitalization and infection characteristics.

STATISTICAL ANALYSIS. We estimated the intraclass correlation (ICC) and interperiod correlation (IPC) from the Ontario Institute for Clinical and Evaluation Sciences ICD registry involving 5,176 patients in a comprehensive single-provider system (19). The ICC in that registry was 0.015, and we assumed that both IPC and ICC in the PADIT trial would be the same. On the basis of published reports, we estimated that device infection rate would be 2.0%/year among high-risk patients receiving conventional treatment (2-7). On the basis of these assumptions, we estimated that treatment of 100 patients for each of 4 treatment periods per site (26 sites in total) would be required to achieve 80% power of detecting a 35% relative risk reduction with a 2-sided significance level of 0.05. To allow for 4% loss to follow-up and death during follow-up, the target was to treat 10,800 patients.

The primary statistical analysis was on the high-risk cohort, and secondarily on the total patient

TABLE 1 Cluster Characteristics for the Overall Population

Sites	28
Total cluster size	436.5 (164.5–877.0)
Cluster-period size	109.5 (41.0–219.5)
Country	
Canada	24 (85.7)
the Netherlands	4 (14.3)
Allocation sequence*	
CIIC	7 (25.0)
CICI	8 (28.6)
ICIC	5 (17.9)
ICCI	8 (28.6)
Starting year	
2012	1 (3.6)
2013	20 (71.4)
2014	5 (17.9)
2015	2 (7.1)
Consent for data collection	10 (35.7)
No. of operators	5.5 (3.5–6.5)
Site operator cardiologist vs. surgeon or mixed operator team	14 (50.0)
Implant location	
EP lab only	16 (57.1)
Operating room only	7 (25.0)
Both EP lab and operating room	5 (17.9)
No. of PM generator replacements/yr	86.0 (46.0–112.0)
No. of ICD generator replacements/yr	34.0 (15.0–63.0)
No. of CRT generator replacements/yr	14.5 (5.0–26.0)
No. of pocket/lead revision/system upgrade/yr	48.5 (27.5–80.0)
No. of new CRT PM/defibrillator/yr	35.5 (20.0–53.5)
% Cases with trainee	20.0 (0.0–95.0)
Type of hospital	
Tertiary care	21 (75.0)
Other	7 (25.0)
Antiseptic skin preparation	
Chlorhexidine	26 (92.9)
Iodine	1 (3.6)
Both	1 (3.6)
Skin barrier	14 (50.0)
Intranasal *S. aureus* decolonization	3 (10.7)

Values are n, median (interquartile range), or n (%). *Sequences are combinations of incremental (I) and conventional (C) strategies.

CRT = cardiac resynchronization therapy; EP = electrophysiology; ICD = implantable cardioverter-defibrillator; PM = pacemaker.

TABLE 2 Baseline Characteristics of the Study Population

	High-Risk Patients				All Patients			
	All	Conventional	Incremental	p Value*	All	Conventional	Incremental	p Value*
Baseline CRF received	12,842	6,293	6,549		19,603	9,627	9,976	
Demographics and medical history								
Age, yrs	72.0 ± 13.0	71.9 ± 13.1	72.2 ± 13.0	0.27	72.0 ± 13.1	72.1 ± 13.2	72.0 ± 13.0	0.53
Female	4,174 (32.5)	2,106 (33.5)	2,068 (31.6)	0.022	6,652 (33.9)	3,342 (34.7)	3,310 (33.2)	0.023
Diabetes	3,323 (25.9)	1,616 (25.7)	1,707 (26.1)	0.62	5142 (26.2)	2,496 (25.9)	2,646 (26.5)	0.34
History of heart failure	5,966 (46.5)	2,928 (46.5)	3,038 (46.4)	0.87	7,843 (40.0)	3,838 (39.9)	4,005 (40.1)	0.69
Renal insufficiency	2,234 (17.4)	1,026 (16.3)	1,208 (18.4)	0.001	3,275 (16.7)	1,537 (16.0)	1,738 (17.4)	0.006
Penicillin allergy	1,303 (10.1)	628 (10.0)	675 (10.3)	0.54	2,001 (10.2)	975 (10.1)	1,026 (10.3)	0.72
Immunocompromised	191 (1.5)	90 (1.4)	101 (1.5)	0.60	322 (1.6)	159 (1.7)	163 (1.6)	0.92
Type of procedure								
New pacemaker	0 (0.0)	0 (0.0)	0 (0.0)	–	4,646 (23.7)	2,321 (24.1)	2,325 (23.3)	0.19
New ICD	0 (0.0)	0 (0.0)	0 (0.0)	–	2,115 (10.8)	1,013 (10.5)	1,102 (11.0)	0.24
Pacemaker generator replacement	4,960 (38.6)	2,416 (38.4)	2,544 (38.8)	0.60	4,960 (25.3)	2,416 (25.1)	2,544 (25.5)	0.51
ICD generator replacement	2,125 (16.5)	1,045 (16.6)	1,080 (16.5)	0.86	2,125 (10.8)	1,045 (10.9)	1,080 (10.8)	0.95
CRT generator replacement	831 (6.5)	419 (6.7)	412 (6.3)	0.40	831 (4.2)	419 (4.4)	412 (4.1)	0.44
Pocket or lead revision/update	2,994 (23.3)	1,470 (23.4)	1524 (23.3)	0.91	2,994 (15.3)	1,470 (15.3)	1,524 (15.3)	0.99
New CRT pacemaker	510 (4.0)	230 (3.7)	280 (4.3)	0.07	510 (2.6)	230 (2.4)	280 (2.8)	0.07
New CRT defibrillator	1,839 (14.3)	945 (15.0)	894 (13.7)	0.027	1,839 (9.4)	945 (9.8)	894 (9.0)	0.04
Duration of procedure				0.46				0.39
<1 h	8,580 (66.8)	4,216 (67.0)	4,364 (66.6)		13,758 (70.2)	6,770 (70.3)	6,988 (70.0)	
1 to 1.5 h	2,022 (15.7)	972 (15.4)	1,050 (16.0)		3,288 (16.8)	1,595 (16.6)	1,693 (17.0)	
>1.5 to 2 h	1,053 (8.2)	539 (8.6)	514 (7.8)		1,266 (6.5)	648 (6.7)	618 (6.2)	
>2 h	1,159 (9.0)	553 (8.8)	606 (9.3)		1,229 (6.3)	583 (6.1)	646 (6.5)	
Other procedure on pocket	2,662 (20.7)	1,235 (19.6)	1,427 (21.8)	0.002	2,665 (13.6)	1,235 (12.8)	1,430 (14.3)	0.002
Number of other procedures				0.002				0.002
1 other procedure	1,968 (15.3)	891 (14.2)	1,077 (16.4)		1,971 (10.1)	891 (9.3)	1,080 (10.8)	
2 other procedures	519 (4.0)	250 (4.0)	269 (4.1)		519 (2.6)	250 (2.6)	269 (2.7)	
>2 other procedures	175 (1.4)	94 (1.5)	81 (1.2)		175 (0.9)	94 (1.0)	81 (0.8)	
Other procedure performed within last month	52 (0.4)	22 (0.3)	30 (0.5)	0.33	52 (0.3)	22 (0.2)	30 (0.3)	0.33

Values are n, mean ± SD, or n (%). Additional characteristics of the population are summarized in the Online Appendix. *p value is from chi-square test for categorical variables and 2-sample Student's *t*-test for continuous variables.

CRF = case report form; other abbreviations as in Table 1.

population, using the intention-to-treat approach. Comparisons of baseline characteristics between conventional and incremental treatments were conducted with use of the 2-sample Student's *t*-test for continuous variables and chi-square test for categorical variables. A hierarchical logistic regression model adjusting for random cluster effect and random cluster-period effect was used to assess the effect of conventional versus incremental antibiotic treatments on risk of hospitalization for infection and other secondary outcomes. Odds ratio (OR) and 95% confidence interval (CI) were reported. ICC and IPC were estimated using a linear mixed model. Homogeneity of treatment effect across the pre-defined subgroups according to cluster, patient, and procedure characteristics was performed by testing an interaction term in the hierarchical logistic model. Three pre-defined sensitivity analyses were performed to examine the robustness of treatment effect observed in the primary analysis: 1) the hierarchical logistic model was adjusted for country, cluster size, percentage of cases with trainee, antiseptic skin preparation, age, sex, history of diabetes, heart failure, renal insufficiency, immunocompromise, type and duration of procedure, and penicillin allergy; 2) the primary analysis was repeated using the on-treatment population (all antibiotics administered, including complete infusion before skin incision); and 3) erosion was excluded from the primary outcome. All analyses were performed with SAS software, version 9.4 (SAS institute, Cary, North Carolina). Statistical significance was established at 0.05 with no adjustment for multiple comparisons.

All centers' ethics boards approved the trial with waiver of consent for treatment. Ten centers required patient consent for data collection, which was generally obtained during follow-up. The steering committee designed the study. The authors attest to

the accuracy and completeness of the reported data. The study was coordinated by the Population Health Research Institute at McMaster University. The principal investigator (A.D.K.) located at the University of British Columbia wrote the first draft of the manuscript, and all coauthors critically approved the final version.

RESULTS

CENTERS. The study was performed between December 2012 and September 2016. There were 24 centers in Canada and 4 in the Netherlands (**Figure 1, Table 1**). The median number of patients undergoing a procedure per treatment period per site was 110. Twenty-one centers were tertiary care centers (75%). The median number of operators per center was 5.5.

PATIENTS. A total of 19,603 patients across 28 centers having device procedures were included in the data collection, of which 12,842 patients were high risk (**Table 2**). The mean age was 72.0 ± 13.1 years, 40% of patients had a history of heart failure, and one-third were female. Most high-risk patients underwent generator change (n = 7,916; 61.6%). There were minor imbalances in baseline characteristics between arms of the study with respect to sex, renal insufficiency, proportion with a new CRT system, and number of preceding pocket procedures.

COMPLIANCE WITH ALLOCATED THERAPY. For patients treated during conventional therapy periods, antibiotics were administered pre-operatively in 9,605 (99.8%) (Online Table 1). Protocol noncompliance under the conventional treatment was mostly due to use of antibiotic pocket wash or post-operative antibiotic. For patients treated during incremental therapy periods, all 4 components of the intervention were administered to 8,922 (89.4%). Noncompliance was most commonly due to failure to administer post-operative oral antibiotic (5.6%). Noncompliance was greater in the incremental arm than in the conventional arm ($p < 0.001$).

OUTCOMES. Hospitalization for infection occurred in 99 (1.03%) patients receiving conventional treatment and in 78 (0.78%) receiving incremental treatment (OR: 0.77; 95% CI: 0.56 to 1.05; $p = 0.10$) (**Table 3**). In high-risk patients, infection occurred in 77 (1.23%) patients receiving conventional treatment and in 66 (1.01%) receiving incremental treatment (OR: 0.82; 95% CI: 0.59 to 1.15; $p = 0.26$). Most events were deep skin and pocket infection (86.7%). Infection requiring surgical intervention occurred in 66 patients receiving conventional treatment (1.05% overall, 86% of infections), and in 62 patients receiving incremental treatment (0.95% overall need for surgical intervention; 94% of infections; OR: 0.90; 95% CI: 0.64 to 1.28; $p = 0.57$). **Figure 2** outlines the forest plot to illustrate evaluation of subgroups for treatment effect. There were no important interactions between treatment effect and baseline, cluster site of procedure, or operator characteristic (Online Table 2). Infection rates analyzed by device type shows a clear gradient of risk from pacemaker to ICD to CRT, with no evidence of interaction between device type and effect of the intervention (**Table 4**).

Microorganisms isolated from infection sites were reviewed by the senior infectious diseases expert (Y.L.), and were mainly gram-positive bacteria (72.3%). On the basis of adjudicated assignment of the main pathogen, *S. aureus* was the most frequently isolated pathogen (31.6%) followed by coagulase-negative staphylococci (29.9%). The etiology of the infections was similar between the 2 treatment arms (Online Table 3). For example, there was no significant difference in the proportion of infections that were due to methicillin-sensitive *S. aureus*, and in the proportion of infections that were polymicrobial. With respect to antimicrobial susceptibility, there was no significant difference in the proportion of organisms that were resistant to cefazolin and vancomycin between the study arms.

Multivariable analyses with adjustment of cluster and patient-level risk factors showed similar results as the primary analysis (Online Table 4). On-treatment analysis including only protocol-compliant patients (all antibiotics administered, including complete infusion before skin incision) (Online Table 4) did not differ from the intention-to-treat analysis (**Table 3**). Adverse events were rare (0.26%), with equivalent adverse events in both arms (Online Table 5).

EFFECT OF USING THE CLUSTER RANDOMIZED CROSSOVER DESIGN. The calculated ICC and IPC after conduct of the study were 0.00077 and 0.00061, respectively, using a linear mixed effects model. Statistical power was re-estimated by applying actual sample size with variable cluster size and actual ICC/IPC values. We estimated that our trial had 86% power to detect the pre-specified 35% difference in infection rates between the 2 treatment arms. The small loss in power due to variation in cluster size and a small difference between the ICC and IPC was compensated for by the extra number of patients recruited. In an analysis that ignored the cluster effect and cluster-period effect, incremental therapy had an OR of 0.82 (95% CI: 0.59 to 1.14) for the high-risk population, and 0.76 (95% CI: 0.56 to 1.02) for

TABLE 3 Primary and Secondary Outcomes of Patients Who Completed Follow-Up*

	High-Risk Patients					
	All (N = 12,826)	Conventional (n = 6,285)	Incremental (n = 6,541)	Incremental vs. Conventional		
				OR†	95% CI	p Value
Hospitalization due to device infection	143 (1.11)	77 (1.23)	66 (1.01)	0.82	0.59–1.15	0.26
Subtype						
Skin, subcutaneous/pocket infection	124 (0.97)	67 (1.07)	57 (0.87)	0.82	0.57–1.17	0.27
Bloodstream infection	34 (0.27)	19 (0.30)	15 (0.23)	0.76	0.38–1.49	0.42
Endocarditis	37 (0.29)	22 (0.35)	15 (0.23)	0.66	0.34–1.27	0.21
Erosion of skin with device exposure	3 (0.02)	1 (0.02)	2 (0.03)	1.96	0.18–21.70	0.58
Bloodstream and/or endocarditis	49 (0.38)	28 (0.45)	21 (0.32)	0.72	0.41–1.28	0.26
Pocket infection and/or erosion	94 (0.73)	49 (0.78)	45 (0.69)	0.89	0.58–1.37	0.59
Requiring surgical intervention						
Yes	128 (1.00)	66 (1.05)	62 (0.95)	0.90	0.64–1.28	0.57
No	15 (0.12)	11 (0.18)	4 (0.06)	0.35	0.11–1.10	0.07
Antibiotics treatment for infection	103 (0.80)	57 (0.91)	46 (0.70)	0.79	0.52–1.20	0.27
Composite of primary outcome and any antibiotics treatment for infection	239 (1.86)	130 (2.07)	109 (1.67)	0.81	0.62–1.05	0.11
Death	1,119 (8.72)	562 (8.94)	557 (8.52)	0.94	0.80–1.09	0.41
Cardiac death	283 (2.21)	145 (2.31)	138 (2.11)	0.91	0.71–1.16	0.44
Vascular noncardiac death	36 (0.28)	18 (0.29)	18 (0.28)	0.89	0.42–1.86	0.75
Noncardiovascular death	272 (2.12)	131 (2.08)	141 (2.16)	1.01	0.77–1.35	0.92
Others	1 (0.01)	1 (0.02)	0 (0.00)	–	–	–
Unknown	527 (4.11)	267 (4.25)	260 (3.97)	0.95	0.77–1.17	0.64

Values are n (%) unless otherwise indicated. *Patients with follow-up time ≥4 weeks or died within 4 weeks. †Odds ratio (OR) was estimated via a generalized linear mixed model with random cluster effects and random cluster-period effects.

CI = confidence interval; OR = odds ratio.

Continued on the next page

the overall population; indicating almost no loss of power due to use of the cluster design.

DISCUSSION

We used a cluster crossover design to test the clinical effectiveness of a policy of incremental antibiotics to prevent implantable device infection, studying almost 20,000 patients treated at 28 centers. Although there was no significant reduction in the rate of hospitalization for infection with this policy, we observed a modest trend in favor of this approach. The ability of the study to demonstrate a statistical difference was limited by a rate of device infection in the conventional treatment arm that was 40% lower than previously reported; and by a more modest observed effect than hypothesized (**Central Illustration**). It was not limited by the use of the cluster crossover design.

Testing the clinical effectiveness of new antibiotic strategies for prevention of uncommon, but serious, infections requires a very large trial to have adequate statistical power. A cluster trial was chosen because devices are often implanted in large centers that use standard procedures in all cases. Cluster trials, however, usually involve large loss of statistical power due to within-cluster correlation. We mitigated this by including crossover between treatment arms within sites. We used multiple crossovers to guard against changes over time. The intracluster and interperiod correlations were in reality very low, so there was little loss of power due to the use of the cluster crossover design, compared with an individual patient randomized design.

The feasibility of executing a trial of this scale was substantially enabled by the use of the cluster crossover design because we randomized centers and not patients, which greatly simplified execution. We obtained data from administrative sources, simplifying data collection. We obtained waiver of individual patient consent because the trial would not be feasible if individual patient consent were required. Furthermore, ethics boards considered the intervention to be of minimal risk. Also, importantly, these aspects of the trial design allowed us to complete a 19,000-patient trial at a cost of ~$3 million U.S. dollars (~$135 per patient). This study establishes the feasibility and modest cost of this trial design for other types of interventions that meet these criteria

TABLE 3 Continued

All Patients					
			Incremental vs. Conventional		
All (N = 19,559)	Conventional (n = 9,605)	Incremental (n = 9,954)	OR†	95% CI	p Value
177 (0.90)	99 (1.03)	78 (0.78)	0.77	0.56–1.05	0.10
151 (0.77)	83 (0.86)	68 (0.68)	0.79	0.57–1.09	0.15
52 (0.27)	30 (0.31)	22 (0.22)	0.73	0.41–1.29	0.27
50 (0.26)	31 (0.32)	19 (0.19)	0.60	0.33–1.08	0.09
4 (0.02)	2 (0.02)	2 (0.02)	0.98	0.14–6.94	0.98
68 (0.35)	40 (0.42)	28 (0.28)	0.68	0.42–1.10	0.11
109 (0.56)	59 (0.61)	50 (0.50)	0.83	0.55–1.25	0.37
157 (0.80)	83 (0.86)	74 (0.74)	0.87	0.62–1.22	0.43
20 (0.10)	16 (0.17)	4 (0.04)	0.24	0.08–0.72	0.011
146 (0.75)	78 (0.81)	68 (0.68)	0.84	0.56–1.27	0.41
314 (1.61)	171 (1.78)	143 (1.44)	0.81	0.63–1.05	0.11
1,717 (8.78)	873 (9.09)	844 (8.48)	0.91	0.79–1.04	0.18
385 (1.97)	207 (2.16)	178 (1.79)	0.81	0.64–1.03	0.08
50 (0.26)	22 (0.23)	28 (0.28)	1.15	0.61–2.16	0.67
390 (1.99)	199 (2.07)	191 (1.92)	0.90	0.71–1.14	0.38
1 (0.01)	1 (0.01)	0 (0.00)	–	–	–
891 (4.56)	444 (4.62)	447 (4.49)	0.98	0.80–1.20	0.86

with clear equipoise. Examples might include perioperative antithrombotic management or wound care strategies.

Previous studies have consistently reported that device infection rates are increasing as more complex procedures are undertaken in patients with a higher burden of comorbidities (20). Greenspon et al. (20) reported infection rates from 4.2 million device surgery records in the Nationwide Inpatient Sample, wherein the infection rate was steady at 1.5% until an inflection point in 2004, when rates rose to 2.5% through 2008. The device infection rate in our study was much lower than anticipated. We included all patients treated at each center, so the lower rates were not due to patient selection. There may have been a "Hawthorne" effect, insofar as being in a research study led centers to increase vigilance to both antibiotic adherence and surgical technique to minimize infection rate. A nonsignificant trend of reduction in infection rate over time was seen in both arms of the study (Online Table 6), consistent with a health system intervention effect. Rates of infection in Canada and the Netherlands may be lower than in other countries. From a microbiology perspective, we observed no significant change in the microbiology of surgical site infection with the use of the incremental arm. Such observation has also been reported in a similar study in orthopedic surgery in which the addition of vancomycin did not lead to a change in the microbiology of infections (21).

There was no statistically significant difference between treatments, although data do provide modest support for a benefit of incremental antibiotics. However, even if a 20% reduction in infection with incremental antibiotics is true, given the low infection rate that we have documented, a treatment effect of this size would only result in prevention of 1 infection for every 500 patients treated, a number that may be of questionable value unless the absolute risk exceeds some level warranting the intervention. Further work is necessary to determine the potential characteristics of those patients that may benefit from this or any incremental intervention, including the WRAP-IT (World-wide Randomized Antibiotic Envelope Infection Prevention Trial; NCT02277990), evaluating the incremental benefit of an antibiotic-impregnated envelope in high-risk CIED patients.

The organisms causing 65% to 75% of device-related infection are gram-positive bacteria (1), a high proportion of which are resistant to cefazolin but remain sensitive to vancomycin. In addition, expert guidelines state that vancomycin can also be an appropriate agent for specific scenarios, such as a proven outbreak or high endemic incidence of surgical site infection due to methicillin-resistant organisms, targeted high-risk patients who are at increased

FIGURE 2 Forest Plot of Subgroup Analysis of the Treatment Effect

Subgroup	Overall	Conventional	Incremental	OR (95% CI)	p value for Interaction
		no. of events/total no. (%)			
Cluster Characteristics					
Country					0.17
Canada	170/18,863 (0.90)	97/9,266 (1.05)	73/9,597 (0.76)	0.73 (0.53-1.01)	
Netherlands	7/696 (1.01)	2/339 (0.59)	5/357 (1.40)	2.37 (0.45-12.47)	
Cluster-Period Size					0.81
≥200	101/12,433 (0.81)	58/6,159 (0.94)	43/6,274 (0.69)	0.74 (0.48-1.13)	
<200	76/7,126 (1.07)	41/3,446 (1.19)	35/3,680 (0.95)	0.80 (0.50-1.27)	
% of Cases with Trainee					0.046
≥20	142/15,667 (0.91)	85/7,716 (1.10)	57/7,951 (0.72)	0.65 (0.46-0.92)	
<20	33/3,747 (0.88)	13/1,822 (0.71)	20/1,925 (1.04)	1.46 (0.72-2.97)	
Patient Characteristics					
Age (Years)					0.98
≤74	69/9,849 (0.70)	39/4,903 (0.80)	30/4,946 (0.61)	0.77 (0.47-1.25)	
>74	108/9,710 (1.11)	60/4,702 (1.28)	48/5,008 (0.96)	0.76 (0.51-1.13)	
Sex					0.69
Female	45/6,637 (0.68)	27/3,338 (0.81)	18/3,299 (0.55)	0.68 (0.37 -1.25)	
Male	132/12,922 (1.02)	72/6,267 (1.15)	60/6,655 (0.90)	0.79 (0.55-1.13)	
Diabetes					0.13
Yes	55/5,131 (1.07)	26/2,492 (1.04)	29/2,639 (1.10)	1.08 (0.63-1.86)	
No	122/14,386 (0.85)	73/7,102 (1.03)	49/7,284 (0.67)	0.66 (0.45-0.96)	
Renal Insufficiency					0.50
Yes	41/3,266 (1.26)	24/1,533 (1.57)	17/1,733 (0.98)	0.63 (0.33-1.19)	
No	136/16,165 (0.84)	75/8,000 (0.94)	61/8,165 (0.75)	0.80 (0.56-1.14)	
Penicillin Allergy					0.85
Yes	28/1,997 (1.40)	16/973 (1.64)	12/1,024 (1.17)	0.72 (0.33-1.53)	
No	149/17,552 (0.85)	83/8,626 (0.96)	66/8,926 (0.74)	0.77 (0.55-1.09)	
Procedure Characteristics					
Duration					0.26
≥1 h	78/5,770 (1.35)	40/2,824 (1.42)	38/2,946 (1.29)	0.92 (0.58-1.45)	
<1 h	98/13,727 (0.71)	59/6,750 (0.87)	39/6,977 (0.56)	0.65 (0.42-0.98)	
Risk Level					0.29
High	143/12,826 (1.11)	77/6,285 (1.23)	66/6,541 (1.01)	0.82 (0.59-1.16)	
Low	34/6,733 (0.50)	22/3,320 (0.66)	12/3,413 (0.35)	0.54 (0.26-1.10)	
Skin Barrier					0.67
Yes	111/10,973 (1.01)	61/5,423 (1.12)	50/5,550 (0.90)	0.81 (0.54-1.21)	
No	66/8,586 (0.77)	38/4,182 (0.91)	28/4,404 (0.64)	0.70 (0.42-1.18)	
Overall	177/19,559 (0.90)	99/9,605 (1.03)	78/9,954 (0.78)	0.77 (0.56-1.05)	

A uniform nonsignificant trend toward benefit is noted across a broad range of sites, procedures, and patient characteristics. CI = confidence interval; OR = odds ratio.

TABLE 4 Primary Outcome by Device Type

	All	Conventional	Incremental	Incremental vs. Conventional OR With 95% CI	p Value for Interaction
Type of procedure					0.92
CRT/revision/upgrade	104/6,103 (1.70)	57/3,021 (1.89)	47/3,082 (1.52)	0.81 (0.54–1.21)	
ICD	35/4,061 (0.86)	20/1,962 (1.02)	15/2,099 (0.71)	0.70 (0.36–1.39)	
Pacemaker	38/9,395 (0.40)	22/4,622 (0.48)	16/4,773 (0.34)	0.72 (0.37–1.38)	

Values are n/N (%) unless otherwise indicated. Infection rates were significantly different between the 3 device types (all pairwise comparisons $p < 0.01$). There was no interaction between device type and treatment effect.

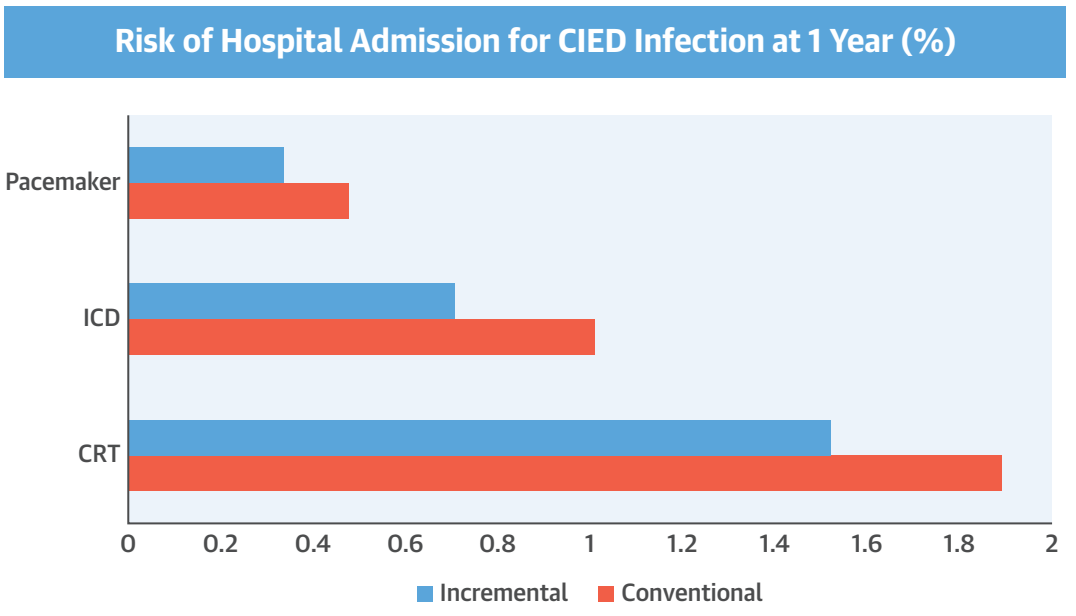
Abbreviations as in Tables 1 and 3.

risk for surgical site infection due to methicillin-resistant organisms, and high-risk surgical procedures (22).

Consequently, vancomycin was the foundation of the incremental intervention tested in the PADIT trial, in conjunction with pocket wash and post-operative cephalosporin known to have broad antimicrobial effects including gram-positive species. The prolongation of cephalosporin prophylaxis by the addition of a 2-day course of oral post-operative antibiotics was based on studies and expert guidelines in cardiac surgery that suggested a potential benefit of prolonged prophylaxis, where the pathophysiology and microbial pattern are similar (22–25).

The findings of our study are relevant to a broad range of other surgical procedures in which a foreign body is implanted (e.g., joint arthroplasty, prosthetic valves, shunts). A single dose of pre-operative antibiotic is recommended for these procedures, yet post-operative infections are commonly due to cefazolin-resistant organisms. Whether the addition of vancomycin to cefazolin could further decrease the incidence of infection remains uncertain. The modest possible benefit seen in the PADIT trial should be

CENTRAL ILLUSTRATION Summary of Infection Risks Across Device Platforms in the Prevention of Arrhythmia Device Infection Trial



Krahn, A.D. et al. J Am Coll Cardiol. 2018;72(24):3098–109.

The consistent modest reduction seen across device types was not significantly different. CIED = cardiac implantable electronic device; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator.

carefully weighed against the potential risks of this intervention, such as the development of antibiotic resistance and toxicity. Adverse events were rare in the PADIT trial, though data collection processes would not have accurately detected apparently unrelated effects on resistance with subsequent non-device infections.

STUDY LIMITATIONS. The PADIT trial was designed as a pragmatic trial that combined multiple interventions to prevent CIED infection. The cluster randomized crossover design may have reduced our ability to detect a difference in outcomes compared with a conventional patient-level randomized trial. Analytic approaches to assess this suggested that the study design retained sufficient power to test the hypothesis. The chosen strategy for infection reduction was based on best practices, steering committee consensus, and agents easily translated into clinical practice. An alternate choice of agents in the PADIT trial may have yielded a more potent treatment effect, because subsequent development of slow-release antibiotic pouches, alternate wash or topical agents, or more prolonged oral antibiotics may have yielded a great reduction in infection. Finally, the very low infection rate could in principle reflect missed outcomes based on the pragmatic nature of the trial. Robust efforts within a single-provider health care system make this an unlikely, albeit potential confounder in detecting both more outcomes and resultant treatment effect.

CONCLUSIONS

This cluster randomized crossover trial failed to demonstrate a significant reduction in device infection with a policy of multiple-component incremental antibiotics, though a uniform effect across subgroups was noted. The observed infection rate was lower than previous reports. The cluster crossover design with patient waiver of consent was shown to be highly efficient, practical, and inexpensive for testing changes in treatment policy, and the design could be used in many areas of medical and surgical practice.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Compared with conventional antibiotic prophylaxis with periprocedural cefazolin in patients undergoing implantation of electronic cardiac arrhythmia devices, a more aggressive multicomponent antibiotic regimen provided no significant efficacy advantage in preventing device-related infections.

TRANSLATIONAL OUTLOOK: Future studies should examine systems of care that reduce the risk of device-related infections without exposing patients to the potential toxicity associated with administration of multiple antibiotics in the periprocedural period.

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KEY WORDS antibiotics, implantable cardioverter defibrillator, infection, pacemaker, prophylaxis

APPENDIX For an expanded Methods section and the supplemental tables, please see the online version of this paper.