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Antibacterial Envelope Is Associated With Low Infection Rates After Implantable Cardioverter-Defibrillator and Cardiac Resynchronization Therapy Device Replacement

Results of the Citadel and Centurion Studies

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ABSTRACT

OBJECTIVE This study sought to determine whether the nonabsorbable TYRX Antibacterial Envelope (TYRX) reduces major cardiovascular implantable electronic device (CIED) infections 12 months after implant.

BACKGROUND TYRX is a monofilament polypropylene mesh impregnated with minocycline and rifampin specifically designed to hold a CIED in place and elute antimicrobials over time. There are limited data on its ability to reduce CIED infections.

METHODS We prospectively enrolled patients who underwent generator replacement with an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy device (CRT), treated with TYRX. The primary endpoints were major CIED infection and CIED mechanical complications. Given the differences in infection rates among ICD and CRT patients, 3 different control populations were used: a published benchmark rate for ICD patients, and both site-matched and comorbidity-matched controls groups for CRT patients.

RESULTS Overall, a major CIED infection occurred in 5 of 1,129 patients treated with TYRX (0.4%; 95% confidence interval: 0.00 to 0.90), significantly lower than the 12-month benchmark rate of 2.2% ($p = 0.0023$). Among the TYRX-treated CRT cohort, the major CIED infection rate was 0.7% compared with an infection rate of 1.0% and 1.3% ($p = 0.38$ and 0.02) in site-matched and comorbidity-matched control groups, respectively. Among the ICD group, the 12-month infection rate was 0.2% compared with the published benchmark of 2.2% ($p = 0.0052$). The most common CIED mechanical complication in study patients was pocket hematoma, which occurred in 18 of the 1,129 patients (1.6%; 95% confidence interval: 0.8 to 2.5), which is comparable with a published rate of 1.6%.

CONCLUSIONS Use of TYRX was associated with a lower major CIED infection rate. (TYRX™ Envelope for Prevention of Infection Following Replacement With a CRT or ICD; [NCT01043861/NCT01043705])
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ABBREVIATIONS AND ACRONYMS

CIED = cardiovascular implantable electronic device

CRT = cardiac resynchronization therapy

CRT-D = cardiac resynchronization therapy with DEFIBRILLATOR

CRT-P = cardiac resynchronization therapy with pacing function only

ICD = implantable cardioverter-defibrillator

TYRX = TYRX antibacterial envelope

Infection is a major complication of cardiovascular implantable electronic device (CIED) therapy and is associated with substantial morbidity, mortality, and expense (1–3). Although systemic antibiotics help reduce CIED infections (4,5), the incidence of CIED infections is increasing (6–9). Hence, novel adjunctive measures to prevent infection could improve CIED therapy outcomes.

The TYRX antibacterial envelope (TYRX), impregnated with minocycline and rifampin, was cleared by the Food and Drug Administration in 2008 for stabilization of CIED implants. The first-generation TYRX is made of nonabsorbable polypropylene mesh and elutes over time. Although an absorbable version was recently cleared for use, all patients in this study were treated with the first-generation, nonabsorbable product. Several nonrandomized retrospective studies have demonstrated that TYRX use is associated with a 60% to 100% relative risk reduction for CIED infection (10–12). However, TYRX envelope performance in a large, prospective CIED population has not been previously reported.

We report on the findings of 2 prospective registry studies conducted to evaluate the effectiveness of TYRX in reducing CIED infections in high-risk patients undergoing implantable cardioverter-defibrillator (ICD) (Citadel Study) and cardiac resynchronization therapy (CRT) (Centurion Study) implantations.

METHODS

STUDY DESIGN. Citadel and Centurion were separate multicenter, prospective, cohort studies that enrolled patients undergoing CIED replacement or upgrade with an ICD (Citadel) or CRT (Centurion) with TYRX. After the interim analysis in 2012, the studies were combined and the analysis plan was updated to analyze patients with TYRX in a single analysis.

The CIED procedure was performed according to usual standards of care including administration of pre-procedural intravenous antibiotics.

Patient follow-up visits were scheduled for 1 to 8 weeks, 3 months, 6 months, and 12 months after implantation. At each visit, wound sites were inspected and patients were assessed for presence of CIED infection, mechanical complication, and other adverse events. The trial protocol was approved by the institutional review board at each participating center, or a central institutional review board registered with the Food and Drug Administration and the Office of Human Rights Protections (Goodwyn Institutional Review Board, Cincinnati, Ohio). All patients provided written, informed consent.

STUDY POPULATION. Eligible patients included those >18 years old undergoing CIED replacement with an ICD (Citadel) or CRT (Centurion), were >18 years with a TYRX (**Figure 1**), and could follow-up in person. Use of an antibiotic eluting flat sheet (TYRX ST Antibacterial Soft Tissue Device, TYRX, Inc., Monmouth Junction, New Jersey) was permitted in lieu of the TYRX Envelope. The antibiotic eluting flat sheet was used in <5% of patients.

Patients were excluded from enrollment if they had a contraindication to receiving TYRX, a current CIED infection, a planned lead extraction, a clinical diagnosis of an active infection at the time of the CIED procedure, were pregnant, could not provide appropriate signed informed consent, had a life expectancy of <6 months, or were expected to undergo heart transplantation within 6 months.

CONTROL GROUPS. Both studies were nonrandomized registries; hence, no formal control group was used. In an attempt to place the findings in proper context, previously published or site-matched and comorbidity-matched controls were used. Additionally, because complication rates differ between ICD

Inc., Spectranetics, and Boston Scientific. Dr. Pachulski was the local principal investigator for contracted research for the Citadel/Centurion Studies and received support from TYRX, Inc. Dr. Dan was the local principal investigator for contracted research for the Citadel/Centurion Studies and received support from TYRX, Inc. Dr. Paladino was the local principal investigator for contracted research for the Citadel/Centurion Studies and received support from TYRX, Inc. Dr. Gleed was the local principal investigator for contracted research for the Citadel/Centurion Studies and received support from TYRX, Inc. Dr. Hanna was the local principal investigator for contracted research for the Citadel/Centurion Studies and received support from TYRX, Inc. Dr. Cheng is employed by Medtronic, Inc., and holds equity ownership in the company. Dr. Lexcen is employed by Medtronic, Inc. Dr. Simons was the local principal investigator for contracted research for the Citadel/Centurion Studies and received support from TYRX, Inc. The Citadel/Centurion Studies were sponsored by TYRX, Inc. Employees of the sponsor participated in the study design and study process, but were blinded to the adjudicated primary endpoint data from the Clinical Events Committee and statistical analyses until the results were reported by the Interim Data Monitoring Committee.

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FIGURE 1 The TYRX Antibacterial Envelope

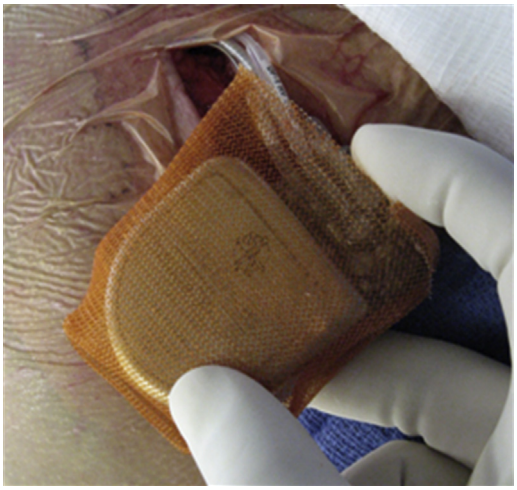


Image courtesy of Christopher R. Ellis, MD, FACC, Vanderbilt Heart and Vascular Institute, Tennessee.

and CRT implants, different control groups were selected to compare the relative event rates for the ICD and CRT cohorts. For the ICD cohort, a 12-month published rate of 2.2% was used (13). For the CRT cohort, 2 control groups were used: a retrospective site-matched control group and retrospective comorbidity-matched control group-derived Medicare claims data. The supplemental material provides details on the selection of control groups.

STUDY ENDPOINTS. The 2 primary endpoints of the study were major CIED infection and CIED mechanical complication (14,15). Major CIED infection was defined according to the Centers for Disease Control and Prevention's surgical site infection criteria (16) as a device infection involving any part of the anatomy other than the incision or subcutaneous tissue, which was opened or manipulated during the CIED implantation operation, or as endocarditis defined according to the modified Duke Criteria (17) (Online Table S1).

CIED mechanical complications included generator or lead malfunction requiring pocket revision, generator or lead dislodgement or migration, lead fracture, skin erosion, wound dehiscence, and generator pocket hematoma (Online Table S1).

All primary clinical endpoints and deaths were adjudicated by an independent Clinical Events Committee consisting of 2 CIED implanting physicians and an infectious disease physician (Online Table S2). The Clinical Events Committee reviewed all adverse events and primary outcome events. Strict definitions for CIED infection were used to minimize bias. Two Clinical Events Committee members adjudicated endpoint events. In the event of disagreement, a third member provided final ruling.

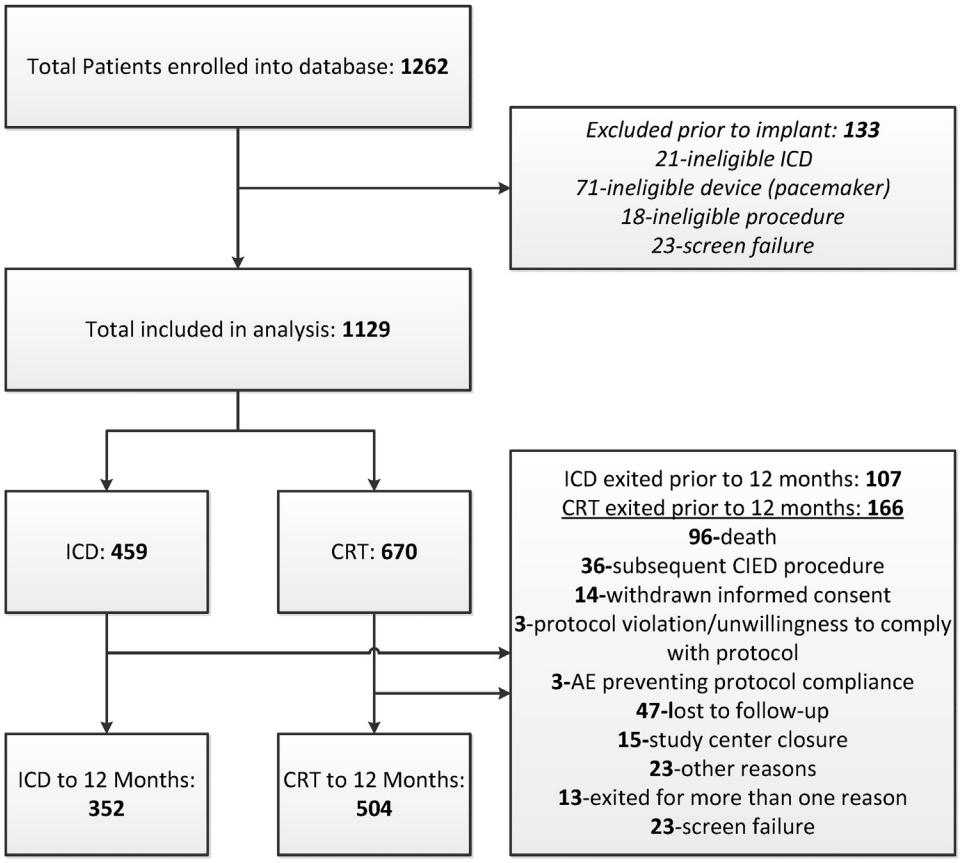
STATISTICAL ANALYSIS. A pre-specified interim analysis of events occurring during the first 3 months after implantation was completed for the first 1,000 subjects enrolled in both studies. The analysis compared the incidence of major CIED infection with a success criteria set as follows: 1,000 subjects from Citadel and Centurion have an infection rate with a statistically significant reduction of the upper bound of a 1-sided 95% confidence interval as compared with the Gould et al. (13) 3-month benchmark rate of 1.88%. The alpha was set to 0.05.

The primary efficacy endpoint, major CIED infection rate at 12 months, was estimated using a 4-sided Clopper-Pearson 95% confidence interval for each treatment group (18). A 2-sample, 1-sided Fisher exact test was used to test the primary efficacy endpoint versus the benchmark rate and to compare the rates of major CIED infection in the CRT cohort and the site-matched retrospective controls. A site-adjusted comparison of the CRT cohort and the site-matched retrospective controls was also conducted using logistic regression, with random site effects. All other statistical testing between cases and controls were performed using a Fisher exact test, chi square test, or Student *t* test. Testing versus the comorbidity-matched rates for both infections and mortality used 1-sample tests. The comorbidity matched rates are based on all Medicare data and not a sample; hence, values are considered fixed and not estimates. The tests of the infection rates against the comorbidity-matched infection rates were 1-sided, exact binomial tests (i.e., Clopper-Pearson tests). The mortality tests are based on the Kaplan-Meier estimated mortality rates and their standard error at the given timepoint. Two-sample, 2-sided *t* tests were used for the case versus control tests and 1-sample, 2-sided *t* tests for the comparison with the fixed comorbidity-matched rate.

MEDICARE DATABASE COMORBIDITY-MATCHED CONTROLS. To match the entire population of Medicare controls with CRT patients, an inverse-probability-weighted estimator calculation was used to estimate treatment effects as evidenced by their inclusion (19,20). A total of 15 covariates were used to balance the inverse-probability-weighted analysis and the model was estimated using a Probit specification to weight the individual variance.

ICD CASES AND COMBINED COHORTS. Baseline characteristics were compared using a Student *t* test for continuous variables or a Fisher's

FIGURE 2 Diagram of Participants



Disposition of subjects enrolled in the trial. CRT = cardiac resynchronization therapy device; ICD = implantable cardioverter-defibrillator.

exact/chi-square test for categorical variables. A Fisher's exact test was used for sparse data (i.e., $np < 5$ or $nq < 5$). CIED infection and mechanical complication data among ICD and CRT subjects were compared using the chi-square or Fisher's exact tests. A Fisher's exact test was used for sparse data.

RESULTS

The Data Management Committee informed the steering committee that the 2 primary objectives of the studies had been met at the first prespecified interim analysis. At that time, there was 1 major infection out of 1,000 subjects at 3 months compared with a 3-month benchmark rate of 1.88% ($p < 0.001$). The Data Management Committee recommended the enrolled cohorts be combined and followed for 12 months, the results of which are presented herein.

A total of 1,262 prospective patients were enrolled in both studies from 55 U.S. academic, community, and Department of Veteran's Affairs Medical Centers between December 30, 2009, and May 7, 2013 (Online Table S3). Among them, 1,129 were included in the analysis (Figure 2), with 459 patients in the ICD group (40.6%) and 670 in the CRT group (59.3%). Of the 670 subjects enrolled in the CRT group, 578 were analyzed because retrospective site-matched controls were not available for 92 of the cases.

COMBINED STUDY (CRT AND ICD). Patient demographics and primary endpoints. Patient demographics for the combined cohorts are shown in Table 1. CRT patients had a significantly higher prevalence of patient and procedure characteristics previously reported to be associated with increased risk for CIED infections (13,21-23).

Primary endpoints. The primary endpoint for major infections occurred in 5 of 1,129 patients at 12-months follow-up (0.4%; 95% confidence interval: 0.02 to 0.95) (Table 2) as compared with the pre-specified benchmark rate of 2.2% ($p < 0.003$) (Figure 3).

There were minor infections in 12 of the 1,129 patients (1.1%) (Table 2). Although these were defined as infections confined to the skin or subcutaneous tissue, the CIED was explanted in 1 case (Table 3). This explantation was a decision by the local clinical team. The remaining 11 patients with minor infections were managed with antimicrobial therapy alone and none relapsed during the follow-up period.

After 12 months of follow-up, there were 50 CIED mechanical complications (4.4%) (Table 2). Generator pocket hematoma was the most common mechanical complication, occurring in 1.6% of cases.

CRT COHORT. Patient characteristics. The baseline patient characteristics of the 578 site-matched prospective and retrospective CRT subjects are outlined in Table 4. Within the CRT case cohort, significantly more patients had diabetes, and were on oral anticoagulation, taking aspirin, or on antiplatelet therapy than the patients found within the CRT site-matched controls. Additionally, there were significant differences in New York Heart Association functional class between the 2 cohorts. The greatest proportion of patients enrolled were indicated for a device replacement due to battery depletion or device upgrade (Table 5). The proportion of patients in these 2 categories differed significantly between the CRT case and site-matched cohorts. The number of leads implanted during the procedure differed significantly ($p = 0.002$); however, the total number of indwelling leads at the end of the procedure was not different between the cohorts ($p = 0.52$).

The inverse-probability-weighted balancing results for the comorbidity-matched controls demonstrated balance in all 15 covariates (Online Table S4). Consistent with this finding, a Probit estimation of the treatment on the weighted covariates was unable to predict which patients received TYRX, whereas a Probit estimation of the treatment on the unweighted covariates had a McFadden R-Square of 0.26, a measure of explanatory power that is nontrivial for patient-level data.

Infections. A total of 4 CIED infections (2 pocket, 1 endocarditis, 1 bacteremia and endocarditis) were observed in the CRT case cohort treated with TYRX, compared with 6 CIED infections in the site-matched control group (Table 6). Within the CRT

TABLE 1 Combined Study Patient and Procedure Characteristics

	Total (TYRX) (n = 1,129)	ICD (TYRX) (n = 459)	CRT (TYRX) (n = 670)	p Value
Demographics				
Age, mean (SD)	70.8 ± 11.5	68.7 ± 12.0	72.2 ± 10.8	<0.001*
Female	276 (24.4)	120 (26.1)	156 (23.3)	0.272†
White	954 (84.5)	371 (80.8)	583 (87.0)	0.026‡
Black/African American	119 (10.5)	59 (12.9)	60 (9.0)	
Asian	6 (0.5)	2 (0.4)	4 (0.6)	
Other	50 (4.4)	27 (5.9)	23 (3.4)	
Comorbidities				
Diabetes mellitus	419 (37.1)	155 (33.8)	264 (39.4)	0.054†
Congestive heart failure	883 (78.2)	255 (55.6)	628 (93.7)	<0.001†
NYHA functional class				<0.001†
I	92 (8.1)	48 (10.5)	44 (6.6)	
II	291 (25.8)	120 (26.1)	171 (25.5)	
III	443 (39.2)	73 (15.9)	370 (55.2)	
IV	26 (2.3)	3 (0.7)	23 (3.4)	
Renal insufficiency	216 (19.1)	72 (15.7)	144 (21.5)	0.015†
Renal failure	192 (17.0)	77 (16.8)	115 (17.2)	0.865†
Fever <24 h before procedure	6 (0.5)	2 (0.4)	4 (0.6)	1.000‡
Admission medications				
Oral anticoagulant	474 (42.0)	153 (33.3)	321 (47.9)	<0.001†
Parenteral anticoagulant	46 (4.1)	8 (1.7)	38 (5.7)	0.001†
Aspirin	690 (61.1)	303 (66.0)	387 (57.8)	0.005†
Clopidogrel/ticlopidine	218 (19.3)	85 (18.5)	133 (19.9)	0.578†
Corticosteroid use	25 (2.2)	9 (2.0)	16 (2.4)	0.632†
Indication for replacement				
End of battery life	879 (77.9)	412 (89.8)	467 (69.7)	<0.001†
Device upgrade	274 (24.3)	39 (8.5)	235 (35.1)	<0.001†
Device infection	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Device malfunction	8 (0.7)	5 (1.1)	3 (0.4)	0.282‡
Manufacturer advisory/recall	13 (1.2)	5 (1.1)	8 (1.2)	0.871†
Lead revision	82 (7.3)	24 (5.2)	58 (8.7)	0.029†
Mechanical complication	2 (0.2)	1 (0.2)	1(0.1)	1.000‡
Other	26 (2.3)	8 (1.7)	18 (2.7)	0.299†
Implanted device				
ICD				
Single chamber	330 (29.2)	330 (71.9)	0 (0.0)	
Dual chamber	128 (11.3)	128 (27.9)	0 (0.0)	
CRT				
Without defibrillator	29 (2.6)	0 (0.0)	29 (4.3)	
With defibrillator	642 (56.9)	1 (0.2)	641 (95.7)	
Leads implanted, n (%)				
0	776 (68.7)	394 (85.8)	382 (57.0)	<0.001†
≥1	353 (31.3)	65 (14.2)	288 (43.0)	
Leads after procedure, n (%)				
0-2	418 (37)	395 (86.1)	23 (3.4)	<0.001†
≥3	711 (63)	64 (13.9)	647 (96.6)	
Lead revision, n (%)	143 (12.7)	45 (9.8)	98 (14.6)	0.017†
Temporary before implant n (%)	22 (1.9)	7 (1.5)	15 (2.2)	0.394†
Early re-intervention	28 (2.5)	18 (3.9)	10 (1.5)	0.010†

Values are n (%) or mean ± standard deviation. *p Value obtained from the Student *t* test. †p Value obtained from the chi-square test. ‡p Value obtained from Fisher's exact test.

CRT = cardiac resynchronization device; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association.

TABLE 2 Combined CIED Infections and Mechanical Complications

	Total (TYRX) (n = 1,129)	ICD (TYRX) (n = 459)	CRT (TYRX) (n = 670)	p Value
CIED infection				
Major	5 (0.4)	1 (0.2)	4 (0.6)	0.325*
Minor	12 (1.1)	5 (1.1)	7 (1.0)	0.648*
CIED mechanical complication				
CIED malfunction with pocket revision	2 (0.2)	2 (0.4)	0 (0.0)	1.000*
Generator dislodgement or migration	2 (0.2)	1 (0.2)	1 (0.1)	0.835*
Lead dislodgement or migration	13 (1.2)	1 (0.2)	12 (1.8)	0.008*
Lead fracture	7 (0.6)	2 (0.4)	5 (0.7)	0.405*
Skin erosion	5 (0.4)	3 (0.7)	2 (0.3)	0.908*
Wound dehiscence	7 (0.6)	4 (0.9)	3 (0.5)	0.898*
Generator pocket hematoma	18 (1.6)	3 (0.7)	15 (2.2)	0.018†
Other	3 (0.3)	1 (0.2)	2 (0.3)	0.639*

Values are n (%). *p Value from the Fisher's exact test, left-sided. †p Value from the chi squared test, one sided.

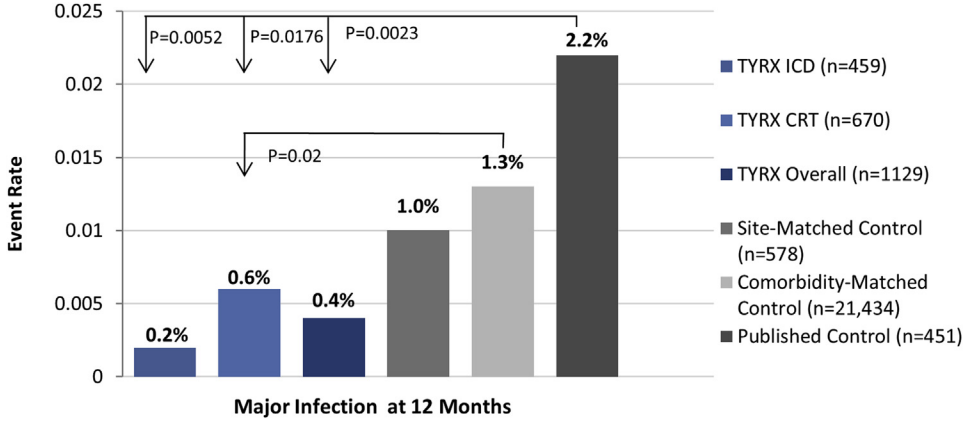
CIED = cardiovascular implantable electronic device; other abbreviations as in Table 1.

case subjects, the mean time from generator replacement to infection diagnosis was 185 ± 98 days. Before 90 days, no pocket infections were observed among the CRT case group, compared with 6 pocket infections among the site-matched controls. Among both case and control groups, staphylococcal species of bacteria were the most common cause of infection (Table 6).

The primary study endpoint, major CIED infection rate at 12 months, was 0.7% among CRT case subjects implanted with the TYRX, 1.0% in the site-matched control group (p = 0.38), and 1.3% in the comorbidity-matched control group (p = 0.02) (Table 6). The site-adjusted analysis of the case and control subjects resulted in a p value of 0.53. The observed 80% relative reduction in infection rate for case subjects at 90 days was significant when compared with the comorbidity-matched controls (p = 0.02), but not significant when compared with the site-matched controls (p = 0.06). After 90 days, the infection rates between the cohorts were not significantly different. At 12 months after implantation, the all-cause mortality rate was 11.0% in the CRT case cohort, 4.3% in the site-matched control group, and 13.4% in the comorbidity-matched control group. The 12-month mortality rate in the CRT case subjects was significantly higher than the site-matched control (p < 0.001), and nonsignificantly lower than the comorbidity-matched control cohort (p = 0.089) (Table 4). The mortality rates at 90 days were not significantly different. Deaths in the CRT case cohort were consistent with the causes of death expected in an older cohort of patients receiving a CRT and none were adjudicated as being related to the TYRX envelope.

ICD COHORT. The Citadel study found a 12-month infection rate of 0.2% (1 in 459), as compared with published control infection rate of 2.2% (13). This is a highly significant difference, and there was no difference in the rates of mechanical complication between the groups (Tables 1 and 2).

FIGURE 3 Major Infection Rates



Major infection rates for the trial (Citadel, Centurion, Centurion matched controls, Medicare controls, and prior published controls) are graphed. Major infection rates were significantly lower in TYRX (p = 0.0023) compared with the benchmark published control rate. Abbreviations as in Figure 2.

TABLE 3 CIED Infections in the Combined Study

Subject	Infection Type	CIED	Age (y)	Gender	Interval to Diagnosis (d)	Infection Type	CIED Explanted	Pathogen Isolated by Laboratory Culture
2007	Minor	CRT	84	Male	160		No	
14009	Minor	CRT	72	Male	3		No	
16001	Major	CRT	75	Male	230	Endocarditis/ Bacteremia	Yes	*Staphylococcus aureus*
16015	Minor	CRT	67	Male	38		No	
30007	Minor	CRT	84	Female	30		No	
36023	Minor	CRT	72	Male	13		No	
36041	Major	CRT	77	Male	278	Pocket Infection	Yes	*Klebsiella oxytoca*
37012	Minor	CRT	76	Male	7		No	
37043	Major	CRT	85	Male	172	Pocket Infection	Yes	Coagulase-negative *Staphylococcus*
37046	Minor	CRT	82	Female	35		No	*Enterococcus faecalis*
58142	Major	CRT	81	Male	55	Endocarditis	No	9 CFU Corynebacterium species, Gram-positive cocci in pairs, chains, and clusters
3008	Minor	ICD	55	Male	18		Yes	Gram-positive cocci in pairs
27023	Minor	ICD	60	Male	338		No	
43008	Major	ICD	54	Male	56	Pocket Infection	Yes	Culture negative
46009	Minor	ICD	78	Male	48		No	Corynebacterium sp.
46018	Minor	ICD	53	Male	10		No	
64002	Minor	ICD	52	Male	22		No	

CFU = colony-forming unit; other abbreviations as in Tables 1 and 2.

DISCUSSION

This analysis demonstrates that the use of TYRX for CIED replacement procedures was associated with a significantly low rate of major CIED infections relative to published controls without an increase of device-related mechanical complications. These findings are consistent with 2 earlier retrospective studies using case- and propensity-matched controls (24).

In an earlier study of 624 CIED implantations with TYRX performed at 10 U.S. centers, Bloom et al. (10) demonstrated a low CIED infection rate (0.48%) after an average follow-up of 1.9 ± 2.4 months. A subsequent investigation by Kolek et al. (1) compared CIED infection rates in 260 patients who had ≥2 pre-specified risk factors for CIED infection and were implanted with TYRX to 639 case-matched retrospective control patients with the same number of pre-specified risk factors who were implanted without TYRX. The CIED infection rate was significantly lower in the TYRX group (0.4% vs. 3.0%; odds ratio [OR]: 0.13; 95% confidence interval: 0.02 to 0.95; p = 0.04). Similarly, Mittal et al. (12) compared CIED infection rates in 275 propensity-matched pairs who underwent CIED implantation, with or without TYRX. The CIED infection rate was significantly lower in the TYRX group (1.1% vs. 3.7%; p < 0.05).

TABLE 4 CRT Cohort Baseline Patient Characteristics

	Case (n = 578)	Site-matched Control (n = 578)	Case vs. Site-matched Control p Value
Age	72.2 ± 10.70	71.5 ± 10.94	0.309*
Male gender	444 (76.8)	434 (75.1)	0.491†
Diabetes mellitus	242 (41.9)	193 (33.4)	0.003†
Congestive heart failure	544 (94.1)	532 (92.0)	0.164†
I	39 (6.7)	27 (4.7)	0.006†
II	144 (24.9)	96 (16.6)	
III	328 (56.7)	357 (61.8)	
IV	18 (3.1)	13 (2.2)	
Renal insufficiency (Cr > 1.5)	133 (23.0)	130 (22.5)	0.833†
Renal failure (dialysis or GFR < 60 ml/min)	105 (18.2)	107 (18.5)	0.879†
Fever < 24 h before implantation	3 (0.5)	1 (0.2)	0.624‡
Medications			
Oral anticoagulant	283 (49.0)	249 (43.1)	0.045†
Other anticoagulants	34 (5.9)	17 (2.9)	0.015†
Aspirin	332 (57.4)	297 (51.4)	0.039†
Clopidogrel/ticlopidine	114 (19.7)	80 (13.8)	0.008†
Other platelet inhibitors	4 (0.7)	10 (1.7)	0.177‡
Corticosteroid use	14 (2.4)	11 (1.9)	0.544†
Other immunosuppressant	7 (1.2)	6 (1.0)	1.000‡
None	64 (11.1)	112 (19.4)	0.001‡

Values are n (%) or mean ± standard deviation. *Student *t* test. †Chi square test. ‡Fisher's exact test.

Cr = creatinine; GFR = glomerular filtration rate; other abbreviation as in Table 1.

TABLE 5 CRT Implant and Device Characteristics

	Case (n = 578)	Site-Matched Control (n = 578)	Case vs. Site-matched Control p Value
Indication for replacement			
End of battery life	397 (68.7)	313 (54.2)	<0.001*
Device upgrade	208 (36.0)	255 (44.1)	0.005*
Device malfunction	3 (0.5)	4 (0.7)	1.000†
Device advisory/recall	4 (0.7)	9 (1.6)	0.264†
Lead revision	46 (8.0)	50 (8.7)	0.670*
Mechanical complication	1 (0.2)	2 (0.3)	1.000†
Other	15 (2.6)	22 (3.8)	0.242*
Early reintervention	7 (1.2)	6 (1.0)	0.780*
Device type			
CRT - ICD	559 (96.7)	553 (95.7)	
CRT - pacemaker	19 (3.3)	23 (4.0)	
Leads implanted			
0	324 (56.1)	262 (45.3)	0.003*
1	151 (26.1)	192 (33.2)	
2	77 (13.3)	98 (17.0)	
≥3	26 (4.5)	24 (4.2)	

Values are n (%). *Chi square test. †Fisher's exact test.
Abbreviations as in Table 1.

Finally, a retrospective analysis by Shariff et al. (25) reported no infections in a cohort of CIED patients with TYRX implanted relative to a non-TYRX cohort infection rate of 1.7% after 6 months of follow-up. The variability in the infection rates across these studies is likely due to different cohorts being studied and variable definitions being used for what constitutes and infection. Nevertheless, all of them demonstrate a significant reduction in CIED infections with TYRX use when compared with usual standard of care. Our study results are consistent with these observations.

TABLE 6 Centurion Major CIED Infection Rate and Mortality

Case (n = 578)	Centurion Control (n = 578)	Medicare Control (n = 21,434)	p Value Case vs. Control	p Value Case vs. Medicare Control
12-Month infection rate				
4 (0.7)	6 (1.0)	285 (1.3)	0.38	0.02
Infection rate before 90 days				
1 (0.2)	6 (1.0)	217 (1.0)	0.062	0.019
Infection rate after 90 days				
3 (0.5)	0 (0.0)	70 (0.3)	NA*	0.293
12-Month mortality				
64 (11.0)	25 (4.3)	2,873 (13.4)	<0.001	0.089
90-Day mortality				
14 (2.5)	6 (1.1)	690 (3.2)	0.083	0.297

Values are n (%). *Comparison cannot be made; one-sided p value = 1.0.
Abbreviation as in Table 2.

In the present study, 4.4% of patients experienced a post-implantation mechanical complication. The most common was generator pocket hematoma, occurring in 1.6% of patients, followed by lead dislodgement and migration (1.2%). These findings are similar to prior publications (26,27) and do not suggest and increased risk of these events associated with the TYRX Envelope. There were a total of 96 deaths which is similar to prior reports (28); none of the deaths were TYRX related.

CRT COHORT. Among the CRT cohort, we observed a low rate (0.7%) of major infection in those who received the TYRX envelope that was statistically significantly lower than a comorbidity-matched control group, but not different than a site-matched control group. This latter discrepancy may be due to an unexpectedly lower rate of infection among the site-matched control group who also appeared to have fewer comorbidities and risk factors, including diabetes, heart failure, and use of anticoagulant or antiplatelet agents. Additionally, all reported infections in the control group occurred within 3 months and no late infections were reported. This is highly unusual and strongly suggests under-reporting of late events or limitations in collecting events during the chart review process (type II error). Nevertheless, the infection rate compares favorably with prospective and retrospective published CIED infection rates in the absence of the TYRX Envelope, which vary from 1.88% to 2.30% over 2.7 to 12.0 months of follow-up (**Table 7**) (13,21,22,26,27,29).

A higher 12-month event rate of 1.3% was observed among a large Medicare claims-based database of >21,000 patients who underwent CRT replacement procedures, which we consider to be a more reliable control dataset due its size and because it was matched by comorbidity. It is conceivable that a claims-based methodology also underestimated the actual major infection rate in this population, due to coding errors, failure to bill, failure to treat invasively, or patient death before system extraction, but the magnitude of these errors was probably small. Because this comorbidity-matched control event rate is derived from such a large database, and the matching criteria were more detailed, we consider it a robust result for comparison with the CRT case population, which was observed to have a statistically significant 46% relative reduction in the rate of major infection at 12 months. Of note, this claims-based control event rate compares favorably with prior published studies, and it may represent an important modern benchmark for future analyses of infection rates

TABLE 7 Published CIED Infection Rates

Author	Year	Study Design	N	Procedure Type	Device	Follow-up (mo)	Infection Rate (%)
Gould et al. (26)	2006	Retrospective	533	Replacement	ICD	2.7 (mean)	1.88
Gould et al. (13)	2008	Retrospective	451	Replacement	ICD	12	2.21
Romeyer-Bouchard et al. (23)	2010	Prospective	303	De novo/ Replacement	CRT-D, CRT-P	12	1.70
Krahn et al. (27)	2011	Prospective	1,081	Replacement	ICD	1.5	1.70
Metais et al. (22)	2011	Prospective	304	De novo	PM, ICD, CRT-D, CRT-P	12	2.30
Uslan et al. (29)	2012	Prospective	1,744	Replacement	PM, ICD, CRT-D, CRT-P	6	1.40

CRT-D = cardiac resynchronization therapy device with defibrillator; CRT-P = cardiac resynchronization therapy device with Pacing function only; PM = pacemaker.

among CRT patients who undergo CIED replacement procedures.

The CRT case population was noted to have a significantly higher 12-month mortality than the CRT site-matched control population (49.5% relative difference; $p < 0.001$), but a nonsignificantly lower mortality rate than the Medicare control group (34% relative reduction). None of the deaths were related to the TYRX envelope and there were no differences in mortality within the first 90 days after implantation. Importantly, the CRT case mortality rate (11.0%) and Medicare comorbidity-matched control mortality rate (13.4%) were similar to a previously reported rate (9.9%) from a cohort of ICD/CRT replacements in the National Cardiovascular Data Registry (30). Similar to the infection results, the differences in comorbidities between the cases and site-matched controls may be responsible for the late difference in mortality and, thus, the Medicare control population may represent a more robust comparison.

ICD COHORT. The Citadel study (ICD Cohort) found a 12-month infection rate of only 0.2% (1 in 459), as compared with a 12-month published control infection rate of 2.2% (13). This is a highly significant difference; there was no difference in the rates of mechanical complication between the groups.

STUDY LIMITATIONS. This nonrandomized study used prospectively collected data from patients treated with TYRX and compared with historical controls, which may introduce recall and selection bias. Additionally, the use of periprocedural antibiotics was not protocolized. We attempted to reduce these biases for the comparison with the Citadel/Centurion patient cohort by selecting a historical published control cohort, site-matched control cohorts, and comorbidity-matched controls that received similar device types with the same infection risk profiles. Nevertheless, the retrospective methodology of the site-matched control group seems to have been fraught with difficulty. We suspect that, at each site, the control patient selection was biased toward patients who were followed up at the study center, and presented to the device clinic reliably, thereby rendering the site-matched group a poor comparator. The Medicare claims database seems to be a more appropriate comparator; however, this has the billing and coding limitations of any administrative database. It is likely that the identification of infections within control groups underestimated the true infection rates in these populations; however, as stated, the claims-based database was probably less susceptible to this flaw. The WRAP-IT Trial (World-wide Randomized Antibiotic Envelope Infection Prevention Trial; NCT02277990), a prospective, randomized, controlled study is currently underway to evaluate infection reduction and mortality associated with the use of TYRX to definitively address these issues.

CONCLUSIONS

The use of TYRX was associated with a low rate of major CIED infections in high-risk patients undergoing ICD/CRT replacement procedures and resulted in a significant reduction in major CIED infections compared with a published cohort without TYRX at 12 months.

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PERSPECTIVES

CLINICAL COMPETENCIES: CIED infection is a feared complication of device implantation. Proper skin preparation, meticulous sterile technique, and pre-procedural intravenous antibiotics have been shown to be effective, but additional methods are needed to further decrease the incidence of device infection.

TRANSLATIONAL OUTLOOK: These studies provide evidence that the use of an antibiotic envelope reduces the incidence of device infection. Further study in a randomized trial evaluating infection reduction with a TYRX absorbable antibiotic envelope is underway to confirm these findings.

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APPENDIX For supplemental material and tables, please see the online version of this article.