Journal of Hospital Infection 103 (2019) 311–320

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Bundled skin antiseptic preparation for complex cardiac implantable electronic device infection: a propensity-score matching cohort study

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ARTICLE INFO

Article history:
Received 2 August 2019
Accepted 19 August 2019
Available online 23 August 2019

Keywords:
Cardiac implantable electronic devices
Cardiac implantable device infection
Skin antiseptic preparation

SUMMARY

Background: Cardiac implantable electronic device (CIED) infection, a major complication of a CIED implant procedure, can prolong hospitalization and cause mortality.
Aim: To evaluate the efficacy of a bundled skin antiseptic preparation for preventing infection after implantation of a complex CIED.
Methods: This study analysed 1163 consecutive patients who had received a bundled skin antiseptic preparation before CIED implantation from July 2012 to December 2017. According to the complexity of the CIED implant procedure, the patients were divided into a complex CIED group ($N = 370$) and a non-complex CIED group ($N = 793$). A complex procedure was defined as a pacemaker replacement, implantation of implantable cardioverter defibrillator and cardiac resynchronization therapy, device upgrade, or lead revision.
Findings: During a mean follow-up of 2.9 ± 1.7 years, CIED infection developed in 15 patients (1.3%), and the incidence of minor and major infection was 1.1% and 0.2%, respectively. The incidence of CIED infection did not significantly differ between the complex CIED group and the non-complex CIED group (1.1% vs 1.4%, respectively; non-significant). Multivariate analysis indicated that procedural complexity was not an independent predictor of CIED infection. After 2:1 propensity score matching, the matched non-complex CIED group and the matched complex CIED group still showed no significant difference in the incidence of CIED infection.
Conclusion: Bundled skin antiseptic preparation is an effective and widely applicable strategy for decreasing infection risk after a complex CIED implantation.

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https://doi.org/10.1016/j.jhin.2019.08.015

Introduction

In the past two decades, the number of cardiac implantable electric device (CIED) implantations has increased worldwide due to population ageing, an increasing prevalence of cardiovascular disease, and to the adoption of clinical guidelines [1–3]. Infection is a major complication of a CIED implant procedure that can prolong hospitalization, increase treatment costs, and cause mortality [2,4,5]. Intravenous administration of prophylactic antibiotics before implantation is the evidence-based strategy for preventing CIED infection [3,6,7]. Nevertheless, the rate of infection remains high with the incidence of 1–4%, possibly attributed to the increasing comorbidities and complexity of CIED, e.g. implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) [2,3,8,9]. Before a CIED implant, skin antisepsis is a vital step for preventing device-related infection since the causative pathogens are usually microbes inhabiting the skin. However, an effective skin antiseptic strategy has not been established [3,6,10]. Of note, our previous study revealed that, in comparison with the standard skin antiseptic preparation, a bundled skin antiseptic preparation reduces CIED infection risk in the general population undergoing CIED implantation [11]. Nowadays, we face a general population with a higher prevalence of comorbidities, and more complex procedures, both of which increase CIED infection risk [2,3,9,11]. Therefore, the purpose of this prospective observational study was to test the hypothesis that a bundled skin antiseptic preparation in complex CIED procedures would reduce the CIED infection risk to as low as that in non-complex CIED procedures.

Methods

Patient population

The standard procedure for CIED implantation in our institution is described in our previous study [11,12]. This study enrolled 1269 consecutive patients who had received CIED implantation from July 2012 to December 2017. The analysis excluded seven patients younger than 18 years, 96 patients with evidence of concurrent infection affecting other organs, and three patients with unavailable medical records. The final analysis included 1163 patients (Figure 1). All CIED implantation procedures, including new device implant, generator replacement, device upgrade, and lead revision were performed by four experienced cardiac electrophysiologists. The study protocol was approved by the Institutional Review Committee for Human Research at our institution (IRB No.: 201900579B0).

The patients were divided into a complex CIED group and a non-complex CIED group according to procedural complexity. A complex CIED was defined as a procedure involving generator replacement, ICD, CRT-P (pacemaker)/CRT-D (defibrillator), device upgrade, and lead revision. The non-complex CIED group included patients who had received implant of de-novo single-chamber or dual-chamber permanent pacemakers.

Strategy for preventing CIED infection: bundled skin antiseptic preparation

All patients showered or bathed using a commercially available non-antimicrobial soap the night before CIED

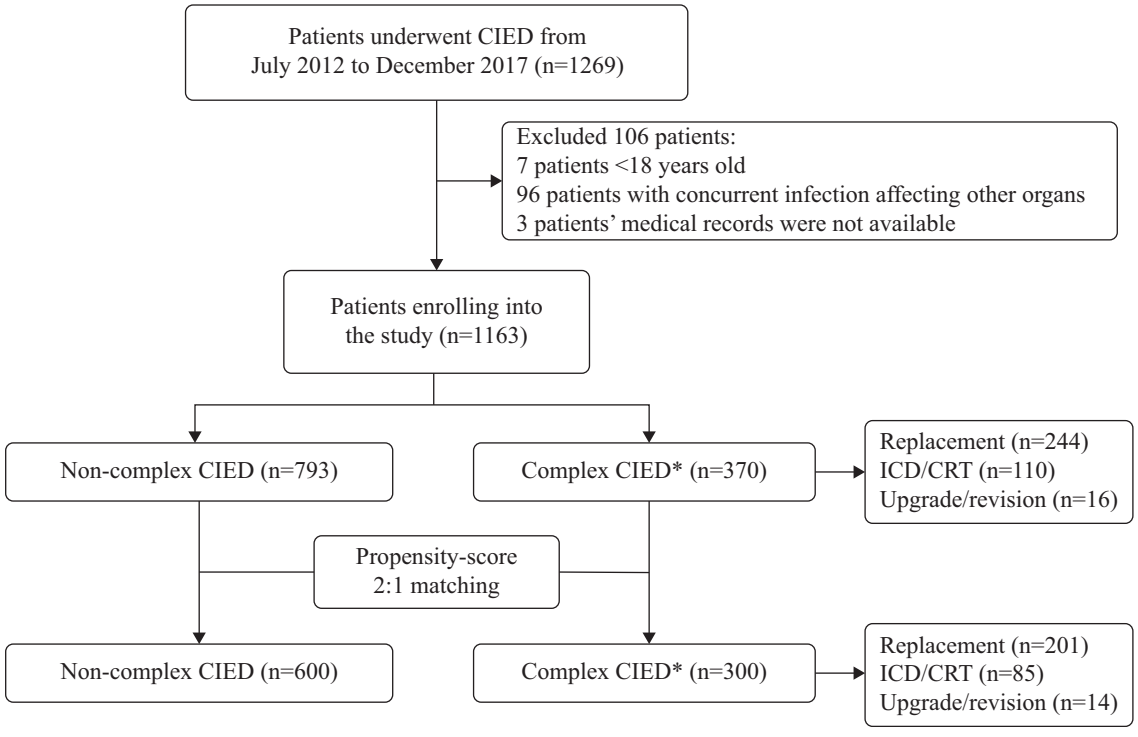


Figure 1. The flow chart of enrolment of patients receiving cardiac implantable electronic devices (CIED). ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy. *Complex CIED included replacement of generators, implantation of ICD/CRT, device upgrade and lead revision.

implantation. Each patient then received a bundled skin antiseptic preparation in the following three steps [11]. (i) The night before the procedure, a 75% alcohol solution (Kespol 75% Ethanol Solution, Kaohsiung, Taiwan) was applied to the entire anterior chest wall, and then the anterior chest wall was covered with a large sterilized gauze pad. (ii) Ten minutes before CIED implantation, the incision site was wiped in concentric circles from the centre to the periphery with sterile gauze pads soaked in povidone–iodine (75 mg/mL) (Sindine Surgical Scrub, Sinphar, Taiwan) and then patted dry. (iii) Finally, we applied the standard skin antiseptic preparation, which included alternately wiping with a 75% alcohol solution (two times) and a povidone–iodine (100 mg/mL)/95% alcohol (0.7 mL/mL) solution (Sindine Alcoholic Solution, Sinphar, Taiwan) (three times). For intraoperative prevention of infection, prophylactic cefazolin was administered intravenously 1 h before skin incision according to guidelines [3,4,6,10]. Pocket irrigation with cefazolin was performed as described in the literature [13]. Postoperatively, prophylactic cefazolin was administered intravenously for one day; the dosage was adjusted according to renal function.

Definitions

A CIED infection was classified as a minor or major infection as defined in our previous study [11]. Minor infection was defined as (1) signs of local inflammation including erythema, warmth, fluctuance, or tenderness at the pocket sites, (2) presentation of any discharge, or (3) wound dehiscence. Major infection was defined as any presentation of: (1) erosive wound, (2) bloodstream infection, (3) CIED-related endocarditis, or (4) need for surgical removal. Moreover, a major infection was also defined as described in the World-wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT) study [14]. Anticoagulant and antiplatelet agents were only discontinued on the day of procedure. Pocket haematoma was defined as a swollen and painful mass that exceeded the margin of generators [12].

Clinical events and follow-up

All procedure-related complications were recorded, including myocardial infarction, stroke/transient ischaemic attack, acute pulmonary embolism, haemo/pneumothorax, and cardiac tamponade. All patients were scheduled for their first clinical visit within one week after discharge. Patients with pocket haematoma, poor wound healing, or local inflammation signs were followed up until total recovery. All other patients were followed up monthly for the first three months and then every three to six months thereafter to examine for any delayed occurrence of CIED infection or other complications. All cardiac events and non-cardiac deaths that occurred during the follow-up period were also recorded.

Statistical analysis

Data were expressed as mean ± SD or percentages. In analyses of clinical and laboratory data, independent *t*-test was used to compare continuous variables, and χ^2-test or Fisher's exact test was used to compare categorical variables. The significance of multiple variables in predicting the development of CIED infection was compared using multiple logistic regression analysis. It was calculated that a sample size of 1163 patients would provide 90% power with the use of a Cox proportional-hazards model to evaluate the primary end-point. According to our prior study, sample size calculation was performed with the use of simulation under the following assumptions: a CIED infection rate of the complex procedure

Table I
Baseline characteristics of the full cohort

	Total ($N = 1163$)	Non-complex CIED ($N = 793$)	Complex CIED ($N = 370$)	*P*-value
CIED infection	15 (1.3)	11 (1.4)	4 (1.1)	0.667
Minor infection	13 (1.1)	9 (1.1)	4 (1.1)	0.935
Major infection	2 (0.2)	2 (0.3)	0	0.334
Major infection defined by WRAP-IT	2 (0.2)	2 (0.3)	0	0.334
Age (years)	72 ± 12	73 ± 11	71 ± 13	0.001
Male	618 (53.1)	407 (51.3)	211 (56.9)	0.077
Body mass index (kg/m^2)	24.8 ± 3.8	24.7 ± 3.9	24.8 ± 3.7	0.616
Hypertension	844 (72.5)	584 (73.6)	260 (70.1)	0.204
Diabetes mellitus	417 (35.8)	299 (37.7)	118 (31.8)	0.05
Coronary artery disease	284 (24.4)	181 (22.8)	103 (27.8)	0.068
Heart failure	272 (23.4)	144 (18.2)	128 (34.5)	<0.001
Valvular heart disease	95 (8.2)	62 (7.8)	33 (8.9)	0.532
Previous stroke/TIA	163 (14.0)	115 (14.5)	48 (12.9)	0.474
Atrial fibrillation	414 (32.3)	294 (37.1)	120 (32.3)	0.116
Renal dysfunction[a]	508 (43.7)	348 (43.9)	160 (43.1)	0.795
End-stage renal disease	62 (5.3)	47 (5.9)	15 (4.0)	0.182
Serum creatinine (mg/dL)	1.48 ± 1.58	1.52 ± 1.68	1.39 ± 1.33	0.201
eGFR (mL/min/1.73 m^2)	64 ± 28	63 ± 29	65 ± 28	0.395
White blood cell count ($\times 10^3/\mu L$)	6.9 ± 2.9	6.9 ± 2.4	6.9 ± 3.7	0.712
Intravenous TPM	310 (26.6)	228 (28.8)	82 (22.1)	0.017
Single antiplatelet	326 (28.0)	209 (26.4)	117 (31.5)	0.067
Dual antiplatelet agents[b]	85 (7.3)	53 (6.7)	32 (8.6)	0.235
Anticoagulant	226 (19.4)	145 (18.3)	81 (21.8)	0.154
Antiplatelet and anticoagulant	16 (1.4)	11 (1.4)	5 (1.3)	0.957
Triple therapy	9 (0.8)	9 (1.1)	0	0.039
Pocket haematoma	45 (3.9)	26 (3.3)	19 (5.1)	0.129

CIED, cardiac implantable electronic device; TIA, transient ischaemic attack; eGFR, estimated glomerular filtration rate; TPM, temporary pacemaker.
Data are presented as mean ± SD or number (%) of patients.
[a] Defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.
[b] Dual antiplatelet agents indicated administration of any two kinds of agents, including aspirin, clopidogrel, ticagrelor, and cilostazol.

was 5.4% in the group using standard antiseptic skin preparation, and 1.1% in the group using bundled antiseptic skin preparation with a 80% lower incidence of CIED infection in the study group than in the control group, and one interim analysis to assess success and futility with the use of group-sequential stopping boundaries to maintain an overall type I error rate of 5% [11]. The multiple logistic regression analysis included parameters that had *P*-values <0.8 in univariate analysis. A 2:1 propensity score matching was performed between the non-complex CIED group and the complex CIED group. Nearest-neighbour matching with a caliper size of 0.1 was performed to reduce imbalance in baseline characteristics of patients and to reduce the effects of potential selection bias. The incidences of CIED infection during long-term follow-up were expressed with Kaplan–Meier survival curves and compared by log-rank test. All *P*-values were two-tailed, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using a statistical software program (Statistics 22, SPSS, IBM, Armonk, NY, USA).

Results

Baseline characteristics and incidence of CIED infection

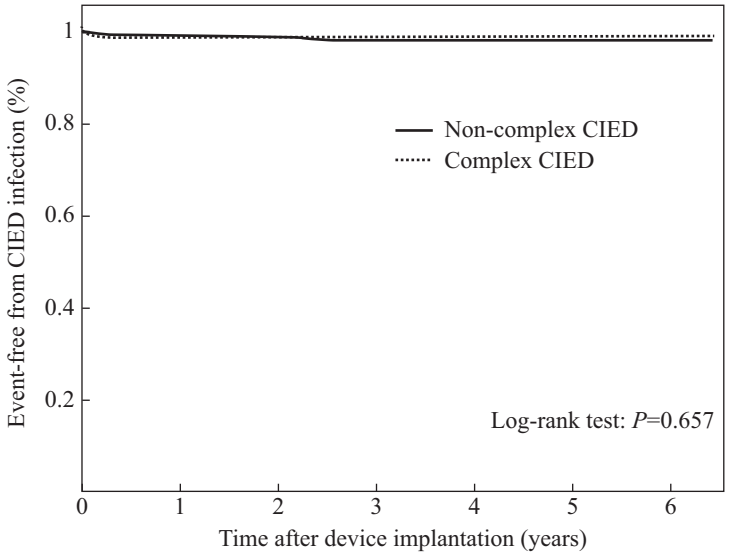
Table I presents the baseline characteristics of the 1163 patients in this study, which included 793 (68.2%) patients in the non-complex CIED group and 370 (31.8%) patients in the complex CIED group. The mean age was 72 ± 12 years, and 53.1% of this cohort were male. The procedures received by the complex CIED group included ICD placement ($N = 85$), CRT-P placement ($N = 22$), CRT-D placement ($N = 3$), generator replacement ($N = 244$), device upgrade ($N = 15$), and lead revision ($N = 1$).

During a mean follow-up of 2.9 ± 1.7 years, with 88.5% of patients completing at least one year of follow-up, 15 patients were diagnosed with an episode of CIED infection (1.3%) (Table I). The incidence of CIED infection did not significantly differ between the complex CIED group and the non-complex CIED group (1.1% vs 1.4%; non-significant) (Table I; Figure 2). Furthermore, the incidence of major or minor CIED infection did not significantly differ between the two groups (Table I).

The two groups had similar distributions of underlying diseases, including hypertension, coronary artery disease, valvular heart disease, previous stroke or transient ischaemic attack, atrial fibrillation, renal dysfunction, and end-stage renal disease. The two groups did not significantly differ in serum creatinine, estimated glomerular filtration rate, or white blood cell count. There was higher prevalence of diabetes mellitus (37.7% vs 31.8%, $P = 0.05$) and lower prevalence of heart failure (18.2% vs 34.5%, $P < 0.001$) in the non-complex CIED group compared with the complex CIED group (Table I). The complex CIED group had a lower prevalence of the placement of intravenous temporary pacemaker (22.1% vs 28.8%; $P = 0.017$) when compared with the non-complex group (Table I). Prescriptions of antithrombotic agents including single antiplatelet, dual antiplatelet, anticoagulant, and antiplatelet plus anticoagulant did not significantly differ between the two groups. Finally, the frequency of triple therapy (anticoagulant plus dual antiplatelet agents) was significantly higher in the non-complex CIED group (0.8% vs 0%, $P = 0.039$), compared to the complex CIED group (Table I).

Clinical features and risk factors of CIED infection

In the 15 patients (1.3%) diagnosed with CIED infection, 13 patients (1.1%) had minor infection, and two patients (0.2%) had major infection (Table I). These infections included two



Numbers at risk							
Non-complex CIED	793	685	496	345	208	94	33
Complex CIED	370	326	241	178	99	45	14

Figure 2. The Kaplan–Meier event-free survival curves showing the time to cardiac implantable electronic device (CIED) infection in the full cohort: the non-complex CIED group vs the complex CIED group.

(13.3%) bloodstream infections (meticillin-resistant *Staphylococcus aureus* ($N = 1$), and coagulase-negative staphylococcus ($N = 1$)), and four (26.7%) culture-positive pocket wound infections (meticillin-susceptible *S. aureus* ($N = 1$), coagulase-negative staphylococcus ($N = 1$), *Enterobacter cloacae* ($N = 1$), and *Achromobacter xylosoxidans* ($N = 1$)). The complex CIED group had four patients (1.1%) with minor CIED infection and none with major infection (Table I). According to the WRAP-IT definition for major CIED infection, no patients in the complex CIED group had pocket revision without removal, recurrent infection after discontinued antibiotic therapy, or death caused by CIED infection (Table I) [14]. In the non-complex CIED group, the two patients (0.3%) who had major CIED infection (Table I) underwent surgical removal of pacing system for uncontrolled infection after antibiotic therapy. Nine patients (1.1%) in the non-complex CIED group had minor CIED infection. In the 13 patients with minor CIED infection, eight patients had local inflammatory signs of pocket wound, two patients had non-purulent discharge from pocket wound, and three patients had wound dehiscence. All of the patients with minor infection were successfully treated with antibiotics and local management with 75% alcohol. On average, CIED infection was diagnosed 154.9 ± 253.7 days after the index procedure in the 15 patients. After the index procedure, the time until diagnosis of CIED infection was shorter in the complex CIED group than in the non-complex CIED group (24.0 ± 13.2 vs 202.6 ± 284.0 days; non-significant). Seven patients (46.7%) had late CIED infection (defined as CIED infection within one to 12 months after surgery), and six patients (40.0%) had acute infection (defined as CIED infection within <30 days after surgery). Moreover, during the three-year follow-up period, another two patients (13.3%) in the non-complex CIED group suffered from very late CIED infection (defined as CIED infection >12 months after surgery).

Patients with and without CIED infection had similar distributions of age, gender, and comorbidities, including hypertension, diabetes mellitus, coronary artery disease, heart failure, atrial fibrillation, previous stroke or transient ischaemic attack, renal dysfunction, and end-stage renal disease (Table II). Patients with and without CIED infection did not significantly differ in the prevalence of intravenous placement of a temporary pacemaker, procedure time, or laboratory data (serum creatinine, estimated glomerular filtration rate, and white blood cell count). Notably, the frequency of anticoagulant administration was higher in the CIED infection group compared with the non-CIED infection group (40.0% vs 19.2%; $P = 0.053$) (Table II). However, the incidence of pocket haematoma did not differ between the two groups (Table II).

After adjustments for age, gender, body mass index, hypertension, heart failure, atrial fibrillation, previous stroke or transient ischaemic attack, renal dysfunction, white blood cell count, placement of intravenous temporary pacemaker, complex CIED procedures, and anticoagulant in multiple logistic regression analysis, implantation of complex CIED was not a predictor of CIED infection and no independent predictor of CIED infection was identified. (Table III). Notably, anticoagulant use tended to increase CIED infection risk (Table III).

Table II
Comparison between patients with and without CIED infection

	Infection ($N = 15$)	Non-infection ($N = 1148$)	*P*-value
Age (years)	69 ± 11	73 ± 12	0.291
Male	9 (60.0)	607 (52.9)	0.583
Body mass index (kg/m^2)	25.1 ± 2.4	24.8 ± 3.8	0.595
Hypertension	9 (60.0)	834 (72.6)	0.260
Diabetes mellitus	5 (33.3)	411 (35.8)	0.843
Coronary artery disease	3 (20.0)	280 (24.4)	1.000
Heart failure	1 (6.7)	270 (23.5)	0.215
Atrial fibrillation	6 (40.0)	408 (35.5)	0.720
Stroke/TIA	3 (20.0)	159 (13.9)	0.453
Renal dysfunction[a]	3 (20.0)	504 (43.9)	0.063
End-stage renal disease	1 (6.7)	61 (5.3)	0.563
Serum creatinine (mg/dL)	1.59 ± 2.54	1.48 ± 1.56	0.866
eGFR (mL/min/1.73m^2)	75 ± 39	64 ± 28	0.278
White blood cell count ($\times 10^3/\mu L$)	6.6 ± 2.9	6.9 ± 2.8	0.693
Intravenous TPM	5 (33.3)	305 (26.6)	0.561
Complex CIED	4 (26.7)	366 (31.9)	0.786
Single antiplatelet	6 (40.0)	320 (27.9)	0.384
Dual antiplatelet agents[b]	1 (6.7)	83 (7.2)	1.000
Anticoagulant	6 (40.0)	220 (19.2)	0.053
Antiplatelet + anticoagulant	0	16 (1.4)	1.000
Triple therapy	0	9 (0.8)	1.000
Pocket haematoma	0	45 (3.9)	1.000

CIED, cardiac implantable electronic device; TIA, transient ischaemic attack; eGFR, estimated glomerular filtration rate; TPM, temporary pacemaker.
Data are presented as mean ± SD or number (%) of patients.
[a] Defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.
[b] Dual antiplatelet agents indicated administration of any two kinds of agents, including aspirin, clopidogrel, ticagrelor, and cilostazol.

Table III
Determinants of cardiac implantable electronic devices infection in the cohort

Variable	Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	0.98 (0.94–1.02)	0.297		
Male	0.75 (0.27–2.12)	0.584		
Body mass index	1.02 (0.90–1.17)	0.729		
Hypertension	0.57 (0.20–1.60)	0.282		
Heart failure	0.23 (0.03–1.77)	0.159		
Atrial fibrillation	1.21 (0.43–3.42)	0.720		
Stroke/TIA	1.56 (0.43–5.57)	0.498		
Renal dysfunction[a]	0.32(0.90–1.14)	0.078	0.28 (0.06–1.35)	0.112
White blood cell count	0.95 (0.76–1.19)	0.673		
Intravenous TPM	1.38 (0.47–4.08)	0.558		
Complex CIED	0.78 (0.25–2.46)	0.667	0.77 (0.23–2.60)	0.668
Single antiplatelet	1.73 (0.61–4.89)	0.305		
Anticoagulant	2.81 (0.99–7.98)	0.052	4.25 (0.89–20.41)	0.071

OR, odds ratio; CI, confidence interval; CIED, cardiac implantable electronic device; TIA, transient ischaemic attack; TPM, temporary pacemaker.
[a] Defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2.

CIED infection in patients with complex CIED and non-complex CIED procedures after propensity score matching

In order to evaluate the incidence of the CIED infection between complex CIED and non-complex CIED patients with matching baseline characteristics, a 2:1 propensity score matching procedure was performed between 793 non-complex CIED patients and 370 complex CIED patients. The final study population included 600 non-complex CIED patients and 300 complex CIED patients (Table IV). After propensity score matching, the two groups did not differ in baseline characteristics except for prevalence of heart failure (Table IV). The incidence of CIED infection did not differ between the matched non-complex CIED group and the matched complex CIED group (Table IV; Figure 3).

Complications of CIED implantation

No patients died during CIED implantation. Only five patients (0.4%) experienced periprocedural complications, including two patients (0.2%) with cardiac tamponade, one patient (0.1%) with haemothorax, and two patients (0.2%) with acute ischaemic stroke. The incidence of pocket haematoma was 3.9% in this study population, and the incidence of pocket haematoma did not significantly differ between the non-complex CIED group and the complex CIED group (3.3% vs 5.1%; non-significant) (Table I). During the follow-up period of almost three years, the total mortality rate was 12.3%, and the cardiovascular mortality rate was 3.7%. No deaths were related to CIED infection.

Discussion

The most serious complication associated with CIED implantation is device-related infection, which prolongs hospitalization, and may even be fatal [4,5,7]. In terms of management of CIED infection, the most crucial step is to prevent it, rather than to treat it. Therefore, this study developed an effective strategy, i.e. a bundled skin antiseptic preparation for preventing CIED infection in patients undergoing complex CIED procedures. During the minimum one-year follow-up period in this study, CIED infection occurred in four (1.1%) patients in the complex CIED group. The percentage approximated that in the non-complex CIED group (Table I; Figure 2). Additionally, no major CIED infections occurred in the complex CIED group (Table I). After adjustment for potential confounders, the risk of CIED infection after a complex CIED procedure performed with bundled skin antiseptic preparation was comparable to the risk of CIED infection after a non-complex CIED procedure (Table III).

Despite the increasing success rate of CIED implantation, CIED infection is still common [2,3,8,9,11,13]. The incidence of CIED infection reported worldwide varies because of differing definitions of CIED infection [3,6,7]. Greenspon *et al.* reported that the rate of CIED infection increased from 1.5% in 2004 to 2.41% in 2008 [2]. Joy *et al.* reported that CIED infections in a US-based population were increasing for all devices and especially for CRT [9]. In our previous study of patients who had received the conventional skin antiseptic preparation before undergoing complex CIED, the incidence of major CIED infection was 1.6%, which was in line with other reports [2,8,9,11,13,15]. One recent study of complex CIED procedures (predominantly CRT-D and ICD) reported that, in patients whose treatment included standard-of-care infection prevention strategies, the rate of the major or minor CIED infection was 2.2%, and the rate of major CIED infection within 12 months was 1.2% [14]. The bundled skin antiseptic preparation used in our study achieved an infection rate of only 1.1% in the complex CIED group, and no major CIED infections occurred in this group (Table I). After 2:1 propensity score matching between the non-complex CIED and complex CIED groups, the incidence of minor or major CIED infection in the complex CIED group that had received a bundled skin antiseptic preparation was still as low as that in the non-complex CIED group (Table IV).

Regarding the time of CIED infection diagnosis, nearly half of the patients in this study had late CIED infection, and two patients (13.3%) had very late CIED infection during the follow-

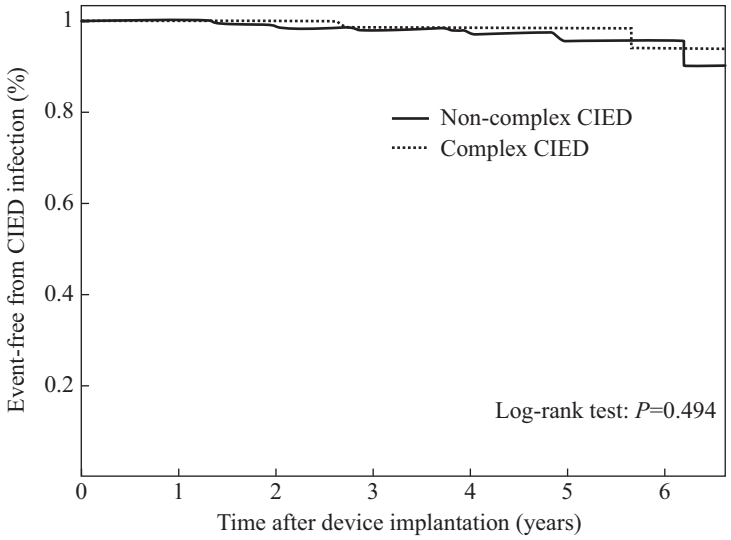
Table IV
Characteristics and clinical outcomes of propensity-score matching patients

	Total ($N = 900$)	Non-complex CIED ($N = 600$)	Complex CIED ($N = 300$)	*P*-value
CIED infection	12 (1.3)	9 (1.5)	3 (1.0)	0.760
Minor infection	10 (1.1)	7 (1.2)	3 (1.0)	1.000
Major infection	2 (0.2)	2 (0.3)	0	0.555
Major infection defined by WRAP-IT	2 (0.2)	2 (0.3)	0	0.334
Age (years)	72 ± 11	72 ± 11	72 ± 13	0.767
Male	484 (53.8)	322 (53.7)	162 (54.0)	0.925
Body mass index (kg/m^2)	24.7 ± 3.8	24.7 ± 3.9	24.9 ± 3.7	0.651
Hypertension	652 (72.4)	436 (72.7)	216 (72.0)	0.833
Diabetes mellitus	316 (35.1)	212 (35.3)	104 (34.7)	0.843
Hyperlipidaemia	222 (24.7)	143 (23.8)	79 (26.3)	0.412
Coronary artery disease	218 (24.2)	136 (22.7)	82 (27.3)	0.123
Heart failure	205 (22.8)	110 (18.3)	95 (31.7)	<0.001
Valvular heart disease	76 (8.4)	49 (8.2)	27 (9.0)	0.672
Previous stroke/TIA	128 (14.2)	86 (14.3)	42 (14.0)	0.893
Atrial fibrillation	314 (34.9)	212 (35.3)	102 (34.0)	0.692
Systemic thromboembolism	7 (0.8)	6 (1.0)	1 (0.3)	0.435
Renal dysfunction[a]	400 (44.5)	265 (44.2)	135 (45.0)	0.829
End-stage renal disease	53 (5.9)	39 (6.5)	14 (4.7)	0.271
Serum creatinine (mg/dL)	1.52 ± 1.68	1.57 ± 1.81	1.44 ± 1.38	0.262
eGFR (mL/min/1.73m^2)	64 ± 28	64 ± 29	63 ± 28	0.957
White blood cell count ($\times 10^3/\mu L$)	6.8 ± 2.4	6.9 ± 2.3	6.8 ± 2.6	0.771
Intravenous TPM	240 (26.7)	169 (28.2)	71 (23.7)	0.150
Single antiplatelet	253 (28.1)	157 (26.2)	96 (32.0)	0.066
Dual antiplatelet agents[b]	69 (7.7)	44 (7.3)	25 (8.3)	0.595
Anticoagulant	187 (20.8)	117 (19.5)	70 (23.3)	0.181
Antiplatelet and anticoagulant	13 (1.4)	9 (1.5)	4 (1.3)	1.000
Triple therapy	7 (0.8)	7 (1.2)	0	0.102
Pocket haematoma	34 (3.8)	21 (3.5)	13 (4.3)	0.536

CIED, cardiac implantable electronic device; WRAP-IT, World-wide Randomized Antibiotic Envelope Infection Prevention Trial; TIA, transient ischaemic attack; eGFR, estimated glomerular filtration rate; TPM, temporary pacemaker.
Data are presented as mean ± SD or number (%) of patients.
[a] Defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.
[b] Dual antiplatelet agents indicated administration of any two kinds of agents, including aspirin, clopidogrel, ticagrelor, and cilostazol.

up period of almost three years, which is consistent with previous reports [3,4,15,16]. Tarakji *et al*. reported that, in more than half (56%) of patients who had experienced device-related infection after CIED, the date of infection onset was more than one year after the date of device implant or the date of the most recent device change [4]. The Danish Pacemaker Register, which enrolled patients who had received new implants of permanent pacemakers or re-surgery for pacemaker hardware changes, reported that 45.5% of CIED infections had occurred more than one year after implantation [16]. These reports highlight the possibility of CIED infection occurring late after a CIED procedure, even when the device pocket wounds have already healed without infection. In our study, CIED infection occurred earlier in the complex CIED group compared with the non-complex CIED group.

Studies of risk factors for CIED infection, including patient-related factors, device factors, and procedural factors, agree that most risk factors are unavoidable [2,3,6,7,9,11,15,16]. As the population ages and with increasing prevalence of heart diseases, more patients with a higher prevalence of comorbidities are indicated for the implantation of complex CIEDs, including generator replacements, new implants or upgrades to ICD/CRT [1–3,8,16]. According to the Nationwide Inpatient Sample discharge records, cases of ICD implantation have increased more than five-fold from 1993 to 2008 [2]. During 2007 to 2016, most countries in Europe reported increased rates of ICD and CRT implantation [1]. The complexity of procedures performed by cardiologists will inevitably increase, which will increase the risk of CIED infection. Accordingly, one possible reason why the incidence of CIED infection has not decreased is the remarkable increase in the number of complex CIED procedures, including new implants or upgrades to ICD/CRT [1–3,7,9,15,16]. Joy *et al*. reported that, after adjustment for demographic factors and associated comorbidities, infection of CRT devices increased 2.43 times from 2000 to 2012 [9]. Another study reported a 4.8% CIED infection rate in 498 consecutive patients undergoing ICD/CRT implantation in a single centre [15]. Our previous study with conventional skin antiseptic preparation indicated that a complex CIED procedure carried a three-fold risk of device-related infection [11]. In the complex CIED procedures performed in the current cohort study, however, the bundled skin antiseptic preparation



Numbers at risk							
Non-complex CIED	600	519	386	277	159	65	22
Complex CIED	300	263	199	143	83	37	10

Figure 3. The Kaplan–Meier event-free survival curves showing the time to cardiac implantable electronic device (CIED) infection in the propensity-score matching patients: the matched non-complex CIED group vs the matched complex CIED group.

achieved a low (1.1%) incidence of CIED infection (Table I) and a complex CIED procedure was not an independent risk factor for CIED infection (Table III).

Replacement is another known risk factor for CIED infection [3,6,16]. The Danish Pacemaker Registry reported that the total incidence of surgical site infection after replacement was 12.12 per 1000 pacemaker-years, and for infections occurring more than 365 days was 3.26 per 1000 PM-years [16]. However, our previous study showed that pacemaker replacement did not increase CIED infection risk and that patients who had undergone replacement procedures had a low incidence of CIED infection (1.7%) during a mean of 2.5-year follow-up [11]. The current study similarly showed that patients undergoing replacement still had a low (1.6%) incidence of minor CIED infection during a mean 2.9-year follow-up. According to previous studies, anticoagulant-related pocket haematoma increases the incidence of CIED infection [3,6,9,11]. The current study indicated that treatment with anticoagulants, including vitamin K antagonists and direct oral anticoagulants, tended to increase CIED infection risk (Tables II and III). Moreover, no CIED infection occurred in the 45 patients who had pocket haematoma, which was consistent with our previous study [11]. Hence, the bundled skin antiseptic preparation strategy might play a role in preventing infection episodes in patients with pocket haematoma.

Established risk factors for CIED infection include patient factors (e.g. male gender, renal dysfunction, and diabetes) as well as procedural factors (e.g. intravenous temporary pacemaker and procedure time) [3,6,7,9,16]. In the current study, however, none of these patient risk factors, including renal dysfunction (43.7%) and diabetes (35.8%), were independent risk factors for CIED infection (Table II and III).

According to current evidenced-based guidelines, the most effective way to prevent CIED infection is intravenous antibiotic prophylaxis at the time of CIED implantation [3,6,7,10]. The Prevention of Arrhythmia Device Infection Trial (PADIT), a cluster cross-over randomized trial, evaluated the clinical effectiveness of incremental perioperative antibiotics for reducing device infection [17]. According to the PADIT trial, the one-year hospitalization rate for device infection in patients undergoing ICD/CRT did not significantly differ between incrementally administered antibiotics and conventionally administered antibiotics (1.01% vs 1.23%, non-significant) [17]. This finding indicates that the efficacy of vancomycin combined with cefazolin for preventing CIED infection is uncertain, possibly due to development of antibiotic resistance. Pocket irrigation with antimicrobial agents (rather than with saline) could be effective for preventing device infection [13]. However, the applicability of this strategy in high-risk patients or in complex procedures is still unknown [13].

Recently, Tarakji *et al.* reported WRAP-IT trial results regarding the safety and efficacy of antibacterial envelopes for preventing CIED infection in patients undergoing pocket revision, generator replacement, system upgrade, or initial ICD/CRT implantation [14]. The TYRX envelope is a sterile absorbable prosthesis designed to hold a generator. The coating on the TYRX envelope releases rifampin and minocycline over a period of at least seven days to reduce CIED infection risk. Over a 36-month follow-up period, CIED procedures performed with this envelope had a lower incidence of major CIED infections (1.3%) compared with conventional strategies (1.9%) (hazard ratio: 0.63; 95% CI: 0.40–0.98) [14]. Although the TYRX envelope has been shown to be effective for preventing infection, its high expense and limited availability make it inaccessible to many patients in developing countries. Skin antisepsis for

surgical sites at the time of surgery is a crucial step for preventing surgical wounds or device infection and should be performed with an alcohol-based antiseptic agent [10]. However, the efficacy of applying antiseptic agent the night before surgery is still controversial [3,6,10]. We hypothesized that, as the duration of antisepsis of the surgical site with alcohol-based antiseptic agents increases, the burden of microbial flora retained on the skin near the surgical site decreases. Hence, this strategy should increase the effectiveness of pre-procedural antibiotic prophylaxis for lowering CIED infection risk. Additionally, a skin antisepsis strategy for eradicating pathogens before the incision is made at the pocket site is more effective than a strategy for eradicating pathogens during or after a CIED procedure. Indeed, the bundled skin antiseptic preparation performed in this study achieved a CIED infection incidence as low as 1.4% in the non-complex CIED group and 1.1% in the complex CIED group (Table I). Moreover, the incidence of major device-related infection in the non-complex CIED group was only 0.3%, and no patient had major infection after a complex CIED implantation during the follow-up period of almost three years (Table I). Although the bundled skin antiseptic preparation may require an additional overnight antiseptic preparation, this effective strategy provides an important option to be considered in regions or countries where a TYRX envelope is unavailable.

This study had some limitations. First, CIED infection was defined in accordance with our previous study [11]. Since no consensus on the definition of CIED infection has been reached, however, the incidence rate of CIED infection could be discrepant [3,6,7,10,14]. For example, early post-implantation inflammation was defined as erythema over the incision site without the occurrence of exudate, dehiscence, or systemic signs of infection within 30 days of implantation [3]. Given the difficulty of distinguishing between inflammation and minor infection, however, the minor infection rate could be overestimated. Although this cohort study enrolled 1269 consecutive patients treated at a single institution, selection bias, such as patient factors, could not be totally excluded. The prevalence of heart failure was higher in the complex CIED group than in the non-complex CIED group (Table I), which was related to the indications of new implant or upgrade to ICD/CRT devices for heart failure. Therefore, using propensity score matching to balance the incidence of heart failure between the two groups was difficult (Table IV). Finally, although the follow-up rate in this study was high (82.3%), some CIED infection events may not have been recorded. Notably, data for very late CIED infection was likely to be accurate because the mean duration of follow-up in the complex CIED patients did not significantly differ from that in the non-complex CIED group.

In conclusion, in patients undergoing CIED implantation, a bundled skin antiseptic preparation is an effective and universally applicable strategy for decreasing device-related infection risk, even in patients undergoing complex CIED procedures.

Conflict of interest statement
None declared.

Funding sources
None.

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