ORIGINAL ARTICLE

Infectious complications in patients with cardiac implantable electronic devices: risk factors, prevention, and prognosis

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KEY WORDS

cardiac device infections, lead-related infective endocarditis, long-term survival, pocket infections, risk factors

ABSTRACT

INTRODUCTION Cardiac implantable electronic device (CIED) infections still constitute a significant challenge. The knowledge of risk factors for CIED infections is crucial for preventing infections and reducing mortality rates.

OBJECTIVES The aim of this study was to assess the risk factors and long-term survival of patients with CIED infections.

PATIENTS AND METHODS We analyzed the clinical data of 1837 patients (including xx [40.9%] patients with CIED infections), who underwent transvenous lead extraction at a single institution between 2006 and 2015. We compared the clinical and procedure-related factors for all types of CIED infections: isolated pocket infection (IPI), isolated lead-related infective endocarditis (ILRIE), and lead-related infective endocarditis with coexisting pocket infection (LRIE + PI). We also analyzed long-term survival rates.

RESULTS The development of IPI and LRIE + PI depended mainly on age, male sex, number of leads, presence of implantable cardioverter–defibrillator (ICD) or cardiac resynchronization therapy defibrillator (CRT-D), and the number of previous procedures. The factors that determined ILRIE included chronic renal failure (CRF), ICD/CRT-D, lead loops, and intracardiac lead abrasion. Chronic anticoagulation and antiplatelet treatment protected against the development of infection. Long-term survival was significantly related to age, heart failure, diabetes mellitus, CRF, malignancy, and chronic atrial fibrillation.

CONCLUSIONS The development of all types of CIED infection was associated mainly with procedure-related factors, while long-term mortality was dependent on clinical factors. The dissimilarity of factors affecting the development of IPI and ILRIE confirms that there are 2 variants of CIED infection. The protective effects of chronic anticoagulation and antiplatelet treatment should prompt us to consider such therapy in the prevention of CIED infection.

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INTRODUCTION Cardiac implantable electronic device (CIED) infections, which develop in patients with pacemakers, implantable cardioverter–defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices, pose a major clinical challenge. The incidence of these infections is estimated to range from 1% to 2% in patients with CIEDs.[1] However, these data are inaccurate because the incidence of CIED infections has been rising due to an increasing number of ICD or CRT device implantations in a specific population of patients with severe heart failure (HF) and comorbidities. Furthermore, recent years have witnessed a tremendous increase in average life expectancy, which translates into a higher number of reinterventions (generator replacement, system upgrade) in patients receiving CIEDs.[2-6] A significant increase in the incidence

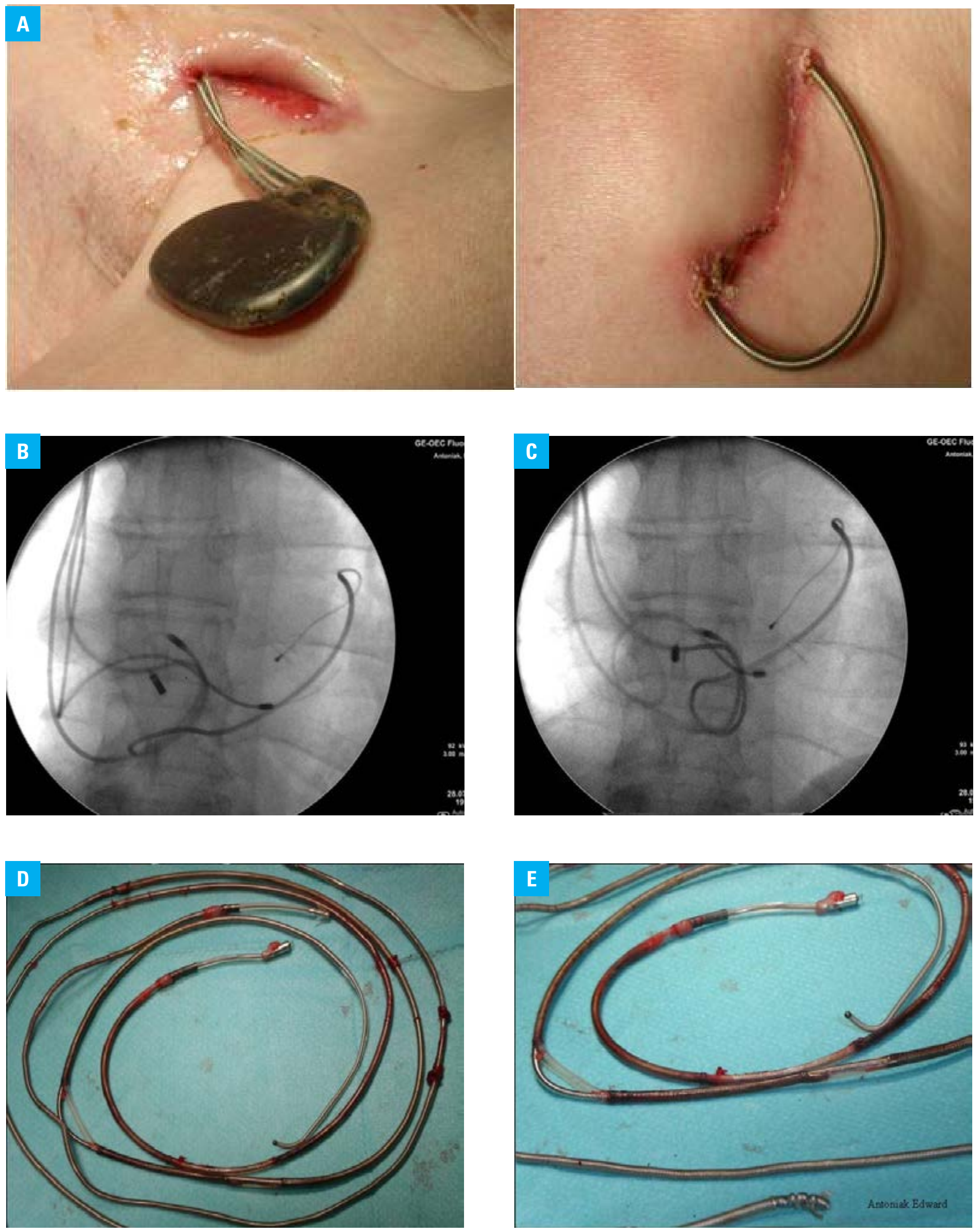


FIGURE 1 **A** – pocket infection; **B**, **C** – lead loops on X-ray fluoroscopy imaging; **D**, **E** – extracted endocardial leads showing abrasive damage to lead loops due to friction

of CIED infections was documented in the United States between 1993 and 2008; however, no such tendency has been confirmed in the European registries.[1,7] CIED infections occur both early and late after implantation of electronic devices (>1 year after the procedure). As for late infections, there are probably other specific factors affecting the development of infections after such a long time. Despite multiple analyses, it is still unclear to what extent various determinants affect the development of CIED infections and how it is possible to prevent the occurrence of infections in high-risk patients.

PATIENTS AND METHODS

Study population Clinical data from 1837 patients undergoing transvenous lead extraction (TLE) in a reference center between 2006 and 2015 due to late (>1 year) complications of CIED were retrospectively analyzed. The study population consisted of 1312 patients (71.4%) with pacemakers, 390 patients (21.2%) with ICDs, and 135 patients (7.3%) with CRT devices. Of the 1837 patients, 750 (40.9%) were selected for TLE because of a CIED infection, whereas 1087 (59.1%), for noninfectious indications. Among patients with CIED infections, there were 541 individuals (62.1%) with pocket infection (PI), including 235 patients (31.3%) with isolated PI (IPI), and 515 patients (68.7%) with lead-related infective endocarditis (LRIE). In the latter group, there were 209 patients (27.9%) with isolated LRIE (ILRIE) and 306 patients (40.8%) in whom LRIE coexisted with PI (LRIE + PI).

The analysis of blood cultures in patients with LRIE showed that the dominant pathogens were *Staphylococcus epidermidis* (about 43.3% of positive blood cultures) and *Staphylococcus aureus* (about 30.3%). However, these results were inconclusive.

Noninfectious indications included lead dysfunction due to fracture, dislodgement, late dry perforation, and the need to remove pacing systems in the presence of venous obstruction preventing from a necessary modification of the pacing mode.

Definitions PI was diagnosed according to the 2015 European Society of Cardiology guidelines,[8] based on the presence of local signs of inflammation involving the skin and connective tissue at the generator pocket, including erythema, warmth, tenderness, wound dehiscence, fluctuation, and purulent drainage (FIGURE 1A).

LRIE was diagnosed according to the Modified Duke Lead Criteria, taking into account additional LRIE-specific criteria such as local PI and septic pulmonary embolism.[8,9]

Pacemaker lead loops were defined as the presence of excessively elongated leads in the atrium or in the ventricle protruding into the tricuspid valve orifice (FIGURE 1B and 1C).[10]

Intracardiac lead abrasion (ILA) was diagnosed if damage to the outer lead insulation in the intracardiac segment (15–20 cm from the lead tip) was detected during visual inspection (FIGURE 1D and 1E).[10]

Data analysis Potential risk factors for infectious complications were analyzed in patients with CIED infections, who were divided into 2 main groups: with PI and with LRIE, and were further subdivided into those with IPI, ILRIE, and LRIE + PI, as compared with patients with noninfectious complications. Patient-dependent and procedure-related factors were evaluated by assessing the efficacy and safety of TLEs in the entire study group and all the subgroups. The univariate and multivariate analyses of potential CIED infection determinants (PI, IPI and LRIE, ILRIE, LRIE + PI) were conducted on the basis of the initial comparative analysis. The efficacy and safety of TLE procedures was assessed according to the 2009 Heart Rhythm Society consensus guidelines.[11]

Data on long-term mortality (mean [SD] follow-up, 3.71 [2.19] years) were obtained from the Ministry of the Interior and were analyzed in patients undergoing TLE both for infectious and noninfectious indications, with consideration of all the subgroups with CIED infections. The study was approved by the local bioethics committee, and written informed consent to participate in the study was obtained from all patients.

Statistical analysis Data were reported for all patients and subgroups divided according to the type of infection. The data of the individual subgroups were compared with the group of patients with noninfectious indications. For significant differences between dichotomous variables, the odds ratios were calculated. Continuous variables were expressed as mean (SD) and were compared using the *t* test. Categorical data were reported as absolute numbers and percentage and were compared using the χ^2 test incorporating the Yates correction. If the *P* value was lower than 0.05, the odds ratio coefficient with confidence intervals was calculated. The Cox proportional hazards regression model (univariate and multivariate) was applied to identify variables associated with infectious complications and with prognosis after TLE. Parameters reaching a significance level of less than 0.05 in the univariate analysis were entered into the multivariate regression model. The Kaplan–Meier curves and log-rank tests were used to evaluate survival after TLE depending on the type of infection. Differences between the groups were considered significant if the *P* value was lower than 0.05 or when the 95% confidence interval did not include 1. The statistical analysis was performed with the Statistica 10.0 software (Statsoft Inc., Tulsa, Oklahoma, United States).

RESULTS

Patient-dependent factors Patients who developed an infection were older than those with noninfectious indications, except for the ILRIE subgroup. There were more men in the entire group with CIED infection. Severe HF was significantly more frequent in the ILRIE subgroup. The risk for developing an infection was higher by 40% in patients with diabetes and observed mainly in the ILRIE subgroup. Infections were significantly more common in patients with chronic renal failure (CRF), especially in the ILRIE and LRIE + PI subgroups. Patients with chronic atrial fibrillation (AF) were at lower risk for developing an infection, with a negative relationship for AF in the IPI subgroup (TABLE 1).

Procedure-related factors Patients with a higher number of leads showed a greater risk for developing CIED infection. Patients with ICD systems were more frequently selected for TLE for noninfectious indications, whereas CRT-D systems were removed in most cases due to CIED infection (most frequently LRIE). ILA contributed to the development of infection, especially in the ILRIE subgroup. The analysis revealed longer lead dwell time in patients with CIED infection than in those with noninfectious indications, with the longest and shortest dwell times in the ILRIE and IPI subgroups, respectively. The number of procedures preceding TLE was significantly higher in the group with CIED infection. In patients with CIED infection, TLE was performed within a shorter time since the last procedure as compared with the group with noninfectious indications, with the shortest interval in the IPI subgroup. The risk for CIED infection was increased in the presence of abandoned leads (especially in the LRIE subgroup) and leads placed on both sides of the chest. Lead loops were equally frequent in patients with infectious and noninfectious indications, whereas ILRIE was more often associated with the presence of loops than IPI (TABLE 2).

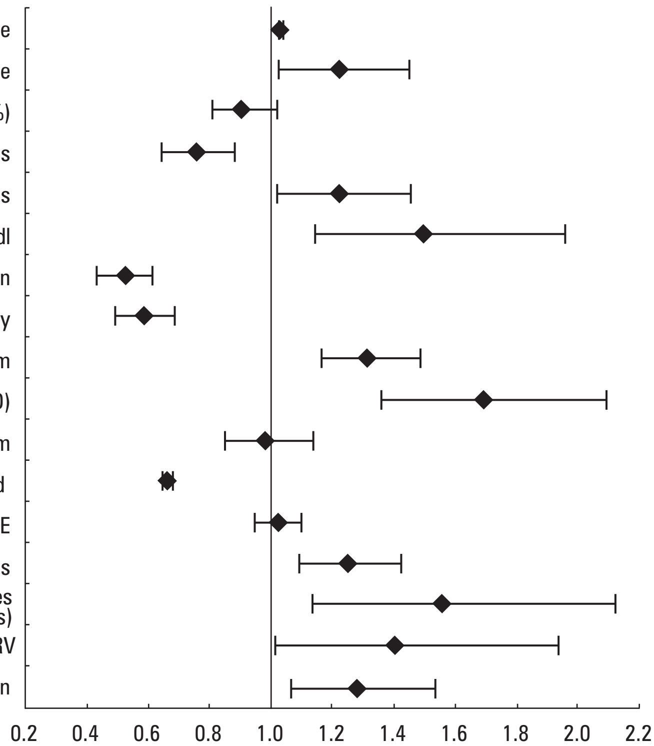
TABLE 1 Incidence of potential patient-related risk factors for developing cardiac implantable electronic device infection

Parameter		NI n = 1087 (59.1%)	PI n = 541 (72.1%)	IPI n =235 (31.3%)	LRIE n = 515 (68.7%)	ILRIE n = 209 (27.9%)	LRIE + PI n = 306 (40.8%)
Age, mean (SD)		62.90 (16.78)	68.54 (13.57) *P* <0.0001	68.69 (14.06) *P* <0.0001	66.98 (13.93) *P* = 0.004	64.59 (14.82) NS	68.43 (13.21) *P* <0.0001
Male sex, n (%)		580 (53.41)	378 (69.87) 2.02 (1.63–2.52)	167 (71.06) 2.14 (1.58–2.91)	344 (67.32) 1.80 (1.44–2.24)	135 (64.29) 1.57 (1.16–2.13)	211 (68.95) 1.94 (1.50–2.54)
BMI, mean (SD)		27.77 (8.03)	27.21 (4.56) NS	27.14 (4.14) NS	27.06 (4.86) NS	26.84 (4.83) NS	27.26 (4.88) NS
LVEF, mean (SD)		41.65 (11.15)	42.15 (10.57) NS	42.17 (10.54) NS	42.17 (10.54) NS	41.12 (11.04) NS	42.12 (10.11) NS
NYHA class, mean (SD)		1.60 (0.71)	1.60 (0.70) NS	1.61 (0.69) NS	1.67 (0.76) NS	1.78 (0.81) *P* = 0.004	1.59 (0.71) NS
NYHA class, n (%)	I-II	955 (87.9)	480 (88.7) NS	208 (88.5) NS	439 (85.2) NS	167 (79.9) 0.53 (0.37–0.78)	272 (88.9) NS
	III-IV	132 (12.1)	61 (11.3) NS	26 (11.5) NS	76 (14.8) NS	42 (20.1) 1.87 (1.28–2.74)	34 11.1) NS
Type 1 and 2 diabetes, n (%)		181 (16.67)	110 (20.33) 1.40 (1.10–1.77)	45 (19.15) NS	118 (23.09) NS	54 (25.71) 1.73 (1.22–2.45)	65 (21.24) NS
CRF, creatinine level, mean (SD)		1.09 (1.56)	1.24 (0.88) *P* <0.000	1.24 (0.94) *P* = 0.026	1.31 (0.90) *P* <0.000	1.40 (0.99) *P* <0.000	1.24 (0.84) *P* = 0.026
CRF, n (%)	Creatinine level >2 mg%	28 (2.58)	30 (5.55) 2.22 (1.31–3.75)	9 (3.83) NS	45 (8.81) 3.65 (2.25–5.92)	24 (11.43) 4.88 (2.77–8.60)	21 (6.86) 2.78 (1.56–4.98)
	Hemodialysis	7 (0.64)	5 (0.92) NS	3 (1.28) NS	7 (1.37) NS	5 (2.38) NS	2 (0.65) NS
Malignancy, n (%)	History	24 (2.21)	11 (2.03) NS	5 (2.13) NS	13 (2.54) NS	7 (3.33) NS	6 (1.96) NS
	Active	45 (4.14)	22 (4.07) NS	4 (1.70) NS	22 (4.31) NS	4 (1.90) NS	18 (5.88) NS
	Total	69 (6.35)	33 (6.10) NS	9 (3.83) NS	35 (6.85) NS	11 (5.24) NS	24 (7.84) NS
Prosthetic or biological valve, n (%)		65 (5.99)	31 (5.73) NS	16 (6.81) NS	31 (6.07) NS	16 (7.62) NS	15 (4.90) NS
Permanent catheter in SVC, n (%)		43 (3.96)	9 (1.66)	2 (0.85) 0.21 (0.05–0.87)	17 (3.33) NS	10 (4.76) NS	7 (2.29) NS
Permanent AF, n (%)		231 (21.27)	138 (25.51)	75 (31.91) 1.74 (1.27–2.37)	111 (21.72) NS	48 (22.86) NS	63 (20.59) NS
Chronic anticoagulation, n (%)		398 (36.65)	154 (28.47) 0.69 (0.55–0.86)	77 (32.77) 0.84 (0.62–1.14)	148 (28.96) 0.70 (0.56–0.88)	73 (34.76) 0.92 (0.68–1.26)	77 (25.16) 0.58 (0.44–0.77)
Chronic antiplatelet therapy, n (%)		456 (41.99)	231 (42.70)	101 (42.78) NS	213 (41.68) NS	84 (40.00) NS	130 (42.48) NS

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CRF, chronic renal failure; ILRIE, isolated lead-related infective endocarditis IPI, isolated pocket infection; LRIE, lead-related infective endocarditis; LRIE + PI, lead-related infective endocarditis coexisting with pocket infection; LVEF, left ventricular ejection fraction; NI, noninfectious indication; NS, nonsignificant; NYHA, New York Heart Association; PI, pocket infection; SVC, superior vena cava

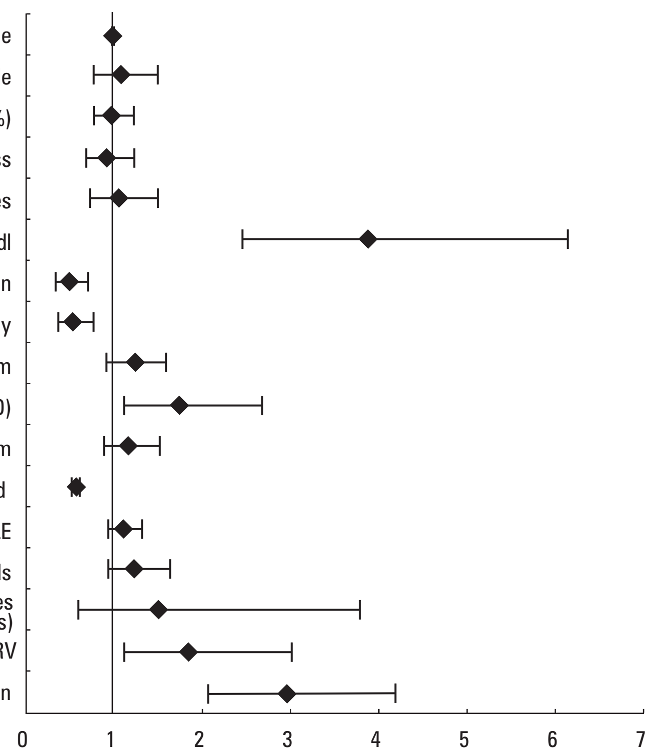
Efficacy and safety of transvenous lead extraction The efficacy and safety of TLE in patients with noninfectious and infectious complications were comparable, only in the LRIE subgroup (especially ILRIE), a higher number of minor complications was observed (TABLE 2). The results of the univariate analysis are presented in Supplementary material, *Table S1*.

Multivariate analysis In the multivariate analysis, the development of infection was associated with age, male sex, diabetes, CRF, multiple leads (including inactive leads), defibrillation leads, lead loops, ILA, and reintervention at less than 2 months prior to TLE. The risk for developing CIED infection was lower in patients receiving anticoagulation (vitamin K antagonists) and antiplatelet therapy, and in those with the longest dwell times. Paradoxically, the presence of HF showed a protective effect against the development of infection (FIGURE 2).



	HR	95% CI	*P*
Age	1.032	1.026–1.037	0.000
Male	1.222	1.03–1.449	0.021
LVEF (by 10%)	0.91	0.811–1.02	0.104
NYHA class	0.754	0.642–0.885	0.001
Type 1 and 2 diabetes	1.219	1.018–1.46	0.031
CRF creatinine level >2 mg/dl	1.498	1.145–1.958	0.003
Chronic anticoagulation	0.516	0.432–0.615	0.000
Chronic antiplatelet therapy	0.58	0.49–0.688	0.000
No. of leads in the system	1.317	1.163–1.491	0.000
Presence of defibrillation lead (ICD/CRT-D)	1.687	1.357–2.099	0.000
CRT-P system	0.981	0.848–1.135	0.795
Dwell time of the oldest extracted lead	0.667	0.651–0.683	0.000
No. of procedures prior to TLE	0.02	0.95–1.096	0.581
No. of abandoned leads	1.248	1.094–1.424	0.001
Early reintervention (2 latest procedures <2 months)	1.553	1.135–2.125	0.006
Lead loop crossing TV and in the RV	1.403	1.016–1.938	0.040
Intracardiac lead abrasion	1.281	1.066–1.539	0.008

FIGURE 2 Multivariate analysis of potential risk factors for cardiac implantable electronic device infection
Abbreviations: CI, confidence interval; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICD, implantable cardioverter–defibrillator; HR, hazard ratio; RV, right ventricle; TLE, transvenous lead extraction; TV, tricuspid valve; others, see **TABLE 1**



	HR	95% CI	*P*
Age	1.006	0.996–1.017	0.229
Male	1.084	0.785–1.496	0.624
LVEF (by 10%)	0.983	0.78–1.238	0.882
NYHA class	0.915	0.683–1.226	0.552
Type 1 and 2 diabetes	1.053	0.731–1.516	0.783
CRF creatinine level >2 mg/dl	3.896	2.467–6.152	0.000
Chronic anticoagulation	0.498	0.35–0.708	0.000
Chronic antiplatelet therapy	0.538	0.371–0.78	0.001
No. of leads in the system	1.252	0.978–1.602	0.075
Presence of defibrillation lead (ICD/CRT-D)	1.738	1.125–2.685	0.013
CRT-P system	1.175	0.904–1.527	0.227
Dwell time of the oldest extracted lead	0.572	0.535–0.611	0.000
No. of procedures prior to TLE	1.108	0.929–1.322	0.252
No. of abandoned leads	1.249	0.946–1.65	0.117
Early reintervention (2 latest procedures <2 months)	1.517	0.607–3.792	0.373
Lead loop crossing TV and in the RV	1.844	1.124–3.027	0.015
Intracardiac lead abrasion	2.949	2.065–4.211	0.000

FIGURE 3 Multivariate analysis of potential risk factors for isolated lead-related infective endocarditis
Abbreviations: see **TABLE 1** and **FIGURE 2**

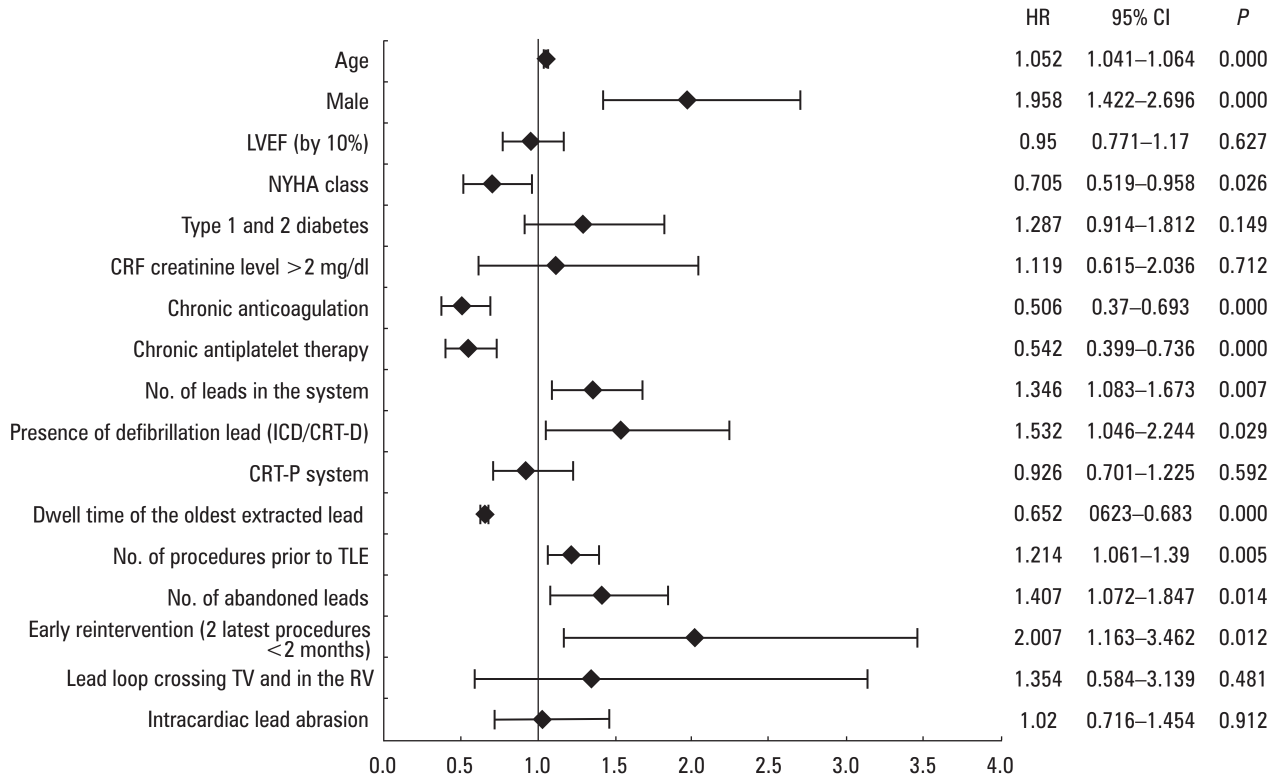
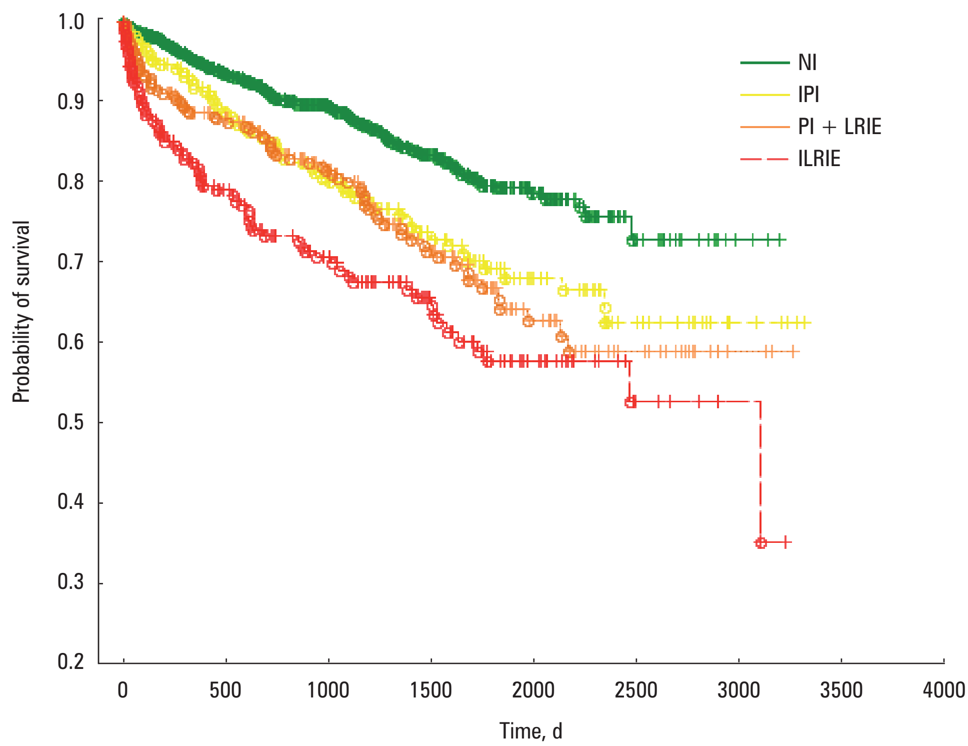


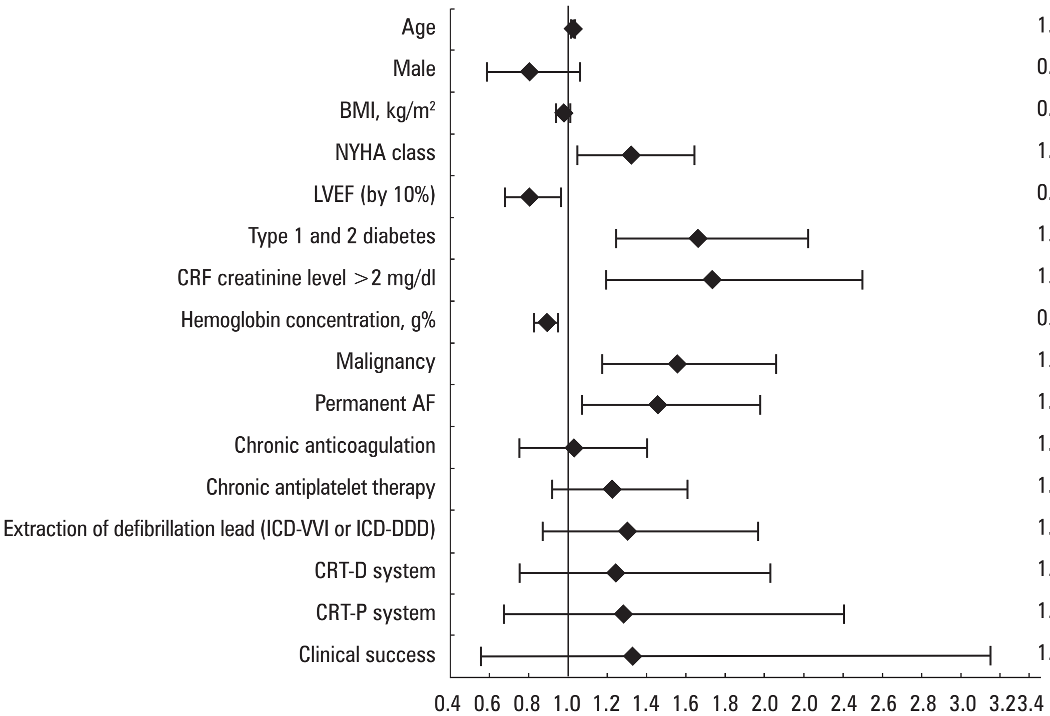
FIGURE 4 Multivariate analysis of potential risk factors for isolated pocket infection
Abbreviations: see TABLE 1 and FIGURE 2

FIGURE 5 Long-term survival curves after transvenous lead extraction in patients with various types of cardiac implantable electronic device infection
Abbreviations: see TABLE 1



In patients with ILRIE, the development of infection was affected by CRF, but not by male sex or diabetes. The risk for ILRIE was significantly higher in patients with defibrillation leads, lead loops, and ILA. A lower risk for ILRIE was observed in patients receiving anticoagulant and antiplatelet therapy and in those with longer dwell times (FIGURE 3).

An increased risk of CIED infection in patients with IPI was associated with age and male sex, but not with diabetes or CRF. Of the system-related risk factors, the presence of multiple leads (active and abandoned) and defibrillation leads affected the development of IPI. IPI was also more frequent in patients undergoing multiple pacing interventions, especially early reinterventions, but



	HR	95% CI	*P*
Age	1.028	1.015–1.042	0.000
Male	0.791	0.590–1.062	0.118
BMI, kg/m^2	0.978	0.943–1.015	0.240
NYHA class	1.315	1.049–1.649	0.018
LVEF (by 10%)	0.811	0.682–0.965	0.018
Type 1 and 2 diabetes	1.663	1.244–2.224	0.001
CRF creatinine level >2 mg/dl	1.732	1.199–2.501	0.003
Hemoglobin concentration, g%	0.887	0.828–0.949	0.001
Malignancy	1.558	1.177–2.062	0.002
Permanent AF	1.456	1.072–1.978	0.016
Chronic anticoagulation	1.026	0.751–1.402	0.873
Chronic antiplatelet therapy	1.219	0.923–1.610	0.164
Extraction of defibrillation lead (ICD-VVI or ICD-DDD)	1.311	0.874–1.968	0.191
CRT-D system	1.240	0.756–2.031	0.394
CRT-P system	1.275	0.675–2.410	0.454
Clinical success	1.324	0.555–3.155	0.527

FIGURE 6 Multivariate cause-specific long-term mortality analysis in patients after transvenous lead extraction
Abbreviations: see TABLE 1 and FIGURE 2

not in patients with lead loops and ILA. A lower risk for IPI was found in patients with a higher New York Heart Association functional class, in patients receiving anticoagulation and antiplatelet therapy, and in patients with the longest dwell times (FIGURE 4).

The average long-term survival (3.71 years) in patients undergoing TLE for infectious indications was 66.7% as compared with 81.7% in patients with noninfectious indications. The highest mortality rate was observed in patients with ILRIE—37.8%; the rates in patients with IPI and LRIE + PI were 31.9% and 30.4%, respectively, at the same time interval after TLE (FIGURE 5).

In the multivariate analysis, long-term survival time after TLE was related to age, HF, diabetes, CRF, malignancy, and permanent AF. There was no significant effect of the procedure-related factors associated with the implanted pacing system or procedural success and TLE complications. The study showed a protective effect of higher hemoglobin levels (FIGURE 6).

The results of the multivariate analysis of the risk factors for LRIE + PI are shown in Supplementary material, *Figure S1*.

DISCUSSION The pathogenesis of late infectious complications following electronic device implantation is unclear and probably multifactorial. Our findings showed subtle differences in the presence of risk factors in patients with various types of CIED infection. The demographic factors that affected the development of infection were older age and male sex. This was shown for all the subgroups except that with ILRIE. There are ambiguous findings regarding the effect of age on the development of CIED infection, with some investigators demonstrating more frequent infections in older patients, while others—in younger individuals.[12,13] There is certainly a significant relationship between this disparity and eligibility of patients for study. In most earlier investigations, clinical data for analysis were obtained from older patients receiving conventional pacing systems, but several studies that included children and adolescents demonstrated increased risk of CIED infection in younger participants.[12] In the present study, we evaluated a specific population of patients referred for TLE, divided into 2 groups with already present electronic device complications. Additionally, this study revealed relatively less frequent CIED infections in patients with longer lead dwell times, meaning that in some patients, the pacing systems had been removed before the development of infection. For this reason, our study showed ambiguous results for the effect of patient age and dwell times.

The more frequent presence of CIED infections in men, which was reported previously, was found to be caused by insertion of more complex electronic systems (ICD, CRT) due to more frequent occurrence of ischemic HF in men.[12,13] The present study demonstrated that male sex had the strongest effect on the risk for developing IPI, whereas in the multivariate analysis, it did not increase the risk for developing ILRIE. This finding may be explained by greater susceptibility of men to superinfection of the pacemaker pocket area due to greater physical activity and perhaps poorer hygiene practices.

TABLE 2 Incidence of potential procedure-related risk factors for developing cardiac implantable electronic device infection (continued on the next page)

Parameter		NI n = 1087 (59.1%)	PI n = 541 (72.1%)	IPI n =235 (31.3%)	LRIE n = 515 (68.7%)	ILRIE n = 209 (27.9%)	LRIE + PI n = 306 (40.8%)
Procedure/system related risk factors							
No. of leads in the system, mean (SD)		1.75 (0.64)	1.84 (0.60) P = 0.014	1.84 (0.63) NS	1.87 (0.63) P <0.0001	1.93 (0.70) P = 0.001	1.84 (0.58) P = 0.078
No. of leads in the system, n (%)	1 lead	387 (35.6)	146 (27.0) 0.67 (0.53–0.84)	67 (28.5) 0.72 (0.53–0.98)	134 (26.0) 0.72 (0.57–0.91)	55 (26.3) 0.64 (0.46–0.89)	79 (25.8) 0.63 (0.47–0.84)
	2 leads	589 (54.2)	341 (63.0) 1.44 (1.17–1.78)	142 (60.4) 1.44 (1.17–1.78)	314 (61.0) 1.31 (1.05–1.62)	115 (55.0) NS	199 (65.0) 1.58 (1.21–2.05)
Defibrillation lead (ICD), n (%)		313 (28.82)	129 (23.84) 0.77 (0.61–0.98)	56 (23.83) 0.77 (0.56–1.07)	122 (23.87) 0.77 (0.61–0.98)	49 (23.33) 0.75 (0.53–1.06)	73 (23.86) 0.77 (0.58–1.04)
CRT-D system, n (%)		44 (4.05)	36 (6.65) 1.69 (1.07–2.66)	16 (6.81) NS	36 (7.05) 1.79 (1.14–2.83)	16 (7.62) 1.95 (1.08–3.53)	20 (6.54) NS
CRT-P system, n (%)		27 (2.49)	16 (2.96); NS	7 (2.98); NS	18 (3.52) NS	9 (4.29) NS	9 (2.94) NS
ILA, n (%)		204 (18.78)	113 (20.89) NS	45 (19.15) NS	161 (31.51) 1.99 (1.56–2.53)	95 (45.24) 3.57 (2.62–4.88)	68 (22.22) NS
Age of extracted lead, mo, mean (SD)		83.58 (61.61)	76.69 (54.34) P = 0.083	72.92 (51.00)	83.42 (58.44) NS	89.86 (60.82) P = 0.060	79.58 (56.68) NS
Longest lead dwell time, mo, mean (SD)		91.32 (72.02)	86.70 (63.89) NS	80.39 (57.88) P = 0.067	95.36 (71.16) P = 0.062	101.4 (75.35) P = 0.033	91.56 (67.86) NS
Sum of lead dwell times before TLE, y, mean (SD)		13.31 (11.79)	12.98 (10.04) NS	12.00 (9.21) NS	15.14 (12.53) P = 0.001	17.29 (14.66) P <0.001	13.73 (10.59) NS
Potential risk factors depending on previous procedures							
No. of previous procedures, mean (SD)		1.75 (3.26)	2.24 (1.27) P <0.0001	2.12 (1.12) p<0.0001	2.22 (1.38) P <0.0001	2.06 (1.37) P = 0.007	2.33 (1.37) P <0.0001
Time interval from the last procedure prior to TLE, mean (SD)		48.37 (35.43	23.64 (23.86) P <0.0001	22.93 (24.00) P <0.0001	30.87 (29.66) P <0.0001	40.99 (34.49) NS	24.18 (23.77) P <0.0001
Early reintervention (two latest procedures < 2 months), n (%)		34 (3.13)	39 (7.21) 2.40 (1.50–3.85)	15 (6.38) 2.11 (1.13–3.94)	29 (5.68) 1.86 (1.12–3.09)	5 (2.38) NS	24 (7.84) 2.63 (1.54–4.51)
Abandoned lead, n (%)		130 (11.97)	106 (19.59) 1.79 (1.38–2.37)	36 (15.32) 1.77 (1.37–2.30)	110 (21.53) 2.02 (1.52–2.67)	40 (19.05) 1.73 (1.17–2.56)	70 (22.88) 2.18(1.58–3.01)
No. of abandoned leads per patient, mean (SD)		0.16 (0.48)	0.28 (0.63) P =0.009	0.22 (0.56) NS	0.31 (0.67) P <0.0001	0.29 (0.66) P = 0.061	0.33 (0.67) P <0.0001
Leads on both sides of the chest, n (%)		39 (3.59)	33 (6.10) 1.74 (1.08–2.81)	14 (5.96) NS	35 (6.85) 1.97 (1.23–3.16)	14 (6.67) 1.92 (1.02–3.60)	19 (6.21) 1.78 (1.01–3.12)
Previous upgrade or implantation of additional lead, n (%)		154 (14.18)	81 (14.97) NS	28 (11.91) NS	85 (16.63) NS	32 (15.24) NS	53 (17.32) NS
Previous upgrade with abandonment of the lead, n (%)		66 (6.08)	39 (7.21) NS	10 (4.26) NS	43 (8.41) NS	14 (6.67) NS	29 (9.84) 1.62 (1.03–2.55)
Coronary angiography or PCI before TLE, n (%)		71 (6.54)	24 (4.44) NS	10 (4.26) NS	34 (6.65) NS	20 (9.52) NS	14 (4.58) NS
Lead loop near the TV and in the RV, n (%)		73 (6.72)	21 (3.88) 0.56 (0.34–0.92)	6 (2.55) 0.36 (0.16–0.85)	38 (7.44) NS	23 (10.59) 1.71 (1.04–2.80)	15 (4.90) NS

TABLE 2 Incidence of potential procedure-related risk factors for developing cardiac implantable electronic device infection (continued from the previous page)

Parameter	NI n = 1087 (59.1%)	PI n = 541 (72.1%)	IPI n =235 (31.3%)	LRIE n = 515 (68.7%)	ILRIE n = 209 (27.9%)	LRIE + PI n = 306 (40.8%)
Effectiveness and safety of TLE procedures						
Radiological success, n (%)	1029 (94.7)	521 (96.3) NS	225 (95.7) NS	486 (94.4) NS	190 (90.9) 1.81(1.05–3.10)	296 (96.1) NS
Clinical success, n (%)	1062 (97.7)	534 (98.7) NS	234 (99.5) NS	502 (97.5) NS	202 (96.7) NS	300 (98.0) NS
Major complications, n (%)	21 (1.93)	4 (0.74) NS	1 (0.43) NS	10 (1.94) NS	7 (3.35) NS	3 (0.98) NS
Minor complications, n (%)	46 (4.23)	26 (4.81) NS	9 (3.83) NS	36 (6.99) 1.70(–1.08–2.67)	19 (9.09) 2.26(1.30–3.95)	17 (5.56) NS

Abbreviations: ILA, intracardiac lead abrasion; PCI, percutaneous coronary intervention; others, see TABLE 1 and FIGURE 2

In the present study, diabetes, CRF, and HF were important clinical risk factors for developing CIED infection. The role of these factors was documented previously.[1,4,14] As for the clinical factors, our study revealed a surprising finding about the protective effects of anticoagulation and antiplatelet therapy. The fact that these protective effects were demonstrated in all the subgroups with CIED infections, including PI, is controversial. The available data on the effect of anticoagulation and antiplatelet therapy on the development of CIED infections are inconsistent. In a number of studies, both anticoagulation and antiplatelet therapy appeared to be a significant risk factor for the development of infectious complications, especially PI, because of the higher risk for postoperative hematoma at the pocket site.[4,15,16] It is, however, noteworthy that these agents have also anti-inflammatory properties, and the presence of complications during implantation probably does not determine the development of late infection evaluated in our study.

There is a growing body of evidence linking the use of acetylsalicylic acid (ASA) with the prevention of infectious complications in patients with CIED. The protective effects of ASA may be associated not only with the anti-inflammatory action through inhibition of prostaglandins, prostacyclin, and thromboxane, but also with direct antibacterial activity. In experimental infective endocarditis, ASA was shown to mitigate the expression of the 2 key genes responsible for the virulence of *Staphylococcus aureus*: α-toxins and fibronectin-binding protein.[17] Clinical findings in dialysis patients with indwelling venous catheters confirmed that ASA had direct antistaphylococcal effects.[18] The protective effects of oral anticoagulants on the development of CIED infection have not been reported yet, but evidence shows that vitamin K antagonists may rather increase the risk for developing infections.[19,20]

The possible protective effects of anticoagulants in the present study may have resulted from the exclusion of early CIED infection such as pocket hematomas from the analysis. Importantly, we observed that the mean time between the implantation and development of infection was over 90 months. In this context, it is evident that the present findings demonstrate an extremely important protective effect of anticoagulation that probably prevents clot formation on the implanted foreign body, and by this mechanism, reduces the risk of inflammatory processes. The concomitant presence, or in fact the induction of an inflammatory state by the mechanism of hypercoagulability, has been observed so far in patients with AF, in whom increased inflammatory markers were shown to be associated with arterial thrombosis.[21] A series of tests in patients with CIED might also demonstrate the presence of a hypercoagulable (inflammatory) state. Similar theories were put forward some time ago in a debate on whether patients with CIED should receive long-term anticoagulation, analogically to patients after artificial valve implantation. Such an approach was justified by the detection of pacemaker lead thrombosis in the right heart chambers and superior vena cava syndrome.[22,23] Currently, the interest in this theory revived especially in high-risk patients, that is, those with low left ventricular ejection fraction and undergoing CRT implantation,[23,24] as well as in relation with CHA_2DS_2-VASc or $CHADS_2$ scores used to stratify patients after pacemaker implantation due to sick sinus dysfunction who, regardless of AF history, had a high thrombotic risk.[25]

Because of the specificity of CIED infection, procedure-related factors appear to play a more important role than the clinical ones. There is no consensus among investigators regarding the relationship between the type of an implanted device, number and dwell times of the leads, lead dislodgement, time elapsing from implantation to infection, or the effect of previous interventions on the development of infection. In our study, the presence of defibrillation leads was a strong risk factor for the development of infectious complications. These findings are consistent with data obtained in our previous studies on a smaller group of patients,[26,27] which showed that there are certainly several possible causes of increased risk for CIED infections in all the subgroups of patients with ICD (large dimensions of the generator, additional proximal coil predisposing to abrasion).[27] Despite conflicting reports regarding the relation between the number of leads and infections,[4,14,15] the former appears to exert an effect because of possible abrasions, which were found to be involved in the development of LRIE in earlier studies.[26,27] In the present study, ILA was shown to be important only in the ILRIE subgroup, confirming that there is a separate mechanism by which ILRIE develops in contrast to potentially latent PI, which emerges late after the procedure and spreads to the endocardium along the leads. Abandoned leads, certainly increasing the risk of ILA, predispose to the development of infection. This view is supported by other investigators. Probably the largest data registry of TLE demonstrated that lead abandonment, apart from possible technical difficulties during lead extraction, favored the development of large vegetations on the lead; moreover, cultures grown from extracted lead tips were more frequently positive.[28]

The presence of lead loops was an important factor that increased the risk for developing infection (especially ILRIE) in the present study. The mechanism for the development of infection in these patients is probably connected with ILA within the looped lead or rubbing against the tricuspid valve. Additionally, the detailed analysis of patient subgroups in the present study confirmed the previous reports that the development of PI and ILRIE is mediated by 2 different mechanisms.[26,27] For this reason, the role of factors predisposing to PI is also different. As mentioned above, ILRIE is associated mainly with ILA, whereas PI results from a larger number of procedures preceding TLE, especially a short time interval between PI and the previous pacing intervention.

It is noteworthy that the crucial role of the procedure-related factors affecting the development of CIED infection is a novel finding in the present study, which, more often than not, should prompt us to consider prophylactic TLE in patients with lead dysfunction. This idea is further confirmed by a decidedly lower long-term mortality in patients undergoing procedures for noninfectious reasons. Moreover, one should bear in mind that the decision about inserting additional leads as well as prolongation of follow-up in patients with lead dysfunction increases the risk for developing CIED infection because of the higher number of electrode years and simultaneously increases the risk associated with TLE because of the lead dwell time. In the meantime, the high efficacy and safety of TLE procedures in an experienced center was demonstrated with more minor complications in patients with infectious indications (LRIE). Therefore, the theory of preventing the development of infectious complications through early resolution of noninfectious problems seems to be correct.

Survival analysis in patients with CIED infection demonstrated that all types of infection were associated with high long-term mortality rates, the highest being in the ILRIE subgroup. The clinical rather than procedure-related factors were found to have a decisive impact on the prognosis after TLE. This finding necessitates further studies to elucidate the direct cause of death in patients with CIED infection undergoing TLE. It is very important to explain why mortality rates in patients with IPI are only slightly lower than in patients with generalized infection. Such an infection requires intensified antibiotic treatment similarly as in patients with LRIE. It is likely that the local infection process more often denotes the involvement of the entire system than has been shown so far.

Our study was based on a select group of patients undergoing TLE. The limitation includes the lack of a comparative assessment with patient populations without complications related to pacing systems, as well as those who had not been referred for TLE despite noninfectious complications. It is possible that one of the subgroups (noninfectious indications) consisted of patients in whom TLE was performed to prevent the development of CIED infection in the future. Therefore, the effect of certain potential infectious risk factors may be difficult to document, providing even varying results in the univariate and multivariate analyses.

In conclusion, our study demonstrated a significant role of procedure-related factors on the development of infectious complications. Additionally, the impact of these factors was different in each subgroup with CIED infection, and the presence of 2 distinct mechanisms for the development of CIED infection was revealed. The relationship between multiple noninfectious indications for TLE (presence of abandoned leads, excessive length of the leads, lead loops, and secondary ILA) suggests the preventive role of early TLE prior to infection. An interesting finding in the present study is the protective effect of anticoagulation and antiplatelet therapy against the development of all types of CIED infection. This observation requires a randomized controlled trial to consider the wide use of this therapy in the prevention of CIED infections. Still, the high long-term mortality rates in patients undergoing TLE due to infection are an important problem, whereas it is especially difficult to explain short survival in patients with IPI, which is comparable to that in patients with LRIE. It is necessary to continue research into the direct causes of this phenomenon.

Supplementary material Supplementary material is available with the article at www.pamw.pl.

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