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Risk factors for Gram-negative bacterial infection of cardiovascular implantable electronic devices: multicentre observational study (CarDINe Study)☆

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The members of the CarDINe Study Group are listed in Appendix at the end of the article.

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ABSTRACT

Background: Infections of cardiovascular implantable electronic devices (CIED) are mainly due to Gram-positive bacteria (GPB). Data about Gram-negative bacteria CIED (GNB-CIED) infections are limited. This study aimed to investigate risk factors, clinical and diagnostic characteristics, and outcome of patients with GNB-CIED.

Methods: A multicentre, international, retrospective, case-control-control study was performed on patients undergoing CIED implantation from 2015 to 2019 in 17 centres across Europe. For each patient diagnosed with GNB-CIED, one matching control with GPB-CIED infection and two matching controls without infection were selected.

Results: A total of 236 patients were enrolled: 59 with GNB-CIED infection, 59 with GPB-CIED infection and 118 without infection. No between-group differences were found regarding clinical presentation, diagnostic and therapeutic management. A trend toward a higher rate of fluorodeoxyglucose positron emission computed tomography (FDG PET/CT) positivity was observed among patients with GNB than in those with GPB-CIED infection (85.7% vs. 66.7%; $P = 0.208$). Risk factors for GNB-CIED infection were Charlson Comorbidity Index Score (relative risk reduction, RRR = 1.211; $P = 0.011$), obesity (RRR = 5.122; $P = 0.008$), ventricular-pacing ventricular-sensing inhibited-response pacemaker implantation (RRR = 3.027; $P = 0.006$) and right subclavian vein site of implantation (RRR = 5.014; $P = 0.004$). At 180-day survival analysis, GNB-CIED infection was associated with increased mortality risk (HR = 1.842; $P = 0.067$).

Conclusions: Obesity, high number of comorbidities and right subclavian vein implantation site were associated with increased risk of GNB-CIED infection. A prompt therapeutic intervention that may be guided using FDG PET/CT is suggested in patients with GNB-CIED infection, considering the poorer outcome observed in this group.

1. Introduction

Cardiac implantable electronic devices (CIED)—including permanent pacemakers (PM), implantable cardioverter-defibrillators (ICD) and cardiac resynchronisation therapy devices (CRTD)—have improved patients' survival and quality of life [1].

Infections are a serious complication of CIED implantation [2,3], with incidence varying from 0.5% – 10% in different studies [3,4]. Gram-positive bacteria (GPB), especially coagulase-negative *Staphylococcus* spp. and *Staphylococcus aureus*, are the most common microorganisms isolated from patients with CIED infections [5,6]. Although less frequently isolated from patients with CIED infection, Gram-negative bacteria (GNB) are currently the most common causative pathogens of healthcare-associated infections and are associated with high morbidity and mortality rates [7,8].

The literature results on CIED infections are mostly derived from cohorts of patients with GPB isolates [9–11]. Thus, data are limited about prevalence, risk factors and clinical presentation of CIED infections due to GNB (GNB-CIED) and the reliability of diagnostic tools in the management of such episodes [12,13].

To fill this gap, a multicentre, retrospective, matched case-control-control study in patients with CIED implantation was conducted to investigate the risk factors for the development of GNB-CIED infections, as well as the clinical and diagnostic characteristics and outcomes of these infections.

2. Material and methods

2.1. Study design and population

A multicentre, international, retrospective, matched, case-control-control study was performed. All adult patients with a diagnosis of CIED infection from 1 January 2015 to 31 December 2019 were screened for enrolment using local registries of implanted cardiac devices at each clinical site. Records were matched with the local microbiology databases to identify patients who developed a CIED infection within 1 year from implantation. Inclusion criteria were: i) adult age (≥ 18 years); ii) implantation with PM, ICD and/or CRTD; and iii) acceptance to participate by informed consent. Patients with CIED infection due to polymicrobial aetiology were excluded.

The included participants were classified as cases or controls according to the following definitions: i) case: a patient diagnosed with a local device infection or CIED-related infective endocarditis with isolation of a GNB (GNB-CIED infection) from the insertion site, the lead and/or blood cultures (BCs); ii) control 1: a patient diagnosed with a local device infection or CIED-related infective endocarditis with isolation of a GPB (GPB-CIED) from the wound, lead and/or BCs; iii) control 2: patients without a diagnosis of local device infection or CIED-related infective endocarditis within 1 year after CIED implantation. For each patient diagnosed with GNB-CIED, one control with GPB-CIED infection and two controls without infection were selected (ratio 1:1:2), matched by implantation period (± 1 year) and study centre. To avoid multiple stratification limiting the sample size, no other matching criteria were employed. All other variables were included as potential confounders in the multivariable multinomial logistic regression.

Hospital records and phone interviews were the sources of the follow-up data. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the ethics committee of the coordinating centre (EM487 2021_117/2021/Oss/AOUBo) and by ethics committees of all participating centres. During the study period, indications for CIED implantation and patient management were determined by the discretion of the attending physicians at each centre.

2.2. Setting

This study was endorsed by the Study Group for Implant-Associated Infections of the European Society of Clinical Microbiology and Infectious Diseases (ESGIAI), the European Society of Clinical Microbiology and Infectious Diseases Study Group for Bloodstream Infections, Endocarditis and Sepsis (ESGBIES) and The Study Group for Carbapenem Resistance (SCARE). Seventeen hospitals performing CIED implantation participated in the study: six from Italy (Bologna, Cotignola, Milan, Rome, Brescia, Naples); five from

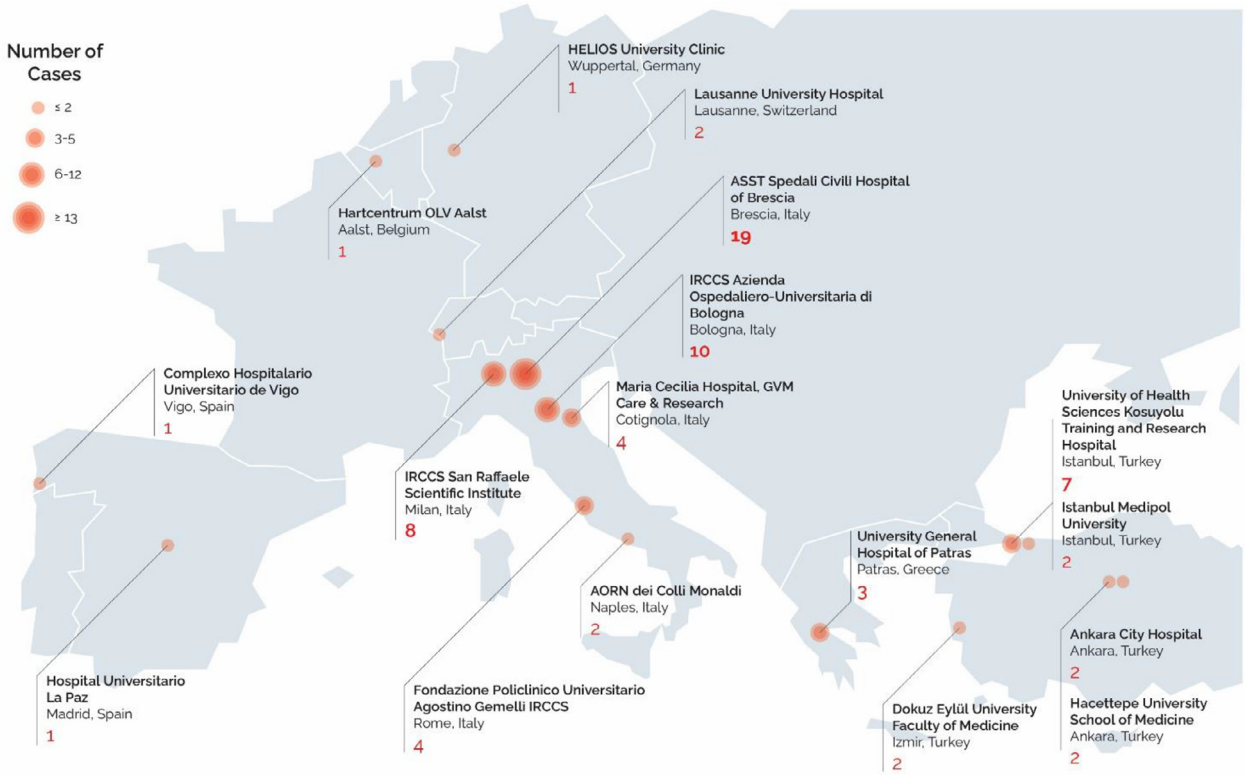

Figure 1. Participating centres.

Turkey (two in Istanbul, two in Ankara, one in Izmir); two from Spain (Madrid and Vigo); one from Germany (Wuppertal); one from Switzerland (Lausanne); one from Belgium (Aalst); and one from Greece (Patras) (Supplementary Table 1 and Figure 1).

2.3. Variables and definitions

Study variables were collected using a dedicated REDCap electronic case report form (eCRF) hosted by IRCCS Azienda Ospedaliero-Universitaria di Bologna [14]. Of note, patients were considered once at the time of their first episode of CIED infection.

The primary endpoint was the diagnosis of CIED infection, defined as local infection or CIED-related infective endocarditis according to ESC guidelines [15] and the last European Heart Rhythm Association (EHRA) international consensus document available during protocol design [16]. Secondary endpoints included: persistence of infection/failure, all-cause mortality, and recurrence at 30, 90 and 180 days from the diagnosis of CIED infection (day of drawing index positive samples). Infection persistence/failure was defined as the persistence of signs and/or symptoms of local or systemic infection at the end of appropriate management according to vital signs, clinical evolution of SOFA score [17] and laboratory data. Recurrence of infection was defined as infection of a newly implanted device after appropriate management of the index CIED infection with isolation of the same microorganism.

Other data included: demographics (age and sex); date of hospital admission and discharge; ward of management; and risk factors classified as:

patient-related: comorbidity according to Charlson Comorbidity Index Score (CCIS) [18]; immunosuppression including neutropenia (absolute neutrophil count $< 500/mm^3$); solid organ transplantation; haematopoietic stem cell transplantation; corticosteroid therapy at a dosage $\geq$ to prednisone 16 mg/day during at least 15 days; uncontrolled HIV infection (< 200 CD4/mm^3); oral anticoagulant use; heparin bridging; aetiology of cardiac disease and indication for cardiac device implantation; and a previous history of CIED implantation/extraction.

procedure-related: characteristics of implanted device (type, site); procedure duration; haematoma; temporary pacing; device replacement/revision/upgrade; generator change; and type of antibiotic prophylaxis.

device-related: epicardial leads; abdominal pocket; two or more leads; and dual chamber device.

The CIED infections were classified according to the timing of implantation into episodes diagnosed before or after 90 days from implantation. Isolates were classified according to the criteria of Magiorakos et al. as multidrug-resistant or extensively drug-resistant [19]. For therapeutic management source control, follow-up BCs, empiric and definitive antibiotic therapy, and treatment duration were analysed. Source control was defined as removal of a generator plus leads. Time from diagnosis to source control was collected. Positive follow-up BCs were defined as those drawn within 2 – 7 days and positive for the same pathogen recovered from the index BCs in bacteraemic CIED infection episodes. Empiric antibiotic therapy was defined as antibiotic administration before the susceptibility report was available, and it was appropriate when at least one in vitro active antibiotic was administered. Treatment duration was defined as the time elapsed from the first to the last day of an appropriate antibiotic regimen.

2.4. Statistical analysis

Demographic and clinical characteristics of patients were compared across the three groups using χ^2 test or Fisher's exact test, or one-way ANOVA with Scheffé post-hoc comparison, according to the distributional properties of variables. To assess differences in the therapeutic management and outcome, patients with GNB infections were compared with those with GPB infections using χ^2 test or Fisher's exact test, and Mann-Whitney U test.

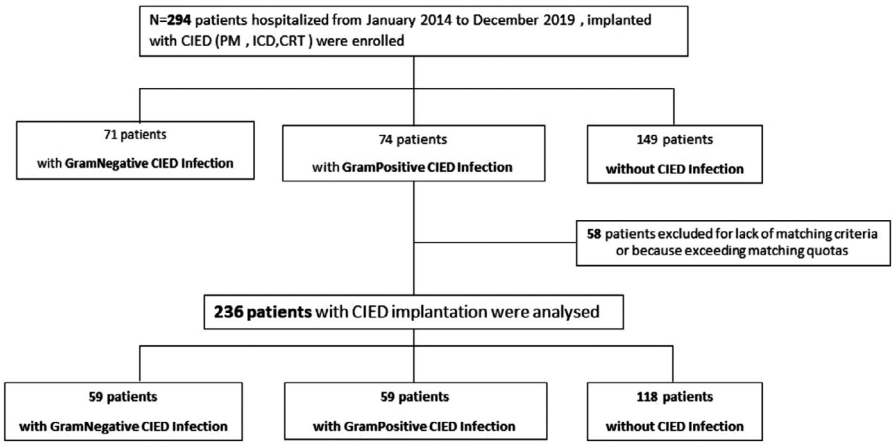

Figure 2. Study flow chart.

Multivariable, multinomial logistic regression was performed to identify factors associated with GPB and GNB infection, using non-infected patients as the reference group. An initial model was created including all variables associated with infection at bivariate analysis with $P < 0.100$ as predictor. The final model was obtained by backward trimming non-significant covariates until all variables retained in the model were associated with at least one of the outcome categories. From this model, predictive margins were calculated and graphically displayed to represent the model-adjusted estimated relationship between significant predictors and the infection outcome.

Mortality at 180 days from infection onset for patients with CIED infection and from CIED implantation for patients without CIED infection was investigated with survival analysis, by means of log-rank test and Cox multivariable regression, in which the type of bacterial infection was imposed as the risk factor of interest and the main known predictors of mortality were added as potential confounders. Patients were censored at death or 1-year follow-up, whichever occurred first.

In both multivariable analyses, robust standard errors were obtained to account for patients' grouping in centres. The analysis was carried out with SPSS 21.0 and Stata v.17.0, and *P*-values < 0.05 were considered statistically significant.

3. Results

Over the study period, 294 patients undergoing CIED implantation were enrolled. Of them, 71 had GNB-CIED infection, 74 had GPB-CIED infection and 149 patients did not develop infection. The yearly prevalence of Gram-negative CIED infections per 1000 CIED in the participating centres ranged between 1.2 – 1.6 during the study period (Supplementary Figure).

After matching, 58 patients were excluded and 236 participants were analysed: 59 with GNB-CIED infection, 59 with GPB-CIED infection and 118 without infection (Figure 2). The characteristics of the study population are shown in Table 1. Among the 236 analysed participants, 174 (73.7%) were male, with mean age of 69.1 ± 12.8 years and CCIS of 5.03 ± 2.34 (Table 1). Among participants with GNB-CIED infection, 41 (69.5%) were male, with a mean age of 71.5 years (SD ± 12.5) and CCIS of 5.69 ± 2.24. The most frequent underlying cardiac diseases requiring CIED implantation in patients developing GNB-CIED infection were bradyarrhythmia (28, 47.5%), heart failure (18, 30.5%) and primary prevention (12, 20.3%) (Table 1).

Infection characteristics and management are summarised in Table 2. Infectious endocarditis accounted for 61.9% of the CIED infection, with no difference in incidence between GPB or GNB aetiology. The remaining subjects had localised device pocket infection. The microorganisms responsible of CIED infection and their susceptibility profiles are reported in Supplementary Table 2. Coagulase-negative *Staphylococcus* spp. (32, 54.2%) and *Staphylococcus aureus* (23, 39.0%) were the most frequent GPB isolates. The most common isolate among GNB infections was *Pseudomonas aeruginosa* (17, 28.8%).

The diagnosis of CIED infection was made after a median time of 11 months (IQR = 1.5 – 31.3) from implantation in case of GNB aetiology and 10 months for GPB aetiology (IQR = 4 – 25) ($P = 0.899$).

Echocardiography was performed in 114 (96.6%) patients, yielding CIED endocarditis in 44 of them (37.2%) (Table 2); the rate of positive echocardiography was similar between GNB and GPB CIED infections ($P = 0.232$). Fluorodeoxyglucose positron emission computed tomography (FDG PET/CT) was performed in 23 patients, yielding CIED infection in 18 of them (78.3%). The FDG PET positivity rate was higher among GNB than GPB infection but did not reach statistical significance (85.7% vs. 66.7%; $P = 0.208$).

Empiric antibiotic treatment was initiated in most patients (87.3%). As expected, appropriate empiric treatment was less frequent in GNB-CIED infection due to the uncommon aetiology (GNB 28.6% vs. GPB 46.3%; $P = 0.007$). The median full course of appropriate antibiotic therapy was 15 days (IQR 8 – 25), which was similar in both groups (Table 2). In a subgroup analysis of patients with a diagnosis of endocarditis, the median time of antibiotic therapy after device removal was 17 days (IQR 12 – 31).

Device extraction was performed in most patients (90.7%), mainly through transvenous lead extraction and without differences between GNB and GPB-CIED infection. Multinomial logistic regression (Table 3) showed that ventricular-pacing ventricular-sensing inhibited-response pacemakers (PM-VVI) were the only variable that was significantly associated with a higher risk of both GNB (relative risk reduction, RRR = 3.027, 95% CI 1.372 – 6.680; $P = 0.006$) and GPB infections (RRR = 3.032, 95% CI 1.058 – 8.691; $P = 0.039$). Among the other variables, CCIS (RRR = 1.211, 95% CI 1.045 – 1.404; $P = 0.011$), obesity (RRR = 5.122, 95% CI 1.536 – 17.085; $P = 0.008$) and right subclavian site of implantation (RRR = 5.014, 95% CI 1.665 – 15.101; $P = 0.004$) predicted a higher risk of GNB infection, while male sex (RRR = 3.617, 95% CI 1.576 – 8.301; $P = 0.002$), age at device implantation (RRR = 1.031, 95% CI 1.001 – 1.063; $P = 0.041$), CRT-D (RRR = 2.692, 95% CI 1.706 – 4.249; $P < 0.001$) and Shariff score (RRR = 1.682, 95% CI 1.234 – 2.293; $P = 0.001$) were associated with a higher risk of GPB infection. Figure 3 shows that patients without PM-VVI had a low

Table 1
Characteristics of the study population.

	Total $n = 236$	Gram-negative $n = 59$	Gram-positive $n = 59$	Not infected $n = 118$	*P*-value	Post-hoc comparisons
Males	174 (73.7)	41 (69.5)	53 (89.8)	80 (67.8)	0.005	
Age at CIED implantation (mean ± SD)	69.1 ± 12.8	71.5 ± 12.5	69.3 ± 12.8	67.7 ± 12.0	0.149	-
Comorbidity						
Charlson Comorbidity Index (mean ± SD)	5.03 ± 2.34	5.69 ± 2.24	5.03 ± 2.34	4.29 ± 2.25	< 0.001	NI < GN
Shariff score (mean ± SD)	1.73 ± 1.17	2.00 ± 1.19	2.14 ± 1.25	1.40 ± 1.02	< 0.001	NI < GN, GP
Solid tumour	11 (4.6)	5 (8.4)	4 (6.7)	2 (1.6)	0.201	
Obesity	19 (8.1)	11(18.6)	3 (5.1)	5 (4.2)	0.005	
Diabetes mellitus	58 (31)	22 (40)	16 (34)	20 (23.5)	0.105	
Underlying cardiac disease						
• Bradyarrhythmia	115 (48.7)	28 (47.5)	23 (39)	64 (54.2)	0.156	
• Primary prevention	71 (30.1)	12 (20.3)	22 (37.3)	37 (31.4)	0.122	
• Secondary prevention	18 (7.6)	6 (10.2)	6 (10.2)	6 (5.1)	0.339	
• Heart failure	65 (27.5)	18 (30.5)	23 (39)	24 (20.3)	0.027	
Ejection fraction						
• > 50%	104 (44.1)	26 (44.1)	21 (35.6)	57 (48.3)	0.275	
• 40% – 50%	26 (11)	9 (15.3)	7 (11.9)	10 (8.5)	0.386	
• < 40%	99 (41.9)	23 (39)	29 (49.2)	47 (39.8)	0.430	
Anticoagulation therapy						
• Warfarin	53 (22.5)	12 (20.3)	19 (32.2)	22 (18.6)	0.113	
• NOAC	33 (14)	5 (8.5)	12 (20.3)	16 (13.6)	0.175	
• Heparin	8 (3.4)	3 (5.1)	2 (3.4)	3 (2.5)	0.678	
Site of implantation ($n = 232$)					0.033	
• left subclavian vein	207 (89.2)	47 (79.7%)	53 (93.0%)	107 (92.2%)		
• right subclavian vein	21 (9.1)	11 (18.6%)	4 (7.0%)	6 (5.2%)		
• subcutaneous vein	4 (1.7)	1 (1.7%)	0 (0)	3 (2.6%)		
Antibacterial envelope ($n = 203$)	20 (9.9)	7 (13.7%)	5 (10.2%)	8 (7.8%)	0.479	
Previous CIED implantation ($n = 233$)	67 (28.8)	19 (32.8)	22 (37.3)	26 (22.4)	0.089	
Previous device extraction	19 (29.7)	5 (27.8)	8 (38.1)	6 (24)	0.568	
Reason for previous device extraction						
• *Infection*	6 (31.5)	1 (20)	4 (50)	1 (16)	0.055	
• *Malfunction*	6 (31.5)	0 (0)	2 (25)	4 (66)	0.358	
• *Other reason (vascular issue, tricuspid regurgitation)*	7 (36.8)	4 (80)	2 (25)	1 (16)	0.088	
Infection episode 90 days prior implantation ($n = 110$)	16 (14.5)	10 (18.2)	6 (10.9)	/	0.279	
Type of infection						
• *UTI*	3 (18.7)	2 (20)	1 (16.6)			
• *IAI*	1 (6.25)	1 (10)	0 (0)			
• *SSTI*	1 (6.25)	0 (0)	1 (16.6)			
• *LRTI*	4 (25)	2 (20)	2 (33)			
• *BSI*	10 (62.5)	6 (60)	4 (66.6)			
Type of implanted CIED						
PM-VVI	26 (11)	10 (16.9)	8 (13.6)	8 (6.8)	0.097	
PM-DDD	86 (36.4)	18 (30.5)	14 (23.7)	54 (45.8)	0.009	
CRT-P	7 (3)	2 (3.4)	1 (1.7)	4 (3.4)	0.802	
CRT-D	56 (23.7)	13 (22)	22 (37.3)	21 (17.8)	0.015	
ICD-VVI	25 (10.6)	5 (8.5)	7 (11.9)	13 (11)	0.818	
ICD-DDD	36 (15.3)	11 (18.6)	7 (11.9)	18 (15.3)	0.592	
ICD Subcutaneous	1 (0.4)	0	0	1 (0.8)	0.605	

Abbreviations: CIED, cardiac implantable electronic devices; CRT, cardiac resynchronisation therapy; CRT-D, cardiac resynchronisation therapy defibrillator; CRT-P, cardiac resynchronisation therapy pacemaker; ICD-DDD, dual chamber - implantable cardioverter-defibrillator; ICD-VVI, ventricular-pacing ventricular-sensing inhibited-response implantable cardioverter-defibrillator; IAI, intra-abdominal infection; ICD, implantable cardioverter-defibrillator; LRTI, lower respiratory tract infection; NOAC, new oral anticoagulants; PM, pacemaker; PM-DDD, dual chamber pacing pacemaker; PM-VVI, ventricular-pacing ventricular-sensing inhibited-response pacemaker; SD, standard deviation; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

risk of both GPB and GNB infections, and that the risk of both infections was higher in patients with PM-VVI at approximately the same magnitude. The risk of a GNB infection clearly increased with obesity and at higher values of CCIS. The opposite trend was estimated for Shariff score, whose higher values predicted a higher risk of GPB infection.

Regarding the outcomes, persistence of infection was observed in 11, three and two patients at 30, 90 and 180 days of follow-up. No between-group differences were observed. Recurrence was observed at 30 and 90 days of follow-up in two patients, both with GNB-CIED infection. All-cause mortality occurred only among infected patients in five (2.1%), 10 (4.2%) and 12 (5.1%) patients, at 30, 90 and 180 days, respectively. The all-cause mortality rates at any time of follow-up were higher for patients with GNB-CIED infection compared with those with GPB-CIED infection, although non-significantly (Table 2).

Since there were no mortality events in uninfected patients, regardless of matching, a 180-day survival analysis was performed in all patients with infection ($n = 136$). The Cox regression model provided the best fit to the data. The type of bacterial infection (GNB vs. GPB) was assumed as the main risk factor, with GNB-CIED showing a marginally significantly higher risk after the first 2 months of follow-up (Figure 4), which was confirmed at Cox regression analysis (HR = 1.842, 95% CI 0.958 – 3.541; $P = 0.067$), adjusted for endocarditis (HR = 3.983, 95% CI 1.320 – 12.014; $P = 0.014$) and device extraction (HR = 0.085, 95% CI 0.014 – 0.533; $P = 0.008$). Age at diagnosis, time from implantation to infection (transformed as natural logarithm) and CCIS were included in the

Table 2
Infection characteristics, management and outcome.

	Total $n = 118$	Gram-negative $n = 59$	Gram-positive $n = 59$	*P*-value
Type of infection and clinical presentation				
Local device infection	45 (38.1)	23 (39.0)	22 (37.3)	0.757
Endocarditis	73 (61.9)	36 (61.0)	37 (62.7)	0.850
Septic embolism	6 (5.1)	3 (5.1)	3 (5.2)	0.983
• *Pulmonary*	4 (66.7)	1 (33)	3 (100)	0.083
• *Central nervous system*	1 (16.7)	1 (33)	0 (0)	0.195
• *Spleen*	1 (16.7)	1 (33)	0 (0)	0.195
SOFA (median, IQR)	1 (0 – 2)	1 (0 – 2)	1 (0 – 2)	0.168
Septic shock	3 (2.7)	0 (0)	3 (5.2)	0.087
Time from CIED implantation to infection diagnosis in months (median, IQR)	10.4 (2.1 – 27.3)	11.0 (1.5 – 31.3)	10.0 (4.0 – 25.0)	0.899
Days from last CIED procedure to infection diagnosis				0.025
• *< 90 days*	31 (26.5)	21 (35.6)	10 (17.2)	
• *> 90 days*	86 (73.5)	38 (64.4)	48 (82.8)	
Instrumental execution				
Echocardiography execution	114 (96.6)	57 (96.6)	57 (96.6)	1.000
Positive echocardiography (vegetations)	44 (37.2)	20 (33.9)	24 (40.7)	0.232
• *Transthoracic*	11 (25)	3 (15)	8 (33)	0.119
• *Transoesophageal*	33 (75)	17 (85)	16 (66)	0.944
Site of vegetations (both ETT/EET)				
• *Lead*	36 (31.6)	17 (29.8)	19 (33.3)	0.689
• *Valve*	3 (2.6)	/	3 (5.2)	0.244
FDG PET/CT execution	23 (9.7)	14 (23.7)	9 (15.3)	0.245
Positive FDG PET/CT	18 (78.3)	12 (85.7)	6 (66.7)	0.280
Site of hypercaptation				
• *Lead*	9 (39)	7 (50)	2 (22)	0.083
• *Generator*	15 (65)	9 (64)	6 (66)	0.407
• *Skin and soft tissue*	3 (13)	3 (21)	0 (0)	0.079
Microbiological diagnosis				
Type of sample				
Swab of pocket	56 (47.5)	31 (52.5)	25 (42.4)	0.269
Generator	25 (21.2)	13 (22)	12 (20.3)	0.822
Leads	53 (44.9)	24 (40.7)	29 (49.2)	0.355
Blood	43 (36.4)	24 (40.7)	19 (32.2)	0.326
Follow-up blood cultures	26 (70.3)	16 (61.5)	10 (90.9)	0.074
• *Positive FU BCs*	10 (38.4)	8 (50)	2 (20)	0.134
Management				
Appropriate empiric antibiotic therapy	39 (57.4)	14 (28.6)	25 (46.3)	0.007
Duration of antibiotic therapy (days) (median IQR)	15 (8 – 25)	16 (9 – 22)	14 (8 – 32)	0.202
Device extraction	107 (90.7)	52 (88.1)	55 (93.2)	0.342
Type of extraction				
• TLE	94 (79.7)	45 (76.3)	49 (83.1)	0.369
• Surgical lead extraction	12 (10.2)	6 (10.2)	6 (10.2)	1
Days from infection diagnosis to extraction (median, IQR)	9 (3 – 27)	15 (4 – 28)	9 (2 – 23)	0.338
Outcome				
Persistent infection/failure				
• *30 days*	11 (9.3)	6 (10.2)	5 (8.5)	0.532
• *90 days*	3 (2.6)	2 (3.4)	1 (1.7)	0.695
• *180 days*	2 (1.7)	1 (1.7)	1 (1.7)	0.231
Recurrence				
• *30 days*	1 (0.8)	1 (1.7)	0 (0)	0.532
• *90 days*	1 (0.8)	1 (1.7)	0 (0)	0.695
• *180 days*	0 (0)	0 (0)	0 (0)	0.231
All-cause mortality ($n = 134$)				
• *30 days*	5(4.2)	3 (5.1)	2(3.4)	0.679 (F)
• *90 days*	10 (8.5)	7(11.9)	3 (5.1)	0.398 (F)
• *180 days*	12 (10.2)	9 (15.2)	3 (5.1)	0.145 (F)

Abbreviations: CIED, cardiac implantable electronic devices; ETT, trans-thoracic echocardiography; EET, transoesophageal echocardiography; FDG PET/CT, fluorodeoxyglucose positron emission computed tomography; FU BCs, follow-up blood cultures; IQR, interquartile range; SOFA, sequential organ failure assessment score; TLE, transvenous lead extraction; (F), Fisher's exact test.

initial model and then removed because they were non-significant (all had $P > 0.300$) (Table 4).

4. Discussion

It is believed that this is the largest series of patients with GNB-CIED infections, collected from 17 centres across Europe over a 5-year period, providing a comparison with GPB-CIED infections and uninfected patients. There was no significant difference between the GNB and GPB groups in terms of clinical presentation, diagnostic and therapeutic issues. The FDG PET/CT seemed to be very useful in diagnosing GNB-CIED endocarditis and GPB-CIED endocarditis (85.7% vs. 66.7%). Risk factors associated with the development of GNB-CIED infection were different from those associated with GPB-CIED infection. Finally, survival probabilities were lower among patients with GNB-CIED infection than those with GPB-CIED infection.

Gram-negative bacteria are relatively infrequent but important pathogens responsible for CIED infections. Knowledge about this type of infection is limited to case reports and case series [12,20–22]. The largest experience reported to date is that of Esquer Garrigos et al., who analysed a single-centre cohort of 31 GNB-CIED

Table 3
Multinomial logistic regression of infection development (not infected = base outcome).

Gram-negative CIED infection risk	RRR	95% CI	*P*-value
Males	0.869	0.425 – 1.776	0.700
Age at device implantation	1.015	0.987 – 1.044	0.303
Charlson Index Score	1.211	1.045 – 1.404	0.011
Obesity	5.122	1.536 – 17.085	0.008
PM-VVI	3.027	1.372 – 6.680	0.006
CRT-D	1.267	0.408 – 3.936	0.682
Right subclavian vein site of implantation	5.014	1.665 – 15.101	0.004
Shariff score	1.270	0.882 – 1.830	0.199
constant	0.315	0.170 – 0.585	< 0.001
Gram-positive CIED infection risk			
Males	3.617	1.576 – 8.301	0.002
Age at device implantation	1.031	1.001 – 1.063	0.041
Charlson Index Score	0.920	0.819 – 1.033	0.159
Obesity	0.987	0.301 – 3.240	0.983
PM-VVI	3.032	1.058 – 8.691	0.039
CRT-D	2.692	1.706 – 4.249	< 0.001
Right subclavian vein site of implantation	1.435	0.448 – 4.601	0.543
Shariff score	1.682	1.234 – 2.293	0.001
constant	0.112	0.050 – 0.250	< 0.001

Abbreviations: CIED, cardiac implantable electronic devices; CRT-D, cardiac resynchronisation therapy devices; RRR, relative risk ratio; PM-VVI, ventricular-pacing ventricular-sensing inhibited-response pacemaker.
RRR for constant was estimated with respect to all covariates at their reference value.

Figure 3. Predictive margins. Abbreviations: PM-VVI, ventricular-pacing ventricular-sensing inhibited-response pacemaker.

infections collected over a 23-year period [12]. The low prevalence of this kind of infections is confirmed by the current study and others in the literature [6].

Regarding clinical presentation of GNB-CIED infection, it was more frequently associated with pocket infection compared with GPB-CIED infection in previous studies [12]. Although these data do not appear to be confirmed in the current study, there are limited studies of this kind of infection and further investigation is required to clarify this aspect.

The FDG PET/CT is a diagnostic tool in several infectious diseases such as prosthetic joint infections, vascular prosthesis infection, vertebral osteomyelitis, septic thrombophlebitis or complicated bloodstream infections with septic metastases [23–25]. Specifically for cardiac infection, FDG PET/CT may provide advantages over echocardiography in patients with foreign bodies [26–28]. The FDG PET/CT was introduced in the 2015 ESC Criteria for the diagnosis of possible endocarditis associated with prosthetic valves [15] and for CIED infections [16,26,29]. According to the cur-

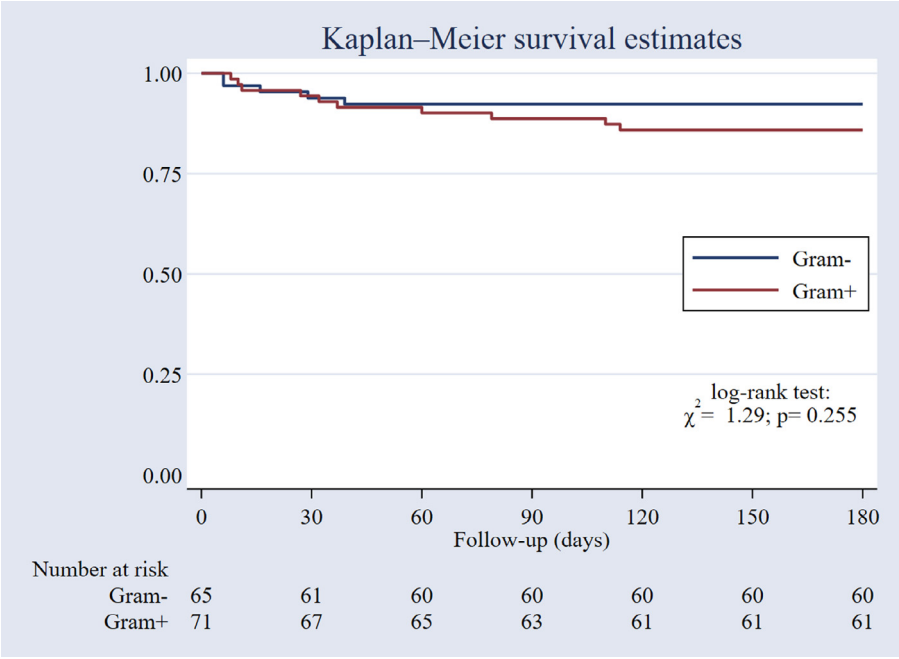

Figure 4. All-cause mortality at 180-days follow-up between patients with Gram-negative and Gram-positive cardiac implantable electronic devices infection.

Table 4
Cox multivariable regression of mortality at 180 days (patients with GNB- or GPB-CIED infection, n = 136).

	Initial model			Final model		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Gram-negative infection	1.828	0.977 – 3.423	0.059	1.842	0.958 – 3.541	0.067
Age at diagnosis of infection (years)	0.974	0.927 – 1.023	0.293			
Time from device implantation to infection (log years)	1.188	0.811 – 1.739	0.377			
Charlson Comorbidity Index Score	1.191	0.936 – 1.516	0.155			
Endocarditis	2.975	0.898 – 9.850	0.074	3.983	1.320 – 12.014	0.014
Device extraction	0.076	0.009 – 0.668	0.020	0.085	0.014 – 0.533	0.008

Abbreviations: HR, hazard ratio; CIED, cardiac implantable electronic devices; GNB, Gram-negative bacteria; GPB, Gram-positive bacteria.

rent data, the yield of FDG PET/CT seems higher for GNB- than for GPB-CIED infection diagnosis. It is worth mentioning that Chesdachai et al. [22] have recently reported 126 patients with CIED and concomitant GNB bacteraemia, finding that 3% of patients had definite CIED infection. Among imaging tools used for CIED diagnosis, echocardiography was the most frequently used. Conversely, FDG PET/CT was performed in two patients. It can be speculated that the rate of GN-CIED infection in this cohort and in general practice may have been underestimated due to the low diagnostic efficiency of traditional assays.

The Shariff score is known to be an indicator of the risk of GPB-CIED infection development in the months following device implantation [30–32]. The Shariff score confirmed its predictive value in the current cohort of patients with GPB-CIED infection; however, its efficacy was not confirmed in the group of patients with GNB-CIED infection.

Two peri-procedural factors appeared to be related to GNB-CIED infection in the current study. The first was implantation in the right subclavian vein. This could have been due to a relatively longer duration of manoeuvres in the right side, which is usually not the first choice for implantation. Due to the retrospective nature of this study, the duration of the procedures was not accurately collected in this population; therefore, this currently remains a speculative observation. The second risk factor for GNB-CIED infection was implantation of PM-VVI. Compared with more complicated procedures, such as biventricular PM/ICD, PM-VVI implantation appears to be related to GNB-CIED infection. A possible explanation of this finding is that patients implanted with PM-VVI are usually older than those implanted with other CIED and with more comorbidities [33]. Consistent with the other findings, this observation could explain the increased risk of GNB-CIED infection in this subgroup of patients; however, further studies are needed to investigate and confirm this finding.

Implantation of cardiac resynchronisation therapy devices (CRT-D) beyond PM-VVI appears to be related to GPB-CIED infection. These findings were already reported from previous studies as risk factors for infection development [4,34], confirming the reliability of the data from the current cohort.

This study found GNB-CIED infection to be associated, with marginal statistical significance, with a higher all-cause mortality rate at 6 months, confirming prior literature data on mortality rates ranging between 2% – 10% [12,20]. At multivariable analysis, infective endocarditis was the only independent risk factor for mortality. Conversely, removal of the device was protective. Recurrence of CIED infection was observed in two patients, both with GNB aetiology. A possible explanation of this finding could be the less frequently appropriate empiric treatment administered in GNB-CIED infection. However, due to the limited number of cases, further investigations are needed to confirm this observation.

Finally, the current patients with a diagnosis of CIED endocarditis received a median 17 days of antibiotic treatment after device removal. The data may support indications from the last EHRA consensus document [16] suggesting that 2 weeks of therapy may be sufficient after device removal in patients with documented nega-

tive follow-up blood culture, absence of echocardiographic signs of valve vegetation or pulmonary abscesses and reporting early clinical improvement.

This study had several limitations. Although this is the largest cohort of patients with GNB-CIED infections currently available in the literature, the limited sample size and number of events may have affected statistical power. However, the comparison of patients with GPB-CIED infections and without CIED infections could have improved the relevance of the results identifying differences between infection aetiologies and the risk factors for GN infection in all patients needing CIED implantation. The retrospective design of the study could have reduced the accuracy and completeness of data collection. However, it was attempted to reduce this limitation by thorough data quality control, creating queries to identify and correct missing and incongruent data. Finally, heterogeneity in local management may have existed - this was unavoidable. Due to the scarcity of available data on GNB-CIED infections, multicentric studies are necessary. Statistical tools were applied with the aim of reducing the effect of heterogeneity on estimates.

In conclusion, despite these limitations, there are some novel key messages from this study. Patients with a high number of comorbidities who undergo right subclavian vein implantation may be patients at high risk of developing a GNB-CIED infection. The higher mortality associated with GNB-CIED infection makes it necessary to suspect and make an early diagnosis of this type of infection. The FDG PET/CT seems to be useful in this framework; however, further studies are needed to confirm this hypothesis.

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Ethics Approval: The study was approved by the Ethics Committee of the coordinating centre (EM487 2021_117/2021/Oss/AOUBo) and by Ethics Committees of all participating centres.

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Diseases, in Lisbon, Portugal & online from 23 – 26 April 2022.

Availability of data and material: All data generated or analysed during this study are included in this published article.

Authors' contributions: RP, AM, DG, ID and MG contributed to conceptualisation and design of the study; AT, ATA, GM, AM, DF, ADA, MR, MEI, YUK, SI, MC, FP, KA, AK, MPO, BK, YAB, EEO, OET, MCI, MTPR, BLY, MY, SP and TDP contributed to acquisition of data; RP, AT, ATA and DG, contributed to analysis and interpretation of data; RP, DG and MG contributed to writing the original draft; ATA, MR, AMQ, TDP, EDM, MA, AC, DG, ID, LS, PV and MG contributed to reviewing and editing; PV and MG supervised the work.

Competing Interests

All the authors report no conflicts of interest.

Appendix. CarDINe Study Group

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.106734.

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