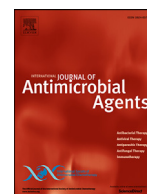




Contents lists available at ScienceDirect

## International Journal of Antimicrobial Agents

journal homepage: [www.elsevier.com/locate/ijantimicag](http://www.elsevier.com/locate/ijantimicag)

## Risk factors for Gram-negative bacterial infection of cardiovascular implantable electronic devices: multicentre observational study (CarDINE Study) <sup>☆</sup>



Renato Pascale<sup>1,2,\*</sup>, Alice Toschi<sup>1</sup>, Abdullah Tarik Aslan<sup>3,4</sup>, Giulia Massaro<sup>5,6</sup>, Angelo Maccaro<sup>1</sup>, Davide Fabbricatore<sup>7,8</sup>, Andrea Dell'Aquila<sup>9</sup>, Marco Ripa<sup>10</sup>, Mehmet Emirhan Işık<sup>11</sup>, Yeşim Uygun Kızılmaz<sup>11</sup>, Saverio Iacopino<sup>12</sup>, Marta Camici<sup>13,14</sup>, Francesco Perna<sup>15</sup>, Karolina Akinosoglou<sup>16</sup>, Arta Karruli<sup>17</sup>, Matthaios Papadimitriou-Olivgeris<sup>18</sup>, Bircan Kayaaslan<sup>19</sup>, Yeşim Aybar Bilir<sup>19</sup>, Emin Evren Özcan<sup>20</sup>, Oğuzhan Ekrem Turan<sup>20</sup>, Muhammed Cihan Işık<sup>21</sup>, María Teresa Pérez-Rodríguez<sup>22</sup>, Belén Loeches Yagüe<sup>23</sup>, Alejandro Martín Quirós<sup>24</sup>, Mesut Yılmaz<sup>25</sup>, Sabine Petersdorf<sup>26</sup>, Tom De Potter<sup>7</sup>, Emanuele Durante-Mangoni<sup>17</sup>, Murat Akova<sup>21</sup>, Antonio Curnis<sup>9</sup>, Dino Gibertoni<sup>27</sup>, Igor Diemberger<sup>5,6</sup>, Luigia Scudeller<sup>27</sup>, Pierluigi Viale<sup>1,2</sup>, Maddalena Giannella<sup>1,2</sup>, CarDINE Study Group<sup>#</sup>

<sup>1</sup> Infectious Diseases Unit, Department of Integrated Management of Infectious Risk, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

<sup>2</sup> Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

<sup>3</sup> Golhisar State Hospital, Department of Internal Medicine, Burdur, Turkey

<sup>4</sup> Hacettepe University School of Medicine, Department of Internal Medicine, Ankara, Turkey

<sup>5</sup> Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy

<sup>6</sup> Institute of Cardiology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

<sup>7</sup> Cardiovascular Center, Onze-Lieve-Vrouwziekenhuis Hospital, Aalst, Belgium

<sup>8</sup> Department of Advanced Biomedical Sciences, Federico II University Hospital, Naples, Italy

<sup>9</sup> Institute of Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, ASST Spedali Civili Hospital of Brescia and University of Brescia, Brescia, Italy

<sup>10</sup> Unit of Infectious and Tropical Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy

<sup>11</sup> University of Health Sciences Kosuyolu Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey

<sup>12</sup> Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy

<sup>13</sup> Institute of infectious diseases, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

<sup>14</sup> HIV/AIDS Clinical Unit, National Institute for infectious Diseases L. Spallanzani IRCCS, Rome, Italy

<sup>15</sup> Cardiac Arrhythmia Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

<sup>16</sup> Internal Medicine Department, University General Hospital of Patras, Greece

<sup>17</sup> Department of Precision Medicine, University of Campania 'L. Vanvitelli', Monaldi Hospital, Naples, Italy

<sup>18</sup> Infectious Diseases Service, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

<sup>19</sup> Ankara Yıldırım Beyazıt University Faculty of Medicine, Ankara City Hospital, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey

<sup>20</sup> Dokuz Eylül University, Heart Rhythm Management Center, İzmir, Turkey

<sup>21</sup> Hacettepe University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey

<sup>22</sup> Infectious Diseases Unit, Department of Internal Medicine, Complejo Hospitalario Universitario de Vigo, Spain Instituto de Investigación Biomédica Galicia Sur, Spain

<sup>23</sup> Infectious Diseases Unit, Hospital Universitario La Paz - IDIPAZ, Madrid, Spain

<sup>24</sup> Emergency Department, Hospital Universitario La Paz - IDIPAZ, Madrid, Spain

<sup>25</sup> Istanbul Medipol University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey

<sup>26</sup> Institute of Medical Laboratory Diagnostics, HELIOS University Clinic Wuppertal, Witten/Herdecke University, Witten, Germany

<sup>27</sup> Research and Innovation Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

<sup>☆</sup> This study is endorsed by the ESCMID Study Group for Implant-Associated Infections (ESGIAI), the ESCMID Study Group for Bloodstream Infections, Endocarditis and Sepsis (ESGBIES) and the Study Group for Carbapenem Resistance (SCARE).

\* Corresponding author: Infectious Diseases Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Department of Medical and Surgical Sciences, University of Bologna, Via Massarenti 11, 40138, Bologna Italy.

E-mail address: [renato.pascale2@unibo.it](mailto:renato.pascale2@unibo.it) (R. Pascale).

<sup>#</sup> The members of the CarDINE Study Group are listed in Appendix at the end of the article.

## ARTICLE INFO

## Article history:

Received 7 November 2022

Accepted 13 January 2023

Editor: Professor Evangelos Giamarellos-Bourboulis

## Keywords:

Gram-negative  
Cardiovascular implantable electronic devices  
CIED infection  
Endocarditis  
FDG PET/CT

## 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.

© 2023 The Authors. Published by Elsevier Ltd.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

## 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 ( $\geq 18$  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 ( $\pm 1$  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 Blood-stream 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

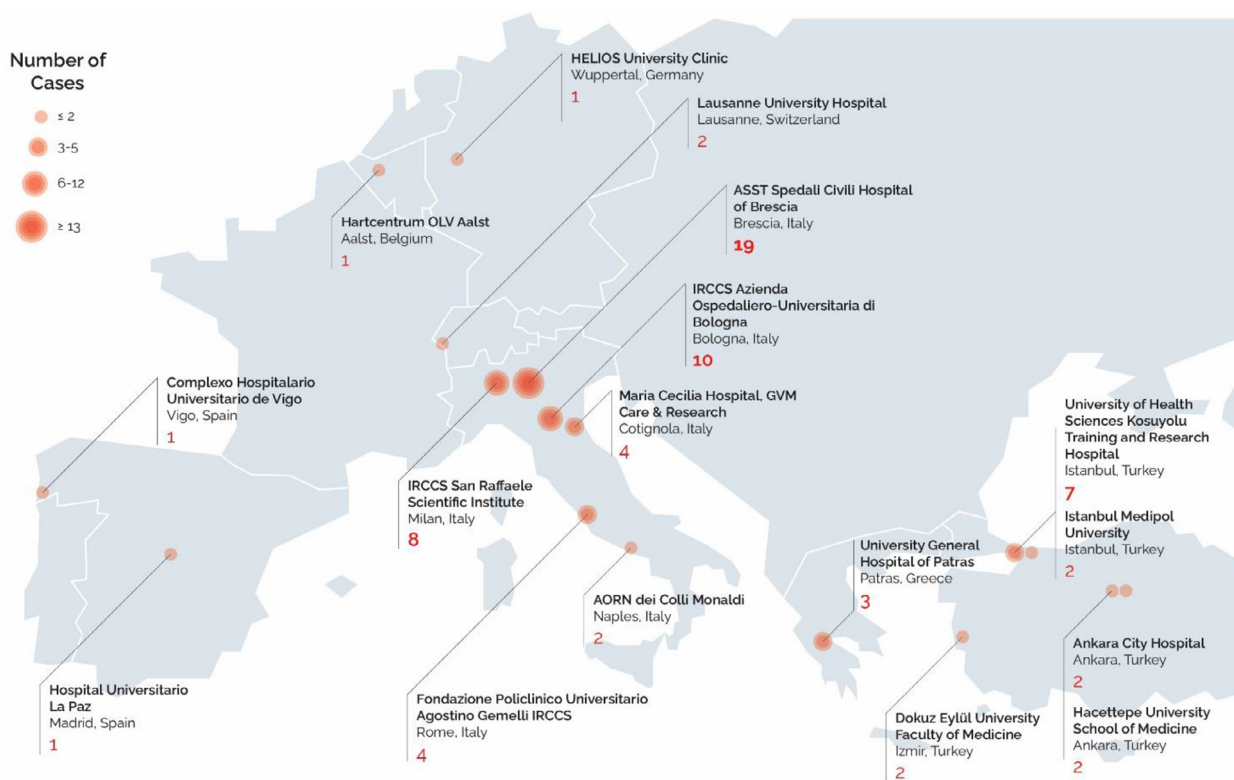


Figure 1. Participating centres.

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  $< 500/\text{mm}^3$ ); 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 ( $< 200 \text{ CD4}/\text{mm}^3$ ); 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  $\chi^2$  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  $\chi^2$  test or Fisher's exact test, and Mann-Whitney U test.

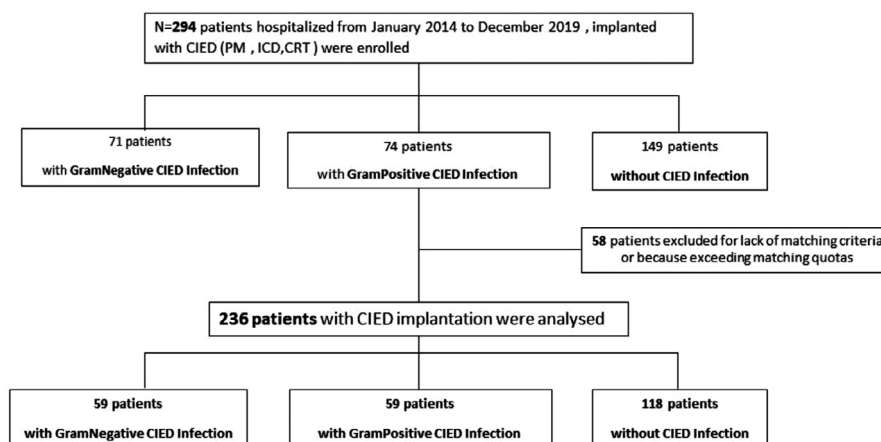


Figure 2. Study flow chart.

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  $69.1 \pm 12.8$  years and CCIS of  $5.03 \pm 2.34$  (Table 1). Among participants with GNB-CIED infection, 41 (69.5%) were male, with a mean age of 71.5 years (SD  $\pm 12.5$ ) and CCIS of  $5.69 \pm 2.24$ . 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	-
<b>Comorbidity</b>						
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	
<b>Underlying cardiac disease</b>						
• 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	
<b>Ejection fraction</b>						
• > 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	
<b>Anticoagulation therapy</b>						
• 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	
<b>Site of implantation (n = 232)</b>						
• 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	
<b>Reason for previous device extraction</b>						
• 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	
<b>Type of infection</b>						
• 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)			
<b>Type of implanted CIED</b>						
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 infec-

tion 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
<b>Type of infection and clinical presentation</b>				
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)	
<b>Instrumental execution</b>				
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
<b>Microbiological diagnosis</b>				
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
<b>Management</b>				
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
<b>Outcome</b>				
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

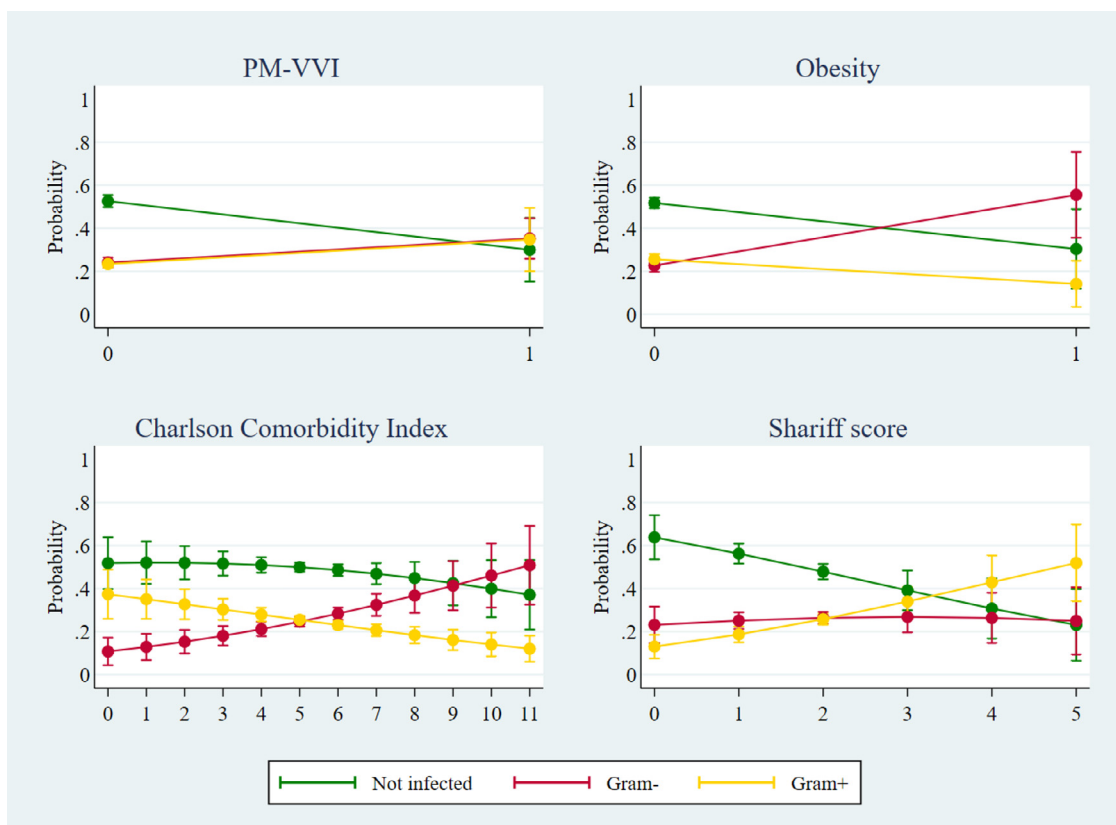
useful in diagnosing GNB-CIED endocarditis and GPB-CIED endocarditis (85.7% vs. 66.7%). Risk factors associated with the development of GNB-CIED infection were different from those associated with GPB-CIED infection. Finally, survival probabilities were lower among patients with GNB-CIED infection than 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 Gar-rigos 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 resynchronization 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.

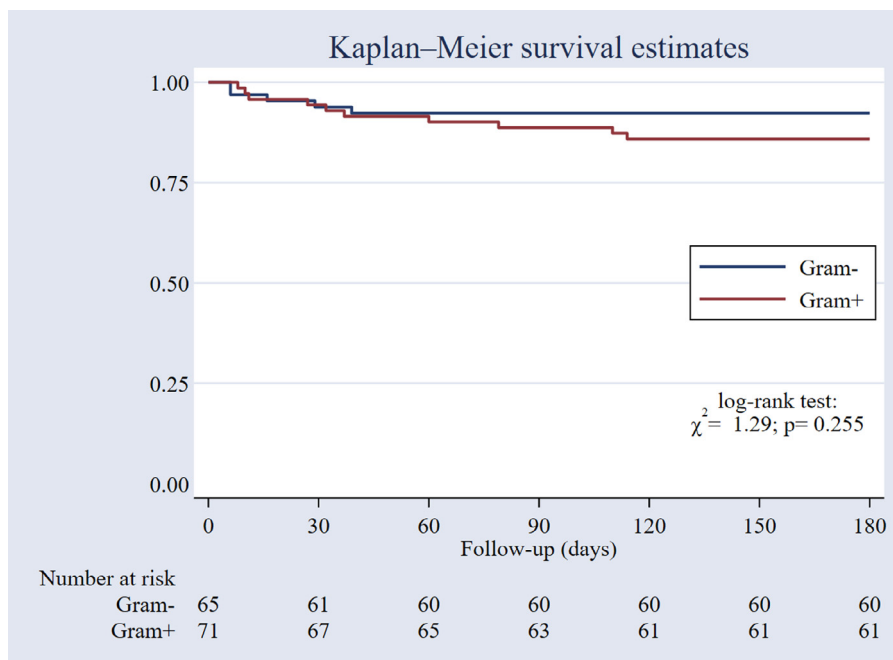


**Figure 3.** Predictive margins. Abbreviations: PM-VVI, ventricular-pacing ventricular-sensing inhibited-response pacemaker.

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.

## Funding

The study received no funding.

**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.

**Sequence Information:** Not applicable.

**Footnote:** Preliminary analyses of these data were presented as abstract no. 1621/O0317 at the 32nd ECCMID, the European Congress of Clinical Microbiology and Infectious

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

Nataschia Carocchia, Francesca Fani, Federica Arbizzani: Infectious Disease Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy. Ramsiya Ramanathan: Infectious Diseases Unit, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, 20122 Milano, Italy. Paolo Scarpellini: Unit of Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy. Alessandra Marzi, Patrizio Mazzone: Unit of Cardiac Electrophysiology, IRCCS San Raffaele Scientific Institute, Milan, Italy. Filippo Placentino, Giulia Sammarini, Elena Tenti: Maria Cecilia Hospital, GVM Care & Research,

Cotignola, Italy. George Leventopoulos: Department of Cardiology, Patras University Hospital Rio, Patras, Greece. Giulia Domenichini: Cardiology Service, University Hospital of Lausanne, Lausanne, Switzerland. Meyha Şahin: Istanbul Medipol University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey. Milagros Suárez-Varela: Infectious Diseases Unit, Department of Internal Medicine, Complejo Hospitalario Universitario de Vigo, Spain; Instituto de Investigación Biomédica Galicia Sur, Spain. Elkin González Villegas: Cardiac Surgery, Hospital Universitario La Paz - IDIPAZ, Madrid, Spain.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijantimicag.2023.106734](https://doi.org/10.1016/j.ijantimicag.2023.106734).

## References

- [1] Choi AJ, Thomas SS, Singh JP. Cardiac resynchronization therapy and implantable cardioverter defibrillator therapy in advanced heart failure. *Heart Fail Clin* 2016;12(3):423–36.
- [2] Rundström H, Kennergren C, Andersson R, Alestig K, Høgevik H. Pacemaker endocarditis during 18 years in Göteborg. *Scand J Infect Dis* 2004;36(9):674–9.
- [3] Johansen JB, Jørgensen OD, Møller M, Arnsbo P, Mortensen PT, Nielsen JC. Infection after pacemaker implantation: infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients. *Eur Heart J* 2011;32(8):991–8.
- [4] Sohail MR, Henrikson CA, Braid-Forbes MJ, Forbes KF, Lerner DJ. Mortality and cost associated with cardiovascular implantable electronic device infections. *Arch Intern Med* 2011;171(20):1821–8.
- [5] Hussein AA, Baghdy Y, Wazni OM, Brunner MP, Kabbach G, Shao M, et al. Microbiology of cardiac implantable electronic device infections. *JACC Clin Electrophysiol* 2016;2(4):498–505.
- [6] Bongioni MG, Tascini C, Tagliaferri E, Di Cori A, Soldati E, Leonildi A, et al. Microbiology of cardiac implantable electronic device infections. *Europace* 2012;14(9):1334–9.
- [7] Diekema DJ, Beekmann SE, Chapin KC, Morel KA, Munson E, Doern GV. Epidemiology and outcome of nosocomial and community-onset bloodstream infection. *J Clin Microbiol* 2003;41(8):3655–60.
- [8] Gaynes R, Edwards JR, System NNIS. Overview of nosocomial infections caused by gram-negative bacilli. *Clin Infect Dis* 2005;41(6):848–54.
- [9] Sohail MR, Usilan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR, et al. Risk factor analysis of permanent pacemaker infection. *Clin Infect Dis* 2007;45(2):166–73.
- [10] Bloom H, Heeke B, Leon A, Mera F, Delurgio D, Beshai J, et al. Renal insufficiency and the risk of infection from pacemaker or defibrillator surgery. *Pacing Clin Electrophysiol* 2006;29(2):142–5.
- [11] Lekkerkerker JC, van Nieuwkoop C, Trines SA, van der Bom JG, Bernardis A, van de Velde ET, et al. Risk factors and time delay associated with cardiac device infections: Leiden device registry. *Heart* 2009;95(9):715–20.
- [12] Esquer Garrigos Z, George MP, Vijayargiya P, Tan EM, Farid S, Abu Saleh OM, et al. Clinical presentation, management, and outcomes of cardiovascular implantable electronic device infections due to gram-negative versus gram-positive bacteria. *Mayo Clin Proc* 2019;94(7):1268–77.
- [13] Klug D, Lacroix D, Savoye C, Goullard L, Grandmougin D, Hennequin JL, et al. Systemic infection related to endocarditis on pacemaker leads: clinical presentation and management. *Circulation* 1997;95(8):2098–107.
- [14] Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The RED-Cap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
- [15] Habib G, Lancellotti P, Antunes MJ, Bongioni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015;36(44):3075–128.
- [16] Blomström-Lundqvist C, Traykov V, Erba PA, Burri H, Nielsen JC, Bongioni MG, et al. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections-endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (IS-CVID) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg* 2020;57(1):e1–e31.
- [17] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315(8):801–10.

- [18] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373–83.
- [19] Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012;18:268–81.
- [20] Falcone M, Tiseo G, Durante-Mangoni E, Ravasio V, Barbaro F, Ursi MP, et al. Risk Factors and Outcomes of Endocarditis Due to Non-HACEK Gram-Negative Bacilli: Data from the Prospective Multicenter Italian Endocarditis Study Cohort. *Antimicrob Agents Chemother* 2018;62(4).
- [21] Fogelson B, Livesay J, Rohrer M, Edwards M, Hirsh JB. cardiac implantable electronic device related endocarditis. *IDCases* 2022;28:e01499.
- [22] Chesdachai S, Baddour LM, Sohail MR, Palraj BR, Madhavan M, Tabaja H, et al. Risk of cardiovascular implantable electronic device infection in patients presenting with gram-negative bacteremia. *Open Forum Infect Dis* 2022;9(9):ofac444.
- [23] Bleeker-Rovers CP, Vos FJ, Wanten GJ, van der Meer JW, Corstens FH, Kullberg BJ, et al. 18F-FDG PET in detecting metastatic infectious disease. *J Nucl Med* 2005;46(12):2014–19.
- [24] Vos FJ, Bleeker-Rovers CP, Sturm PD, Krabbe PF, van Dijk AP, Cuijpers ML, et al. 18F-FDG PET/CT for detection of metastatic infection in gram-positive bacteremia. *J Nucl Med* 2010;51(8):1234–40.
- [25] Yamanaka K, Matsueda T, Miyahara S, Nomura Y, Sakamoto T, Morimoto N, et al. Surgical strategy for aortic prosthetic graft infection with (18)F-fluorodeoxyglucose positron emission tomography/computed tomography. *Gen Thorac Cardiovasc Surg* 2016;64(9):549–51.
- [26] Graziosi M, Nanni C, Lorenzini M, Diemberger I, Bonfiglioli R, Pasquale F, et al. Role of <sup>18</sup>F-FDG PET/CT in the diagnosis of infective endocarditis in patients with an implanted cardiac device: a prospective study. *Eur J Nucl Med Mol Imaging* 2014;41(8):1617–23.
- [27] Ghanem-Zoubi N. FDG PET/CT in Cardiac Infection: Does It Matter? A Narrative Review. *Infect Dis Ther* 2022.
- [28] Saby L, Laas O, Habib G, Cammilleri S, Mancini J, Tessonnier L, et al. Positron emission tomography/computed tomography for diagnosis of prosthetic valve endocarditis: increased valvular 18F-fluorodeoxyglucose uptake as a novel major criterion. *J Am Coll Cardiol* 2013;61(23):2374–2382.
- [29] Jerónimo A, Olmos C, Vilacosta I, Ortega-Candil A, Rodríguez-Rey C, Pérez-Castejón MJ, et al. Accuracy of <sup>18</sup>F-FDG PET/CT in patients with the suspicion of cardiac implantable electronic device infections. *J Nucl Cardiol* 2022;29(2):594–608.
- [30] Shariff N, Eby E, Adelstein E, Jain S, Shalaby A, Saba S, et al. Health and economic outcomes associated with use of an antimicrobial envelope as a standard of care for cardiac implantable electronic device implantation. *J Cardiovasc Electrophysiol* 2015;26(7):783–9.
- [31] Diemberger I, Migliore F, Biffi M, Cipriani A, Bertaglia E, Lorenzetti S, et al. The "Subtle" connection between development of cardiac implantable electrical device infection and survival after complete system removal: An observational prospective multicenter study. *Int J Cardiol* 2018;250:146–149.
- [32] Balla C, Brieda A, Righetto A, Vitali F, Malagù M, Cultrera R, et al. Predictors of infection after "de novo" cardiac electronic device implantation. *Eur J Intern Med* 2020;77:73–8.
- [33] Greenspon AJ, Patel JD, Lau E, Ochoa JA, Frisch DR, Ho RT, et al. Trends in permanent pacemaker implantation in the United States from 1993 to 2009: increasing complexity of patients and procedures. *J Am Coll Cardiol* 2012;60(16):1540–5.
- [34] Olsen T, Jørgensen OD, Nielsen JC, Thøgersen AM, Philbert BT, Johansen JB. Incidence of device-related infection in 97 750 patients: clinical data from the complete Danish device-cohort (1982–2018). *Eur Heart J* 2019;40(23):1862–1869.