

## **SUPPLEMENTARY DATA**

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### **[18]FDG-PET/CT methodological considerations**

Whole-body FDG-PET/CT studies were acquired 60 minutes after 18F-FDG injection (4.0 MBq/kg) in a hybrid scanner (Biograph mCT 64S; Siemens) with a myocardial uptake suppression protocol consisting of a 12-hour fasting period and intravenous administration of 50 IU/kg of unfractionated heparin 15 minutes before 18F-FDG injection.

Images were reconstructed using the iterative True X + TOF (Ultrahigh definition PET) algorithm (2 iterations, 20 subsets) with point spread function (PSF) and time of flight (TOF) corrections. All images included a Gaussian postfilter of 2 mm FWHM and were reconstructed into a matrix size of 200 and a voxel size of 4.1 x 4.1 x 3 mm<sup>3</sup>. CT parameters were approximately 100 kV and 120 mA, adjusted to patient morphology.

### *Visual analysis*

The primary endpoint was the FDG-PET/CT result, which was assessed qualitatively by visual evaluation. Images were interpreted separately by 2 blinded, independent nuclear medicine specialists. Each topographical region was visually classified as positive or negative for infection. Positivity criteria were the presence of any focal or heterogeneous uptake related to each topographical region identified in both attenuation-corrected and uncorrected images. Additionally, whole-body images were carefully assessed to detect any other signs of infection, embolic event, or neoplastic lesion.

#### *Semiquantitative analysis*

A semiquantitative analysis was performed in all FDG-PET/CT studies by measuring the maximum standardized uptake value ( $SUV_{max}$ ) of a volume of interest (VOI) sphere including the totality of the pocket and a VOI sphere placed on the most active part of each segment of the lead (subcutaneous, endovascular and intracardiac).

For reference, blood pool- $SUV_{mean}$  was calculated by setting a 3 cm<sup>3</sup> spherical VOI at the descending thoracic aorta as well as the liver  $SUV_{mean}$  placing a 5 cm<sup>3</sup> spherical VOI in the liver avoiding the inclusion of any abnormal area. SUV ratios were calculated by dividing the  $SUV_{max}$  of the area of interest by the liver  $SUV_{mean}$  was calculated with the aim of overcoming any bias related to individual physiological fluctuations in 18F-FDG distribution in each participant.

#### *Spleen and bone marrow metabolism*

Values of  $SUV_{mean}$  were obtained from the spleen and bone marrow (BM) to assess indirect signs of infection/inflammation as described in Boursier et al.<sup>2</sup> For this purpose, a 5-cm<sup>3</sup> spherical VOI was positioned close to the center of the spleen carefully avoiding the inclusion of any abnormal area secondary to possible lesions (neoplastic, abscesses, ischemic, etc). Lumbar column BM  $SUV_{mean}$  was obtained by placing a spherical VOI placed on the bodies of the third lumbar vertebra (L3) with a diameter set at the vertebra height. In case of a damaged L3 (eg, crushed vertebra, severe discarthrosis, or spondylitis), the VOI was placed in another lumbar vertebra.

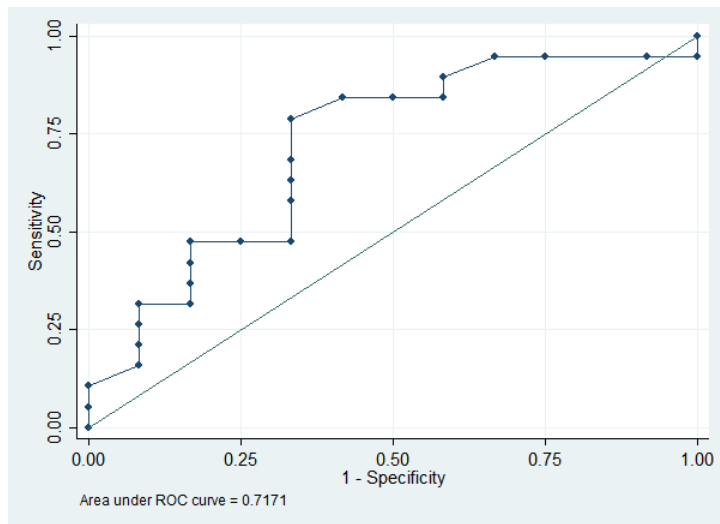
*Follow-up FDG-PET/CT*

At least 1 FDG-PET/CT scan was performed within the first 6 months after discharge in all patients with complete device removal. Some patients underwent more than 1 FDG-PET/CT scan every 4 to 6 months.

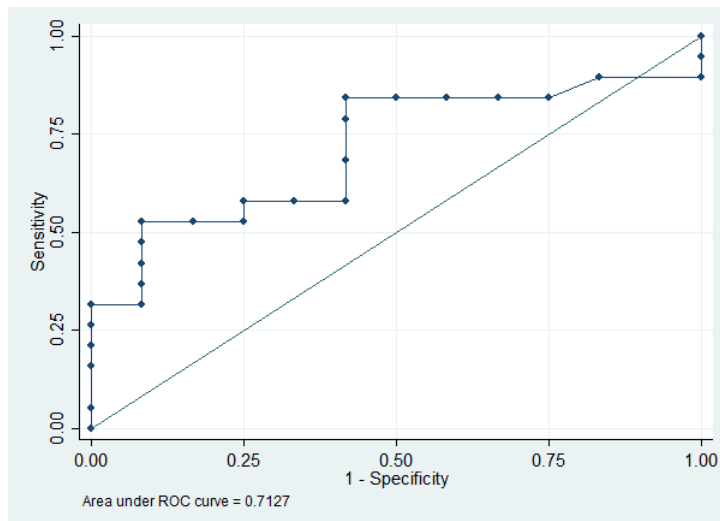
Data on ABS, its duration, and type of infection were also analyzed.

**Figure 1 of the supplementary data.** S1a ROC curve for bacteremic CIED infections spleen SUV<sub>mean</sub> cutoff point 1.7 [Sn: 84.2%, Sp: 58.3%]. S1b ROC curve for bacteremic CIED infections BM SUV<sub>mean</sub> cutoff point of 1.6 [Sn: 79% Sp: 66.7%].

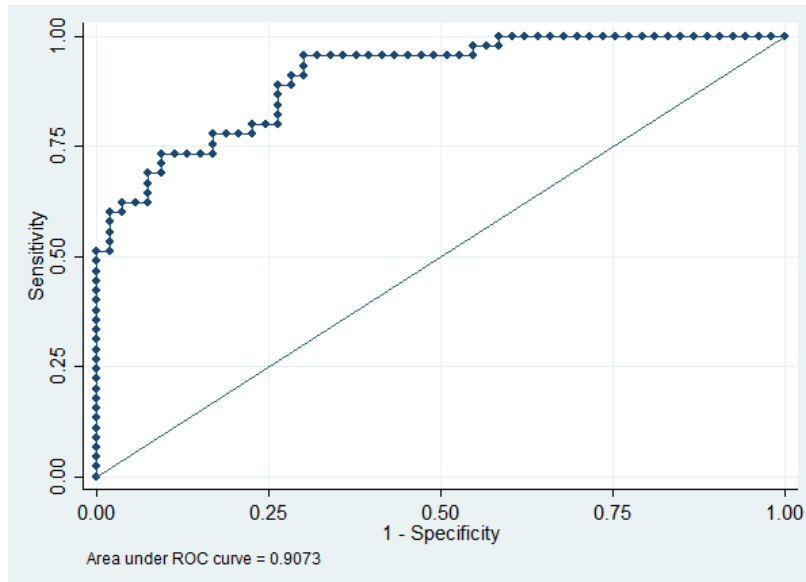
**A**



**B**

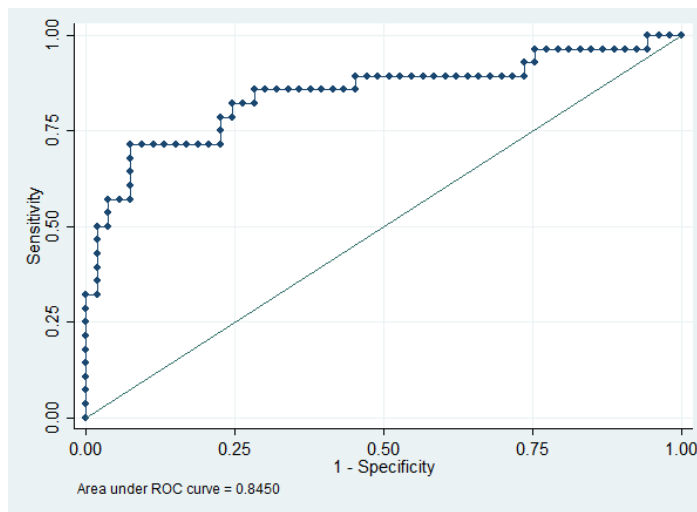


**Figure 2 of the supplementary data.** ROC curve for CIED pocket according to the  $SUV_{max}/SUV_{mean}$  vascular pool with a cutoff point of 0.9 [Sn 88.9% Sp 73.6%].

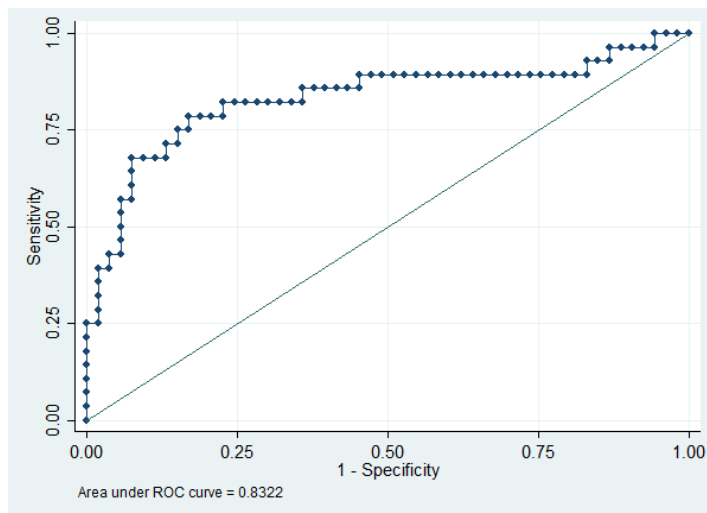


**Figure 3 of the supplementary data.** ROC curve for CIED subcutaneous lead according to the liver SUV<sub>max</sub>/SUV<sub>mean</sub> with a cutoff point of 0.6 [Sn 85.7% Sp 71.7%] in S3a. ROC curve for CIED subcutaneous lead according to the SUV<sub>max</sub>/SUV<sub>mean</sub> vascular pool with a cutoff point of 0.6[Sn 82.1% Sp 77.4 %] in S3b.

**A**

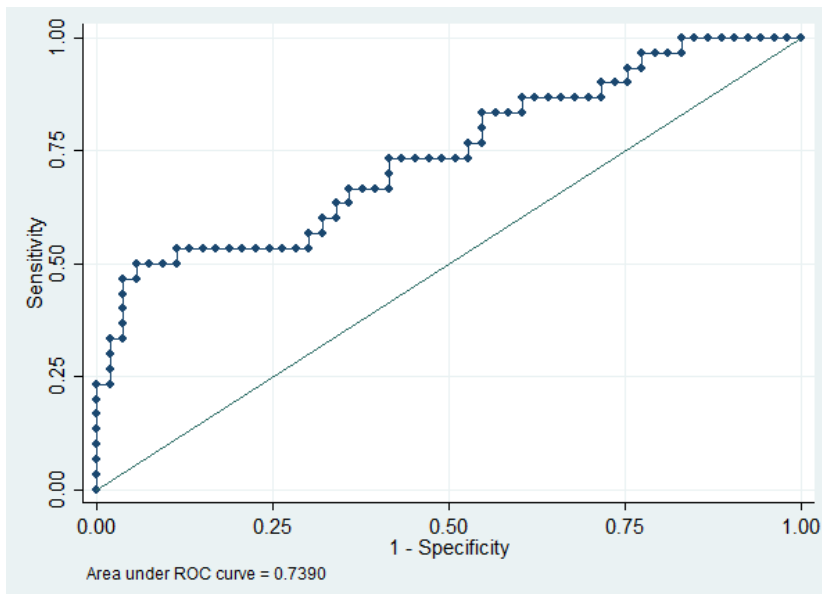


**B**

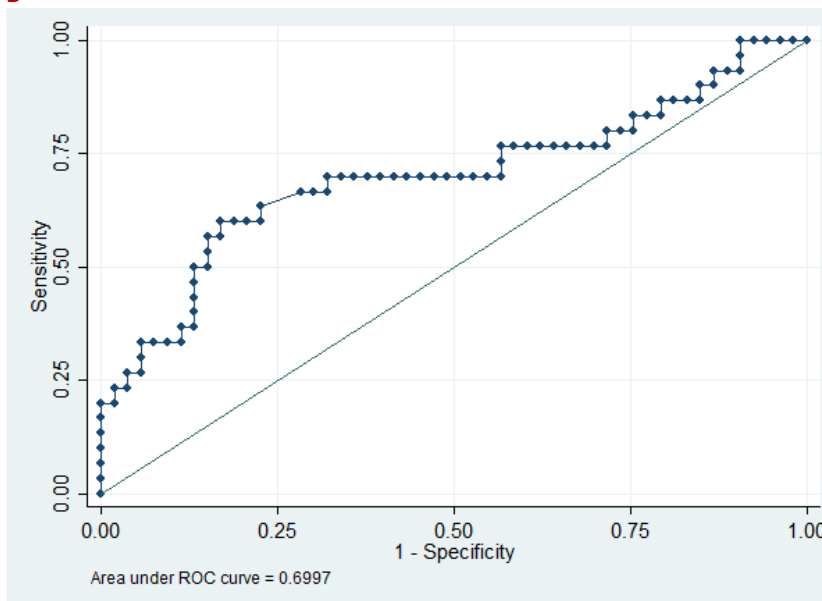


**Figure 4 of the supplementary data.** ROC curve for CIED endovascular lead according to the liver  $SUV_{max}/SUV_{mean}$  with a cutoff point of 1.2 [Sn 50% Sp 94.3%] in S4a. ROC curve for CIED endovascular lead according to the  $SUV_{max}/SUV_{mean}$  vascular pool with a cutoff point 1.1 [Sn 50% Sp 86.8%] in S5b.

**A**

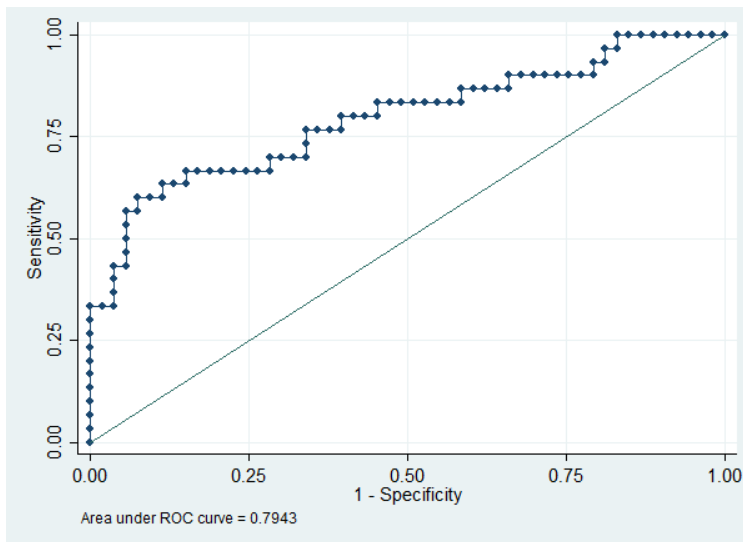


**B**

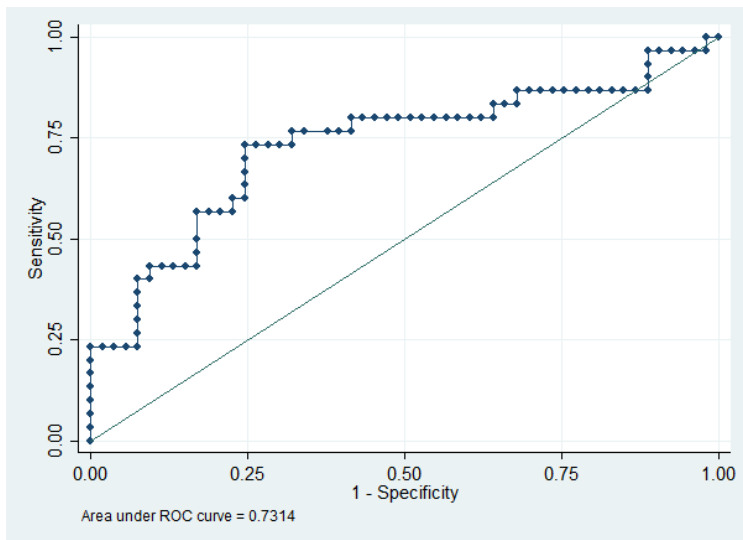


**Figure 5 of the supplementary data.** ROC curve for CIED intracardiac lead according to the liver SUV<sub>max</sub>/SUV<sub>mean</sub> with a cutoff point of 1.1 [Sn 66.7% Sp 84.9%] in S6a. ROC curve for CIED intracardiac lead according to the SUV<sub>max</sub>/SUV<sub>mean</sub> vascular pool with a cutoff point of 1.1 [Sn 56.7% Sp 83%] in S6b.

**A**

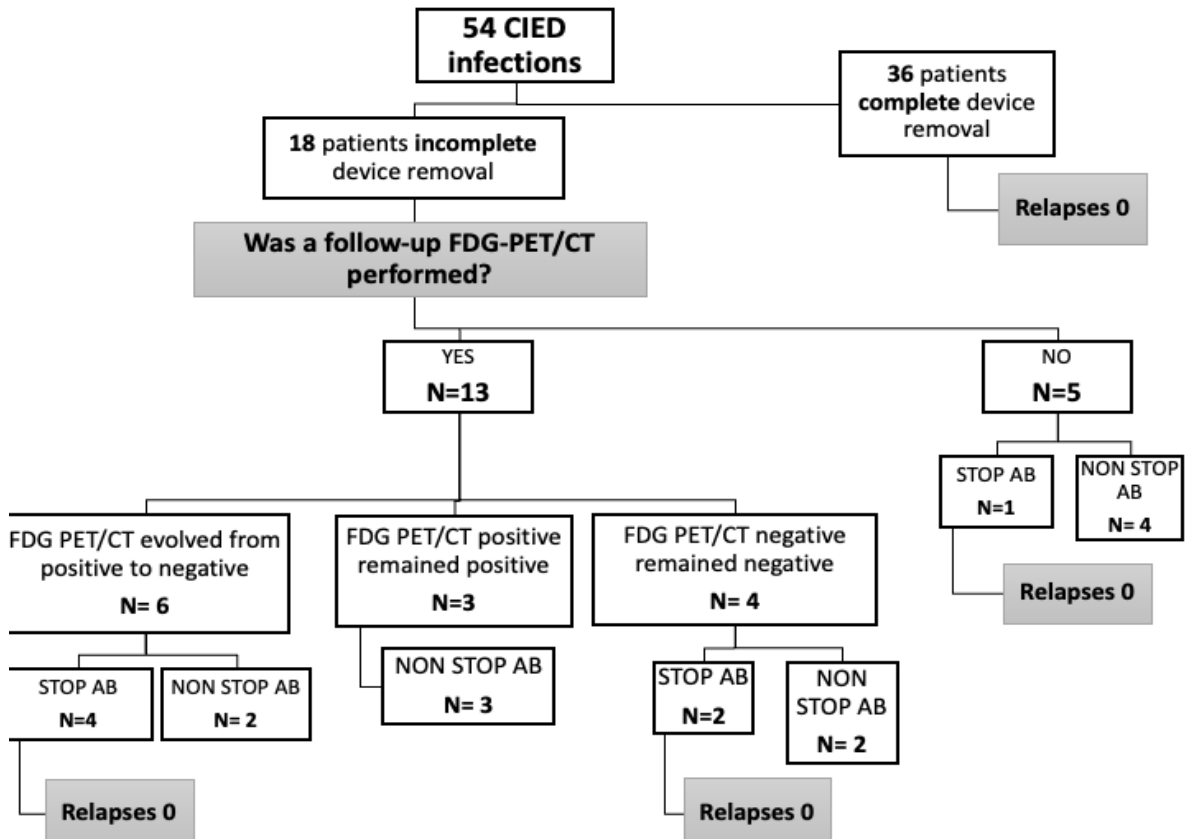


**B**





**Figure 6 of the supplementary data.** Flowchart for patients without complete device removal.



CAS, chronic antibiotic suppression.

**Table 1 of the supplementary data**

Global characteristics of patients with CIED infections according to isolated local CIED infection or systemic

CIED infection

	Total	Isolated local infections n = 13	Systemic infections n = 41	P
<b>Clinical features</b>				
<i>Fever</i>	29 (53.2)	0	29 (70.7)	< .01
<i>Local signs of device infection</i>	47 (87.0)	13 (100)	34 (82.9)	< .01
<i>C-reactive protein, mg/dL</i>	1.3 [0.4–3.32]	1.2 [0.9–2.9]	1.3 [0.4–3.32]	.64
<b>Diagnosis criteria</b>				
<i>Patients with positive cultures</i>	49 (90.7)	10 (76.9)	39 (95.1)	.14
<i>Positive pocket swab</i>	29 (53.7)	10 (76.9)	19 (46.3)	.03
<i>Positive device culture</i>	18 (33.3)	3 (23.1)	15 (36.6)	.33
<i>Positive blood culture</i>	18 (33.3)	0	18 (43.9)	< .01
<i>Positive lead culture</i>	39 (90.7)	0	39 (95.1)	< .01
<i>Device 16-S RNA PCR positive<sup>a</sup></i>	4 (7.4)	1 (7.6)	3 (7.3)	.96
<i>Lead 16-S RNA PCR positive<sup>a</sup></i>	5 (9.3)	0	5 (12.2)	.02
<i>Patients with negative cultures</i>	5 (9.3)	3 (23.1)	2 (4.8)	.14
<i>Positive echocardiography</i>	14 (25.9)	0	14 (34.1)	< .01
<b>Microbiology</b>				
<i>CoNS<sup>b</sup></i>	27 (50)	6 (46.1)	21 (51.2)	.75
<b>MRSE</b>	11 (20.3)	1 (7.7)	10 (24.4)	.10
<b>Other CoNS</b>	6 (11.1)	3 (23.0)	3 (7.3)	.19
<i>S. aureus</i>	13 (24)	2 (15.4)	11 (26.8)	.35
<b>MRSA</b>	1 (1.9)	0	1 (2.4)	.31
<i>Gram-negative non-HACEK</i>	4 (7.4)	1 (7.7)	3 (7.3)	.96
<i>Polymicrobial<sup>b</sup></i>	3 (5.5)	1 (7.7)	2 (4.8)	.73
<b>Outcome</b>				
<i>Complete device removal</i>	36 (66.7)	6 (46.2)	30 (73.2)	.03
<i>Incomplete device removal</i>	9 (16.7)	5 (38.5)	4 (9.8)	< .01
<i>No device removal</i>	9 (16.7)	2 (15.3)	7 (17)	.15
<b>CAS</b>	18 (33.3)	8 (61.5)	10 (24.4)	.01
<b>Reimplant</b>	36	8	28	.54

	(66.6)	(61.5)	(68.3)	
<b>In-hospital mortality</b>	3 (5.6)	0	3 (7.3)	.07
<b>Relapses</b>	2 (3.7)	1 (7.7)	1 (2.4)	.50

CAS, chronic antibiotic suppression; CoNs, *Coagulase*-negative staphylococci; MRSE, methicillin-resistant *Staphylococcus epidermidis*; MRSA, methicillin-resistant *Staphylococcus aureus*.

The data are expressed as No. (%) or median [interquartile range].

<sup>a</sup>16SrRNA-PCR was not performed in all cases, because it was not systematically included in the diagnostic procedure when the study protocol was designed.

<sup>b</sup>Other coagulase-negative bacteria: *S. schleiferi*, *Cultibacterium. acnes*, *Corynebacterium jeikeium*. <sup>c</sup>Polymicrobial flora includes *S. aureus*, *S. epidermidis*, and mixed flora.

### Table 2 of the supplementary data

Systemic CIED infection characterization according to the EHRA consensus diagnostic criteria <sup>2</sup>

	<b>Systemic infections n = 41</b>
<b>SI with positive BC</b>	18 (43.9)
Positive BC + positive TEE	7/18 (38.9)
Positive BC + negative TEE	11/18 (61.1)
<b>SI with positive LC without positive blood culture</b>	23 (56.1)
Positive LC + positive TEE	7/23 (30.4)
Positive LC + negative TEE*	16/23 (69.6)

BC, blood cultures; LC, lead cultures; SI, systemic infection; TEE, transesophageal echocardiography.

The data are expressed as No. (%).

\*All these patients showed systemic signs of CIED infection, eg, persistent fever and local signs of device infection with positive local cultures.

**Table 3 of the supplementary data**

Comparison according to the interval between CIED implantation/replacement and [18F]FDG-PET/CT

	< 3 months n = 9	> 3 months n = 45	P
<b>Baseline and matching characteristics</b>			
Age, y	72.0 [59.0-79.0]	81.0 [72.0-86.0]	.12
Female sex	3 (33.3)	13 (28.9)	.80
<b>CIED type</b>			
PPM	8 (88.8)	33 (73.3)	.21
ICD	1 (11.1)	11 (24.4)	.28
CRT	0	1 (2.2)	.31
Local infection signs	8 (88.9)	39 (86.7)	.85
<b>Echocardiography</b>			
Echo vegetation	2 (22.2)	12 (26.7)	.85
Lead vegetation	2 (22.2)	12 (26.7)	.85
Tricuspid valve vegetation	0	2 (4.4)	NA
<b>[18F]FDG-PET/CT</b>			
Positive [18F]FDG-PET/CT	8 (88.9)	38 (84.4)	.71
Pocket	8 (88.9)	29 (64.4)	.06
Subcutaneous lead	3 (33.3)	24 (53.3)	.26
Endovascular lead	2 (22.2)	7 (15.6)	.66
Intracardiac lead	1 (11.1)	3 (6.7)	.69
Systemic emboli	0	1 (2.2)	NA
Pulmonary emboli	0	1 (2.4)	NA
Interval between CAS initiation and [18F]FDG-PET/CT, dDays, IQR)	6.0 [0-13.0]	6.5 [0.0-18.5]	.88
Interval between in-hospital admission and device removal, d	13.0 [11.0-14.0]	7.0 [1.0-14.0]	.42

CAS, chronic antibiotic suppression; CIED, cardiac implantable electronic device; CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator; NA, not available; PPM, pacemaker.

**Table 4 of the supplementary data** Comparison of spleen and bone marrow SUV<sub>mean</sub>

	SUV <sub>mean</sub> spleen	SUV <sub>mean</sub> bone marrow lumbar column
<b>Cases vs controls</b>		
<i>Cases</i>	1.8 [1.6-2.1]	1.75 [1.5-1.9]
<i>Controls</i>	1.9 [1.7-2.1]	1.74 [1.39-2]
<b>P-value</b>	.4	.9
<i>Cases/liver SUV<sub>mean</sub></i>	0.9 [0.8-0.9]	0.9 [0.7-1]
<i>Controls/liver SUV<sub>mean</sub></i>	0.9 [0.8-0.9]	0.8 [0.7-0.9]
<b>P value</b>	.4	.3
<b>Isolated LI vs SI</b>		
<i>Isolated local Infection</i>	1.8 [1.6-1.9]	1.75 [1.6-2]
<i>Systemic Infection</i>	1.8 [1.7-2.2]	1.6 [1.1-1.9]
<b>P value</b>	.5	.2
<i>LI/liver SUV<sub>mean</sub></i>	0.9 [0.9-1.1]	0.9 [0.8-1]
<i>SI/liver SUV<sub>mean</sub></i>	0.9 [0.7- 0.9]	0.8 [0.7-0.9]
<b>P value</b>	.06	.2

CIED, cardiac implantable electronic device; LI, local CIED infection; SI, systemic CIED infection.

Unless otherwise indicated, the data are presented as median [interquartile range].

**Table 5 of the supplementary data** Clinical characteristics and outcomes of 18 patients with incomplete device removal on chronic antibiotic suppression therapy

Case	Sex/age, y	Clinical presentation	Microbiology	TEE	Baseline FDG-PET/CT	Surgery <sup>a</sup>	Reason for incomplete removal	CAS therapy	Follow-up FDG-PET/CT (months)	CAS Duration	Outcome treatment, mo
1	Male/93	Pocket + CIED-IE	MSSA Negative BC	Negative	Positive pocket and SC lead	Not performed	Comorbidities	Levofloxacin plus TMP-SMX	Negative (4)	4 mo	No relapses after 43 mo off CAS Unrelated death
2	Male/60	Pocket + CIED lead infection	CoNS Positive BC	Positive: Lead veg	Positive pocket	Not performed	Medical agreement IE Team	Linezolid	Negative (6)	8 mo	No relapses after 44 mo off CAS
3	Male/89	Lead CIED infection	MSSA Repeated positive BC	Positive: Lead veg	Negative	Not performed	Comorbidities	Levofloxacin plus rifampicin	Negative (5)	6 mo	No relapses after 38 mo off CAS Unrelated death
4	Female/75	Pocket +SC CIED infection	C. acnes Negative BC	Negative	Positive pocket and SC lead	Only pocket Abandoned lead	Comorbidities	Linezolid	Negative (2)	2 mo	No relapses after 38 mo off CAS
5	Female/85	Pocket + lead CIED infection	MSSA Negative BC	Positive: lead veg	Positive pocket- SC lead	Only pocket. Abandoned lead (> 4 cm)	Comorbidities	Levofloxacin and rifampicin	Negative (3)	3 mo	No relapses after 17 mo off CAS
6	Female/80	Pocket CIED infection	MRSA Negative BC	Negative	Negative	Not performed	-	Linezolid	Negative (1)	1 month	No relapses after 36-mo off CAS
7	Male/78	EV Lead CIED infection	MSSA Repeated positive BC	Positive: lead veg	Negative	Not performed	-	Levofloxacin*/TMP-SMX	Negative (3)	Ongoing	No relapses after 38 mo on CAS
8	Male/51	CIED IE	MSSA Repeated positive BC	Positive: lead veg	Negative	Only pocket. Abandoned lead <sup>a</sup> (< 4 cm)	Comorbidities	Levofloxacin	Negative (6)	Ongoing	No relapses after 9 mo on CAS Unrelated death
9	Female/82	Pocket CIED infection	CoNS Negative BC	Negative	Positive pocket and SC lead	Only pocket Abandoned lead (> 4 cm)	Comorbidities	TMP-SMX	Negative (12)	Ongoing	No relapses after 29 mo on CAS
10	Female/81	EV Lead CIED infection	C. acnes Positive BC	Negative	Positive EV lead	Not performed	Comorbidities	Amoxicillin	Negative (10)	Ongoing	No relapses after 26 mo on CAS
11	Female/85	Pocket SC lead CIED infection	S. epidermidis Negative BC	Negative	Positive pocket- SC lead	Only pocket Abandoned lead (> 4 cm)	Comorbidities	TMP-SMX	Positive pocket - SC lead (12)	Ongoing	No relapses after 20 mo on CAS
12	Male/56	Pocket-SC lead CIED infection	C. acnes and K. oxytoca Negative BC	Negative	Positive pocket- SC lead	Only pocket Abandoned lead (> 4 cm)	Comorbidities	Amoxicillin	Positive pocket- SC lead (3)	Ongoing	No relapses after 9 mo on CAS
13	Male/77	Pocket + EV lead CIED infection	MSSA Positive BC	Positive: lead veg	Positive EV lead	Only pocket Abandoned lead (> 4 cm)	Comorbidities	Levofloxacin plus rifampicin	Positive EV lead (1)	Ongoing	No relapses after 30 mo on CAS

14	Female/73	EV lead CIED infection	MSSA Repeated positive BC	Negative	Negative	Not performed	Comorbidities	Levofloxacin	Not performed	2 mo	No relapses after 29 mo off CAS
15	Female/96	Pocket SC lead CIED infection	Mixed flora	Negative	Positive pocket and SC lead	Only pocket Abandoned lead (> 4 cm)	Comorbidities and patient's refusal	Ciprofloxacin	Not performed	Ongoing	No relapses after 25 mo on CAS Unrelated death
16	Male/85	Pocket SC lead CIED infection	CoNS	Negative	Positive pocket and SC lead	Only pocket Abandoned lead (> 4 cm)	Comorbidities	TMP-SMX	Not performed	Ongoing	No relapses after 35 mo on CAS
17	Male/82	Pocket CIED infection	<i>S. epidermidis</i>	Negative	Negative	Not performed	Comorbidities	Tedizolid	Not performed	Ongoing	No relapses after 28 mo on CAS Unrelated death
18	Male/59	CIED IE	MRSA Positive BC	Positive: lead veg	Positive EV lead	Not performed	Comorbidities	Tedizolid	Not performed	Ongoing	No relapses after 6 mo on CAS Unrelated death

BC, blood cultures; CAS, chronic antibiotic suppression; CIED-IE, cardiac implantable electronic device infective endocarditis; CoNS, coagulase negative staphylococci; EV, endovascular; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus* SC, subcutaneous lead; TMP-SMX, trimethoprim-sulfamethoxazole; veg, vegetation. CoNs, *Coagulase*-negative staphylococci.

<sup>a</sup>Surgery: all patients underwent percutaneous manual traction surgery except for patient 8, who underwent open surgery and whose lead was fragmented during the procedure.

<sup>b</sup>Levofloxacin was switched to TMP-SMX because of toxicity.