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18-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Infective Endocarditis

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Short title: Prognostic value of 18F-FDG PET/CT in endocarditis

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Tweet: In addition to its diagnostic value, ^{18}F-FDG PET/CT also has the potential to predict the occurrence of embolism and death in infective endocarditis.

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Abstract
Background: ^{18}F-Fluorodeoxyglucose Positron Emission Tomography (^{18}F-FDG PET/CT) is commonly used for the diagnosis of infective endocarditis (IE), but its prognostic value remains unknown.
Objectives: This study sought to assess the prognostic value of ^{18}F-FDG PET/CT in prosthetic (PVE) and native valve endocarditis (NVE).
Methods: We prospectively included 173 consecutive patients (109 PVE and 64 NVE) with definite left-sided IE who performed a ^{18}F-FDG PET/CT and were follow-up for 1 year. Primary endpoint was a composite of major cardiac events: death, recurrence of IE, acute cardiac failure, non-scheduled hospitalization for cardiovascular indication and new embolic event.
Results: ^{18}F-FDG PET/CT was positive in 100 (58%) patients, 83% (n=90/109) in the PVE and 16% (n=10/64) in the NVE group. At a mean follow of 225 days (199 to 251 days), the primary endpoint occurred in 94 (54%) patients, 63 (58%) in the PVE group and 31 (48%) in the NVE group. In the PVE group, positive ^{18}F-FDG PET/CT was significantly associated with higher rate of primary endpoint (HR=2.7, IC95%=1.1 to 6.7; p=0.04). Moderate to intense ^{18}F-FDG valvular uptake was also associated with worse outcome (HR=2.3; IC95%=1.3 to 4.5; p=0.03) and to new embolic events in PVE (HR= 7.5; IC95%= 1.24 to 45.2; p=0.03) and in NVE (HR=8.8; IC95%= 1.1 to 69.5; p=0.02). In the NVE group, ^{18}F-FDG PET/CT was not associated with occurrence of the primary endpoint
Conclusion: In addition to its good diagnosis performance, ^{18}F-FDG PET/CT is predictive of major cardiac events in PVE and new embolic events within the first year following IE.

Key words: valve disease, endocarditis

Condensed Abstract
This study evaluated the prognostic value of 18-FDG-PET/CT in infective endocarditis. Primary endpoint included major cardiac events: in-hospital and one-year death, IE recurrence, new embolism, urgent rehospitalization and acute cardiac failure. In 109 patients with prosthetic valve endocarditis, ^{18}F-FDG-PET/CT was associated with occurrence of the primary endpoint (HR=2.7, IC95%=1.1 to 6.7; p=0.04). Moderate to intense ^{18}FDG uptake was also associated to worse outcome (HR=2.3; IC95%=1.3 to 4.5; p=0.03) and to new embolic events in PVE (HR= 7.5; p=0.03) and in NVE (HR=8.8; p=0.02). In 64 patients with native valve endocarditis, the NVE group, ^{18}FDG-PET/CT was not predictive of primary endpoint.

Abbreviations
^{18}F-FDG PET/CT: ^{18}F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography
MSCT**:** multislice cardiac Tomography
CRP: C-reactive protein
IE: infective endocarditis
IQR: interquartile range
NVE: native valvular endocarditis
PVE: prosthetic valve endocarditis
TEE: transoesophageal echocardiographic
TTE: transthoracic echocardiography

Introduction

Prognosis of infective endocarditis (IE) is poor with a still unacceptable reported in-hospital (1-3) and long-term (4-6) mortality rate. Recent guidelines (7,8) emphasize the benefits of a multidisciplinary approach led by the Endocarditis Team, the key role of an early surgery in the active phase of IE (9,10), and the importance of an early prognostic assessment allowing an earlier management. Several prognostic factors have been identified such as advanced age, multiple comorbidities, heart failure, uncontrolled infection, embolic event, diabetes mellitus, renal insufficiency, staphylococcus-related IE, ischemic stroke or brain hemorrhage and echocardiographic findings (11-13). However, the individual prediction of event is still difficult and additional prognostic markers may be useful to rapidly choose the best therapeutic option.

^{18}F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (^{18}F-FDG PET/CT) demonstrated to be able to improve the diagnosis of prosthetic valve endocarditis (PVE) (14-16) increasing the sensitivity of the modified Duke criteria from 70% to 97 % (14). Multi-imaging approach is nowadays essential in the diagnostic work out of IE (17,18) and has been integrated in the 2015 European Society of Cardiology criteria (7). However, to date and to our best knowledge, no study focused on the prognostic value of ^{18}F-FDG PET/CT in IE.

Therefore, we aimed to assess the prognostic value of ^{18}F-FDG PET/CT in patients with PVE and NVE.

Methods

Population

From January 2011 to October 2017, all consecutive adults admitted in the Department of Cardiology in the teaching hospital La Timone (Marseille, France) with a definite diagnosis of left-sided IE were prospectively eligible to enter the study. Whether admitted for PVE or NVE,

patients underwent a clinical 18F-FDG PET/CT which was realized as soon as possible after their admission. All patients had a follow up at 1, 3, 6 and 12 months after discharge including a physical examination, echocardiographic and biological evaluation. If the patient did not complete the follow up, the patient, his family or his cardiologist was reached by phone. Patient exclusion criteria were: incapacity to lie flat, pregnancy, need for urgent cardiac surgery, hemodynamic instability and blood glucose level >1.8 g/L at time of ^{18}F-FDG PET/CT, cardiac surgery during the 3 preceding months, right sided-IE or intra cardiac device infection and ^{18}F-FDG PET/CT performed more than 14 days after antibiotic initiation. Written informed consent was obtained from all patients using an approved protocol, which was validated by the institutional board.

Clinical and imaging data

Several data were collected during hospitalization and during follow up: age, sex, age and type of prosthetic valve, Charlson comorbidity index, history of diabetes, cancer, chronic renal insufficiency, high blood pressure, C-reactive protein level (CRP), causative pathogens, heart failure episode, embolic events (before treatment or under antibiotics), need for surgery and its indication, recurrence of IE, re-hospitalization, in hospital death and death during the 1 year follow up. Echocardiographic and multislice cardiac tomography (MSCT) data were also gathered. Transthoracic (TTE) and transesophageal echocardiographic (TEE) analyses were interpreted by experienced senior cardiologists. Echocardiographic data included the presence of vegetation, its length and mobility and the presence of paravalvular complications including abscesses, pseudo-aneurysm and fistula. Measurements of vegetation length were performed in various planes, and maximal length was used. Mobility was defined by vegetation with a fixed base but with a mobile free edge or pedunculated vegetation remaining within the same chamber

or a vegetation prolapsing and crossing the coaptation plane of the leaflets during the cardiac cycle. An abscess was defined as a thickened area or mass with a heterogeneous echogenic or echo lucent appearance (7). Recurrence included relapse due to a repeat episode of IE caused by the same microorganism and reinfection due to an infection by a different microorganism.

^{18}F-FDG PET/CT.

Patients fasted for 12 hours before ^{18}F-FDG PET/CT to limit physiological myocardial 18-FDG uptake. Patients received a low carbohydrate, high fat and protein meal before ^{18}F-FDG PET/CT (Discovery PET/CT 710, General Electric, Milwaukee, Wisconsin). Imaging started 60 min after 18-FDG injection (5mBq/kg) with a non-enhanced, low dose computer tomography scan (120kV, 80mA) with a whole-body PET acquisition in 3-dimensional (3D) mode. Transverse PET slices were reconstructed into a 256x256 matrix using the OSEM (ordered-subset-expectation-maximisation) algorithm. The PET data were linked with the CT data. The data analysis (Xeleris, General Electric before 2013 and Advantage Workstation, General Electric after 2013) was based on visual interpretation. Assessment of 18- FDG uptake was performed by 2 experienced and blinded nuclear medicine physicians. Examination was considered positive when uptake was focal i.e less than 50% of the circumference's valve. Otherwise examination was considered negative. Pathological uptake had to be confirmed in the uncorrected images. Abnormal valvular uptake was graded in 3 level scales: low intensity uptake when intensity in the valvular area was lower than the intensity in the liver, moderate intensity when it was equal or slightly superior and intense when uptake was far greater. If examination showed intense and homogenous myocardial uptake with poor images, patient was excluded from the study. Mean radiation dose for a whole-body ^{18}F-FDG PET/CT was 15mSv.

Definition of primary endpoint.

Primary endpoint was a composite of major adverse cardiac events, i.e. in-hospital and one-year death, recurrence of IE, acute cardiac failure, non-scheduled hospitalization for cardiovascular reason, and new embolic event under antibiotics.

Statistical analysis

Continuous variables were expressed as the median (interquartile range [IQR]) and compared using the t-test or Mann-Whitney U test when the former could not be performed. Categorical data were expressed as numbers (percentages) and compared using the Chi-square or Fisher exact test when the former could not be performed. Predictors of ^{18}F- FDG PET/CT were analyzed by a logistic regression (logit model). Predictors of primary composite endpoint were analyzes using univariate and multivariate proportional hazard model (cumulative outcomes). Hazards proportional assumption was evaluated by using the Schoenfed residual. Number of predictors to include in the multivariate analysis were determined using Akaike's information criterion. Smaller AIC values indicated a better model fit. Survival rates from admission to primary endpoint were summarized using Kaplan-Meier survival curve and log rank test were used to perform comparison between positive and negative ^{18}F- FDG PET/CT groups. Statistical analyses were separately conducted in the NVE and the PVE groups. Results with p values <0,05 were considered significant. Statistical analysis was conducted by Statview version 5.0 for Windows.

Results

Baseline characteristics.

Three hundred sixty-seven patients were hospitalized for IE and underwent a ^{18}F-FDG PET/CT study. We excluded one hundred twenty-two patients because IE involved cardiac devices, pulmonary or tricuspid valves. Flowchart of the study is shown in **Figure 1**. Median age

was 67 years (interquartile range (IQR): 59-77 years old) and most of patients were men (70%). The baseline characteristics are summarized in Table 1 for the overall population, the PVE and NVE groups. Echocardiographic paravalvular complications included abscesses (n=46/67, 69%), pseudo-aneurysm (n=20/67, 30%) and fistula (n=1/67, 1%). MSCT showed 4 abscesses, 5 pseudoaneurysms, 3 vegetations and one aortic cusp thickening. Theoretical indication for surgery was present in 127 (73%) patients and 54 % (n=93) finally underwent surgery. Indications for surgery were heart failure (48%, n=61), prevention of embolism (30%, n= 38) and uncontrolled infection (22%, n=28).

^{18}F-FDG PET/CT findings.

Median time from first antibiotic to examination was 7 days (IQR: 4 to 8 days). Characteristics of patients according to the ^{18}F-FDG PET/CT are shown in Table 2. ^{18}F-FDG PET/CT was positive in 58 % (n=100/173), more often in the PVE than in the NVE group (83% and 16% respectively). By univariate analysis, age, prosthetic valve, atrial fibrillation, CRP level and paravalvular complications were associated with a positive ^{18}F-FDG PET/CT, while male sex was associated with a negative ^{18}F-FDG PET/CT. By multivariable analysis, prosthetic valve (OR= 31 (10.8-93.1); p=0.0001), CRP (OR =1.1 (1.02-1,2); p=0.02) and presence of paravalvular complications (OR = 3.1 (1.2-8.2); p=0.02) were independent predictors of positive ^{18}F-FDG PET/CT.

In the PVE group (n=109), 19 false negative PET studies were observed. Median CRP level was lower in these patients (51.5 mg/L (24- 80) as compared with the 90 PVE with positive PET/CT (89 mg/L (26-126)), p=0.04.

At time of admission, secondary septic locations were detected by ^{18}F-FDG PET/CT in 36% of patients (n=62/173), including splenic (n=24), spondylodiscitis or arthritis (n=24), pulmonary

(n=20), vascular (n=5) or renal (n=2) uptakes. Portal of entry was identified in 16 patients by ^{18}F-FDG PET/CT, colic in 10 patients, dental in 3, cutaneous in 2 and on an orthopedic material in 1.

Incidence of primary endpoint and major cardiac events

At a mean follow-up of 225 days (IQR: 199 to 251 days), primary composite endpoint occurred in 94 (55%) patients, 63 (58%) in the PVE group and 31 (48%) in the native valve EI group (Table3). Median time from first day admission to composite endpoint was 45 days (IQR:18 to 115 days). Cumulative incidence of endpoint criteria at one-year follow-up was 53 % (95 % IC: 46% to 62 %) (**Figure 2**). Fourteen (8%) patients died during hospitalization from post-operative complication (n=4), infective complication (n=4) cardiogenic shock (n=4), and neurological complication (n=2). One-year mortality was 20% (n=35 patients), 25(23%) in the PVE group and 10 (16%) in the NVE group. Median time to death was 51 days (IQR: 30 to 142 days). Unplanned re-hospitalization during the year following admission occurred in 40 (23%) patients and was related to acute cardiac failure (n=20), septicemia (n=8), stroke (n=5), atrial fibrillation (n=3), atrioventricular block (n=2), vascular aneurysm (n=1) and acute coronary syndrome (n=1). Recurrence occurred in 15 patients (9%) including 5 relapses and 10 reinfections with another pathogen. Median time to recurrence was 104 days (IQR: 33 to 224 days). Symptomatic embolic events after treatment occurred in 22 (13%) patients at a median time of 14 days (IQR: 7 to 27 days). Location of embolism was cerebrovascular in 17 patients (77%), vascular in 3 (14%), involving superior mesenteric artery (2) and right coronary artery (1), hepatic (1) and renal (1).

Prognostic value of ^{18}F-FDG PET/CT in the PVE group

Predictors of the primary endpoint are shown in Table 4. By univariate analysis, age ≥ 70 years, history of coronary artery disease, left ventricular ejection fraction ≤ 45 %, renal insufficiency at admission, *staphylococcus aureus* as causative pathogen, severe valve regurgitation, CRP level ≥ 100 mg/L, leukocytes count>10000/mm3, vegetation length > 10 mm, positive ^{18}F-FDG PET/CT and moderate to intense valvular ^{18}F-FDG PET/CT uptake were associated with increased rate of primary endpoint. The best model selected by AIC was a model with four predictors (CRP>100mg/L, severe valvular regurgitation, positive 18-FDG PET/CT and moderate to intense 18-FDG valvular uptake) (AIC=53.3). By multivariate analysis, CRP level ≥ 100mg/L, a positive ^{18}F-FDG PET/CT and a moderate to intense ^{18}F-FDG PET/CT valvular uptake remained associated with a higher rate of primary endpoint. Proportional hazards assumption was confirmed by the Schoenfed residual as the test was not statistically significant for each of the covariate (p>0.05) and the global test (p= 0.296). **Central illustration** (A,B) shows the Kaplan-Meier survival curves and their comparisons for primary endpoint in case of positive ^{18}F-FDG PET/CT or in case of moderate to intense valvular uptake and cumulative incidence of primary-endpoint.

Positive ^{18}F-FDG PET/CT was not associated with each separate criterion of the primary composite endpoint (Table 5), except for new embolic events, which were more frequent in case of moderate to intense ^{18}F-FDG PET/CT valvular uptake in the PVE group (HR: 7.5; IC95%= 1.2 to 45.2; p=0.03) (Figure 3). New embolic events occurred in 16 patients with moderate to intense ^{18}F-FDG PET/CT uptake (1 in the NVE group and 15 in the PVE group) and 6 patients with negative or low ^{18}F-FDG PET/CT uptake (Figure 3A).

Prognostic value of ^{18}F-FDG PET/CT in the NVE group.

Predictors of primary endpoint are shown in Table 4. By univariate analysis, only diabetes mellitus, history of high blood pressure, vegetation length > 10 mm, and severe valve regurgitation were associated with increased rate of primary endpoint. ^{18}F-FDG PET/CT was not predictive of the primary composite endpoint whether considered positive or moderate to intense 18-FDG uptake. However, when displaying a moderate to intense uptake, ^{18}F-FDG PET/CT was associated with more frequent new embolic events in the NVE group (HR: 8.8; IC95%= 1.1-69.5; p=0.02) (**Table 5, Figure 3B**).

Discussion

To our best knowledge, this is the first study assessing the prognostic value of ^{18}F-FDG PET/CT in IE. In case of PVE, positive ^{18}F-FDG PET/CT was a predictor of bad outcome. In addition, positive ^{18}F-FDG PET/CT was also associated with a higher risk of new embolism both in the PVE and the NVE groups. Primary endpoint including all major cardiac events occurred in more than half of the patients (55%), confirming the need for systematic and regular patient's follow-up after discharge (4,5).

1. ^{18}F-FDG PET/CT in infective endocarditis:

^{18}F-FDG PET/CT is now a recognized diagnostic method in suspected endocarditis, particularly in suspected PVE (14-19), both for the diagnosis of cardiac (major criterion) and peripheral (minor criterion) localization (7). However, a meta-analysis showed that pooled sensitivity (when including NVE and PVE) of ^{18}F-FDG PET/CT for diagnosis of IE is only 76.8% and this relatively low accuracy was primarily due to the poor sensitivity for NVE (17). Therefore, as recommended by current guidelines (7,8), the use of ^{18}F-FDG PET/CT for IE diagnosis is only restricted to PVE. This was clearly confirmed by our study where sensitivity for PVE was much higher than for NVE. Several factors have been associated with a positive

PET/CT in previous studies (20), including PVE, timing of the ^{18}F-FDG PET/CT study, and high inflammatory activity (21). In a recent study (21), Swart et al. showed that low CRP level (<40mg/L) was predictive of false negative ^{18}F-FDG PET/CT. Similar results were observed in our series, in which median CRP levels were lower in 19 patients with PVE and false negative ^{18}F-FDG PET/CT, as compared with 90 patients with PVE and positive ^{18}F-FDG PET/CT. By multivariable analysis, only prosthetic valve, high CRP value and presence of paravalvular complications were independent factors of positive ^{18}F-FDG PET/CT. CRP level was an independent predictor of positive ^{18}F-FDG PET/CT both in the PVE group and in the overall population. Physician should be aware of the risk of false negative ^{18}F-FDG PET/CT in case of low systemic inflammation.

2 – ^{18}F-FDG PET/CT predicts bad outcome in PVE:

Early and accurate prognostic assessment is a key issue in IE. In addition to conventional clinical, biological, and echocardiographic markers (11, 12, 22), our study showed that ^{18}F-FDG PET/CT was able to provide independent information about the risk of occurrence of complications (heart failure, in-hospital and one-year death, recurrence, new embolism and re-hospitalization) in patients with IE. We also observed a "dose-effect" relationship as a moderate to intense uptake was even more strongly associated with major cardiac event, as compared with negative or low intensity uptake. Interestingly, systemic inflammation measured by C-reactive protein was also an independent predictor of adverse cardiac events. Therefore, inflammation either systemic or focal has a key role in the prognosis of IE. High level of inflammation suggests poor outcomes and occurrence of major cardiac adverse event.

3 – ^{18}F-FDG PET/CT predicts embolic events:

Embolic events are a frequent and life-threatening complication of IE related to the migration of cardiac vegetations. Although several factors have been associated with an increased risk of embolism (23), its prediction is still difficult in the individual stratification. Our study showed that both in case of PVE or NVE, ^{18}F-FDG PET/CT was an independent predictor of new embolism. To date, the size of the vegetation is acknowledged to be the best predictor of new embolic event and our study shows that, independently of the vegetation size, the presence of a high level of local inflammation-assessed by ^{18}F-FDG PET/CT is also predictive of new embolic event. Vegetation length and ^{18}F-FDG uptake seem to be two complementary predictors of new embolism. Therefore, in addition to echocardiographic findings, a positive ^{18}F-FDG PET/CT at time of admission might be considered as an additional indication for prophylactic surgery in patients with large vegetations. However, since our study is the first to have highlighted this finding, additional studies are warranted to demonstrate that the addition of a positive ^{18}F-FDG PET/CT to echocardiographic data at time of admission may help deciding the indication and timing of surgery in these patients.

Study limitations

Our study is limited by the relative low number of patients and events, particularly in NVE since the number of positive ^{18}F-FDG PET/CT was low in this group. Thus, the prognostic value of ^{18}F-FDG PET/CT has only been demonstrated in PVE with a composite endpoint but not with the in-hospital nor long-term mortality. Despite this limitation, we were able to demonstrate the value of ^{18}F-FDG PET/CT in predicting embolic events even if, given the low event count of new embolic event, statistical tests were performed without adjustment. Finally, our results cannot be applied in critically ill patients since they were unable to perform ^{18}F-FDG PET/CT, representing a selection bias.

Conclusion

This is the first study assessing the prognostic value of ^{18}F-FDG PET/CT. Our study showed that the nuclear imaging technique was predictive of major adverse cardiac event (in hospital death, one-year death, recurrence or IE, acute cardiac insufficiency, symptomatic embolism under antibiotics and non-scheduled rehospitalization for cardiovascular indication) in case of PVE. These results reinforce the utility of ^{18}F-FDG PET/CT in PVE, and justify its use in this population, not only for diagnostic purpose but also for prognostic assessment. ^{18}F-FDG PET/CT enables a prognostic stratification and should be used in clinical practice for optimal patient's management and therapeutic decision, particularly in PVE.

Perspectives

Competency in Patient Care and Procedural Skills: 18F-Fluorodeoxyglucose Positron Emission Tomography /Computed Tomography (18F-FDG PET/CT) can be useful for diagnosis and estimation of prognosis in patients with infective endocarditis (IE).

Translational Outlook: Future studies should focus on defining the appropriate use of 18F-FDG PET/CT imaging in the evaluation of patients with IE.

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Figure Legends

Central Illustration: Prosthetic Valve Endocarditis: Kaplan-Meier Curves. (A1) Kaplan-Meier curve at 1-year follow-up for the primary endpoint incidence in the PVE group comparing positive versus negative ^{18}F-FDG PET/CT. A2 shows cumulative incidence curve for the primary endpoint in case of positive ^{18}F-FDG PET/CT (62% (95% IC:53% to 73%)) or in case of negative ^{18}F-FDG PET/CT (38% (95% IC:27% to 47%)). (B1) shows Kaplan-Meier curve comparing negative or low ^{18}F-FDG uptake versus moderate to intense ^{18}F-FDG uptake. B2 shows cumulative incidence curve for the primary endpoint in case of moderate to intense ^{18}F-FDG uptake (64% (95% IC: 54% to 76%)) or of negative ^{18}F-FDG PET/CT or low ^{18}F-FDG uptake (36% (95% IC:26% to 46%)). Abbreviations. PVE: prosthetic valvular endocarditis. ^{18}F-FDG PET/CT**:** ^{18}Fluorodeoxyglucose Positron Emission/ Computerized Tomography.

Figure 1: Flowchart of the study. Blue boxes indicate patients included in the final analysis. Red boxes indicate the reason for exclusion and the number of patients. IE: infective endocarditis. ^{18}F-FDG PET/CT: ^{18}Fluorodeoxyglucose Positron Emission/ Computerized Tomography. PVE: prosthetic valve endocarditis. NVE: native valve endocarditis.

Figure 2: Primary Endpoint Incidence. Figure 2A shows B Kaplan- Meier curve at 1 year follow up in the overall population. The blue curve represents cumulative incidence of primary endpoint in the overall population and red curves its 95% confidence interval. Cumulative incidence was 54 % (95 % IC: 46% to 62 %) in the overall population. Figure 2B represents cumulative incidence of primary endpoint and its 95% confidence interval in the NVE group. Cumulative incidence was 48 % (95 % IC: 38% to 62 %) in the NVE population. Figure 2C represents cumulative incidence in the PVE group. Cumulative incidence was 58 % (95 % IC: 48

% to 67 %) in the PVE population Abbreviations: NVE: native valvular endocarditis. PVE: Prosthetic valvular endocarditis.

Figure 3: 18-FDG PET/CT as a Predictor of New Embolism. Figure 3A shows survival curve without new embolism in the PVE group and log rank test p value when comparing in blue, negative versus positive ^{18}F-FDG PET/CT**:** and in red, negative or low ^{18}F-FDG uptake versus intense uptake. Figure 3B shows survival curve without new embolism in the NVE group when comparing in blue negative versus positive ^{18}F-FDG PET/CT and in red negative or low ^{18}F-FDG uptake versus intense uptake. Abbreviations: NVE: native valvular endocarditis. PVE: Prosthetic valvular endocarditis. ^{18}F-FDG PET/CT**:** ^{18}Fluorodeoxyglucose Positron Emission/ Computerized Tomography.

TABLE1. Patients characteristics

	All (n=173)	PVE (n=109)	NVE (n=64)	p-value
Demographic and clinical data				
Age, (years, range)	67 [59-77]	69 [62-77]	66 [55-74]	0.03
Male sex, n (%)	121 (70)	70 (64)	51 (80)	0.04
Charlson comorbidity index (n, range)	3 [2-4]	3 [2-5]	2 [1-4]	0.05
Aortic prosthesis, n (%)	80 (46)	80 (73)	-	-
Mitral prosthesis, n (%)	29 (17)	29 (27)	-	-
Diabetes mellitus, n (%)	34 (20)	24 (22)	10(16)	0.3
Coronary artery disease, n (%)	20 (12)	15 (14)	5 (8)	0.3
Renal insuficiency, n (%)	20 (12)	15 (14)	5 (8)	0.03
Cancer, n (%)	24 (14)	13 (12)	11 (17)	0.4
Biological data, mean(range)				
GFR µmol/L/1.73m^2	61 [46-93]	51 [38-71]	90 [60-120]	0.04
Leukocytes count, /mm3	9 250 [7150-1200]	9500 [7100-11000]	8800 [7200-12000]	0.6
CRP, mg/L	62 [27-110]	64 [23-120]	60 [31-104]	0.9
Causative pathogens				
- *Staphylococcus species, n (%)*	50 (29)	34 (31)	16 (25)	0.8
- aureus, n (%)	44 (25)	30 (28)	14 (22)	0.7
- coagulase negative, n (%)	6 (3)	4 (4)	2 (3)	0.8
- *Streptococcus species, n (%)*	48 (28)	26 (24)	22 (34)	0.05
- *Enteroccocus species, n (%)*	32 (18)	19 (17)	13 (20)	0.2
Echocardiographic data				
Location of IE:				
- Aortic valve, n (%)	107 (62)	78 (72)	29 (45)	0.04
- Mitral valve, n (%)	90 (52)	47 (43)	43 (67)	0.02
- Both valves involved, n (%)	24 (14)	16 (15)	8 (13)	0.3
LVEF (%), mean (range)	60 [59-65]	60 [50-62]	65 [60-66]	0.09
Paravalvular complications, n (%)	67 (39)	54 (50)	13 (20)	0.006
Vegetation >10mm, n (%)	60 (35)	35 (32)	25 (39)	0.5
Vegetation >15mm, n (%)	29 (17)	15 (14)	14(22)	0.2
Mobile vegetation, n (%)	103 (60)	60 (55)	43 (67)	0.1
Surgery, n (%)	93 (54)	44 (40)	49 (77)	0.0001
Positive MSCT, n (%)	12 (7)	9 (8)	3 (5)	0.6
Positive ^{18}F-FDG PET/CT , n (%)	100 (58)	90 (83)	10 (16)	0.0001
Primary outcome endpoint, n (%)	94 (54)	63 (58)	31 (48)	0.6

Relevant population characteristics data. Positive CMCT refers to examination positive in the valvular area. Abbreviations : PVE: Prosthetic valve endocarditis, NVE: native valvular endocarditis. CRP: C-reactive protein. LVEF: left ventricular ejection fraction. GFR: Glomerular filtration rate, MSCT : multisliced cardiac tomography^{18}F-FDG PET/CT : ^{18} fluorodeoxyglucose Positron Emission/ Computerized Tomography.

TABLE 2. Predictors of 18-FDG PET/CT results.			
	Negative 18-FDG PET/CT (n=73)	**Positive 18-FDG PET/CT (n=100)**	**p-value**
Demographic data			
Age, year	65.8 (55.7-73)	71 (62-78)	0.04
Male sex, n (%)	59(81)	61 (61)	0.007
High blood pressure, n (%)	28 (38)	44 (44)	0.5
Diabetes, n (%)	13 (18)	21 (21)	0.7
Prosthetic valve	19 (26)	90 (90)	0.0001
Atrial Fibrillation	18 (26)	38 (44)	0.03
Clinical data			
Fever at admission, n	21 (44)	36 (36)	0.5
Leukocytes count, mm3	8.9(6.8-11)	9.6(7.6-13)	0.2
Creatinine level serum, µmol/L	84 (72-117)	95 (76-129)	0.2
BNP, ng/l	237 (129-462)	299(133-549)	0.4
CRP, mg/L	56 (23-98)	75(29-129)	0.05
Positive blood culture	53 (73)	75 (75)	0.7
Vegetation >10mm	24 (33)	37(37)	0.5
Paravalvular complication	14 (19)	51 (51)	0.0001
Time from first antibiotic to PET/CT, days	7 (4-8)	6(4.5-8.0)	0.57
Primary outcome endpoint, n (%)	26 (54)	30(30)	0.6

Table 2 shows characteristics of patients according to 18-FDG PET/CT results. Abbreviations: BNP: brain natriuretic peptide; CRP: C-reactive protein; 18-FDG PET/CT: 18-fluorodeoxyglucose Positron Emission/ Computerized Tomography. PVE: prosthetic valve endocarditis

TABLE 3 INCIDENCE OF PRIMARY ENDPOINT AND MAJOR CARDIAC EVENTS

	All (n=173)	PVE group (n=109)	NVE group (n=64)
Primary endpoint, n (%)	94 (55)	63 (58)	31 (48)
In-hospital death, n (%)	14 (8)	9 (8)	5 (8)
1-year death, n (%)	35 (20)	25 (23)	10 (16)
Recurrence, n (%)	15 (9)	8 (7)	7 (11)
New embolic event, n (%)	22 (13)	16 (15)	6 (9)
Acute cardiac failure, n (%)	66 (38)	33 (30)	33 (51)
Re-hospitalization, n (%)	40 (20)	27(20)	13 (20)

Incidence of primary endpoint and major cardiac events in the overall population, the prosthetic valve endocarditis (PVE) group and native valve endocarditis (NVE) group.

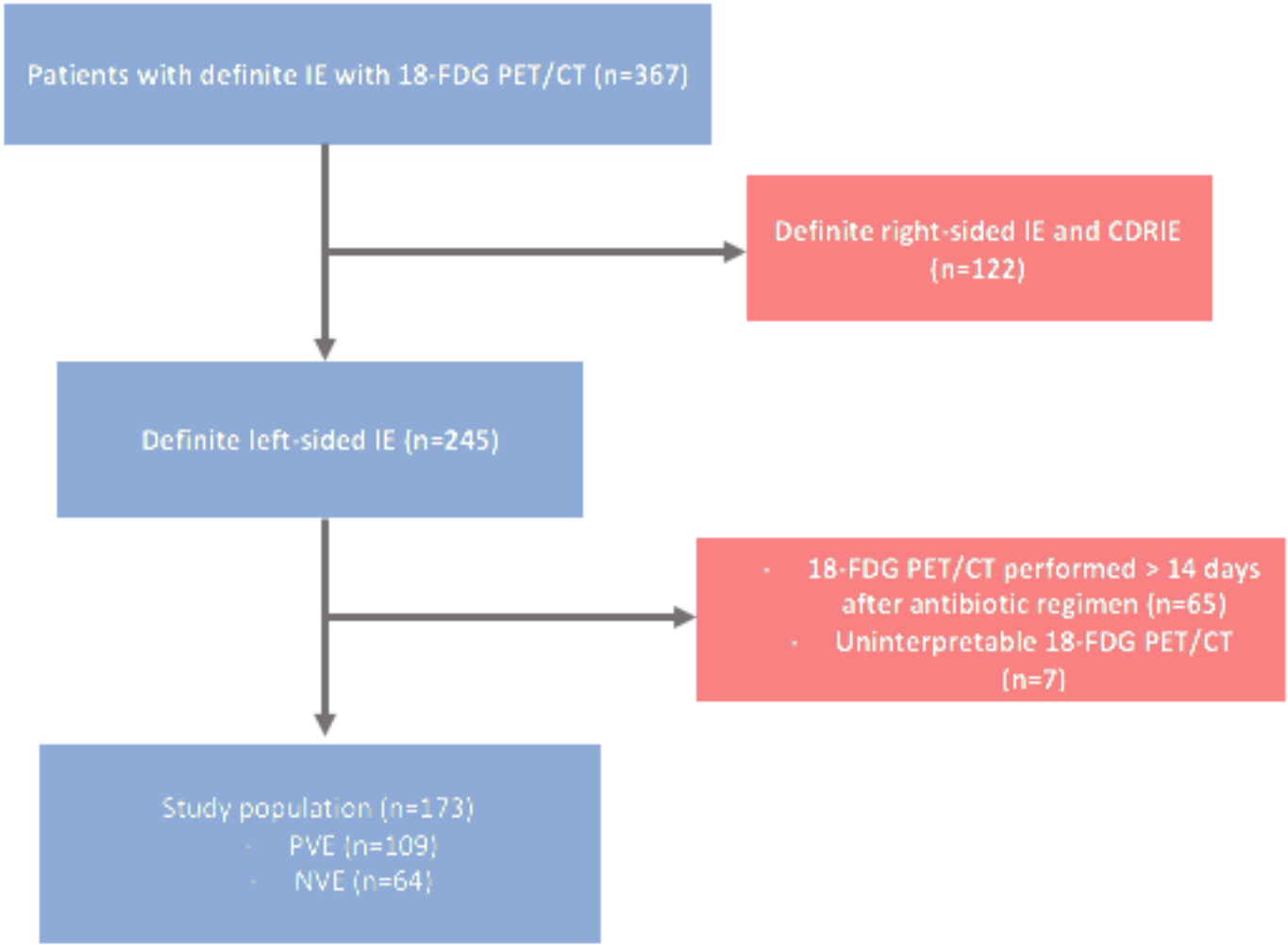
TABLE 5. MAJOR CARDIAC EVENTS IN THE PVE AND NVE GROUPS ACCORDING TO 18-FGD PET/CT RESULTS

	PVE GROUP (n=109)				NVE GROUP (n=64)	
	PVE GROUP (n=109)				NVE GROUP (n=64)	
	Positive 18-FDG	Moderate to intense 18-FDG uptake	Mutlivariate HR		Positive 18-FDG	Moderate to intense 18-FDG uptake
	Univariate HR (95% IC)	p value	(95% IC)	p value	Univariate HR (95% IC)	p value
Age ≥ 70 years	2.5 (1.14-5.48)	0.02			1.29 (0.59-4.65)	0.33
Male	0.96 (0.42-2.06)	0.86			2.53 (0.69-9.28)	0.15
Charlson comorbidity index >4	1.04 (0.48-2.06)	0.92			1.5 (0.51-4.25)	0.6
Diabetes mellitus	2.06 (0.77-5.48)	0.14			5.39 (1.04-27.8)	0.03
History of high blood pressure	0.6 (0.28-1.29)	0.29			3.96 (1.33-11.8)	0.02
Atrial fibrillation	1.73 (0.8-3.73)	0.16			3.72 (0.69-20)	0.1
Coronary artery disease	3.84 (1.18-12.55)	0.02			1.13 (0.17-7.8)	0.89
Respiratory insufficiency	0.83 (0.26-2.66)	0.76			3.69 (0.36-37.61)	0.91
Intra-cardiac device	1.31 (0.47-3.64)	0.6			1.11 (0.15-8.41)	0.92
Surgery	1.54 (0.72-3.31)	0.26			0.54 (0.17-1.75)	0.3
LVEF ≤ 45 %	3.57 (1.11-11.5)	0.03			1.07 (0.06-17.88)	0.99
BMI ≥ 30	1.02 (0.3-3.44)	0.99			1.92 (0.42-8.82)	0.40
Fever at admission	0.58 (0.27-1.25)	0.17			0.68 (0.25-1.83)	0.44
Renal insufficiency at admission	2.16 (1-4.68)	0.05			0.78 (0.25-2.43)	0.66
Leukocytes count ≥10000/mm3	2.13 (0.97-4.69)	0.06			0.75 (0.27-2.06)	0.56
CRP ≥ 100 mg/L	2.46 (1.04-5.89)	0.02	1.9 (1.1-3.4)	0.03	1.27 (0.43-3.72)	0.66
Staphylococcus aureus	2,7 (1,1-6,55)	0,03			1.52 (0.49-4.75)	0.47
Severe valvular regurgitation	2.55 (1.01-6.41)	0.05	1.2 (0.7-2.1)	0.68	3.38 (1.03-11.1)	0.04
Echographic complications	1.15 (0.54-2.46)	0.72			2.29 (0.67-7.82)	0.28
Vegetation length > 10 mm	2.53 (1 .19-4.6)	0.03			2.74 (1.2-7.67)	0.05
Mobile vegetation	1.82 (0.29-11.4)	0.51			1.15 (0.21-6.18)	0.86
Positive MSCT	2.2 (0.2-25.7)	0.5				
Positive ^{18}F-FDG PET/CT	3.74 (1.3-10.8)	0.02	2.7 (1.1-6.7)	0.04	1.75 (0.44-6.87)	0.43
Moderate to intense ^{18}FDG valvular uptake	2.7 (1.2-6.3)	0.02	2.3 (1.3-4.5)	0.03	1.39 (0.34-5.74)	0.64

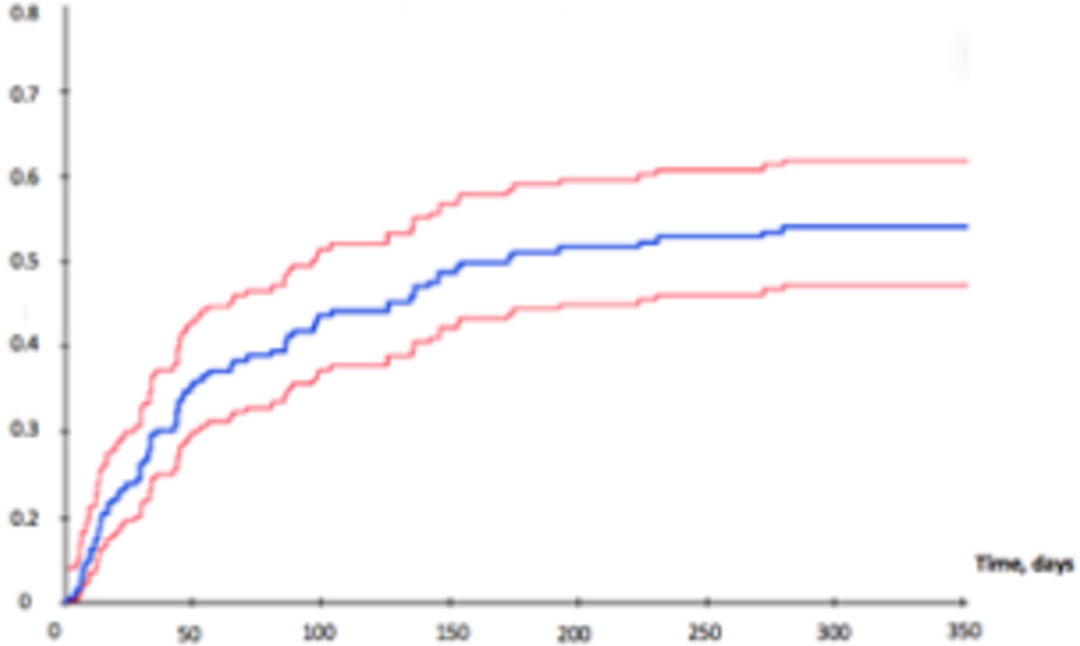
Univariate and multivariate analysis in the PVE and the NVE groups for primary endpoint incidence. Abbreviations. PVE: prosthetic valvular endocarditis. NVE: native valvular endocarditis. HR: Hzard ratio. LVEF: left ventricular ejection fraction. BMI: body mass index. CRP: C-reactive protein. MSCT: multislice cardiac tomography. ^{18}F-FDG PET/CT :^{18}Fluorodeoxyglucose Positon Emission/ Computed Tomograph

	HR (IC95%)	p value	HR (IC95%)	p value	HR (IC95%)	p value	HR (IC95%)	p value
In-hospital death	0.49 (0.5 – 2.6)	0.36	0.43 (0.1 – 1.8)	0.25	2.78 (0.44-17.5)	0.25	1.53 (0.16-16.1)	0.69
One year death	1.43 (0.41-6.0)	0.5	1.4 (0.51-3.97)	0.5	1.35 (0.26-8.06)	0.68	1,77 (0,64-4.93)	0.27
Recurrence	1.24 (0.14-10.98)	0.84	3.1 (0.37- 26.28)	0.28	2.45 (0.4-14.85)	0.67	3.0 (0.35-26)	0.3
New embolic event	3.1 (0.37-26)	0.82	7.5 (1.24-45.2)	0.03	3.13 (0.5-20)	0.21	8.8 (1.1-69.5)	0.02
Acute cardiac failure	1.97 (0.6 -0.45)	0.25	1.0 (0.44-2.57)	0.89	1.87 (0.56-6.24)	0.31	1.3 (0.54-3.13)	0.55
Re hospitalization	3.27 (0.7-15.2)	0.11	3 (0.94-9.47)	0.05	2.5 (0.53-11.9)	0.24	3.57 (1.1-11.3)	0.03

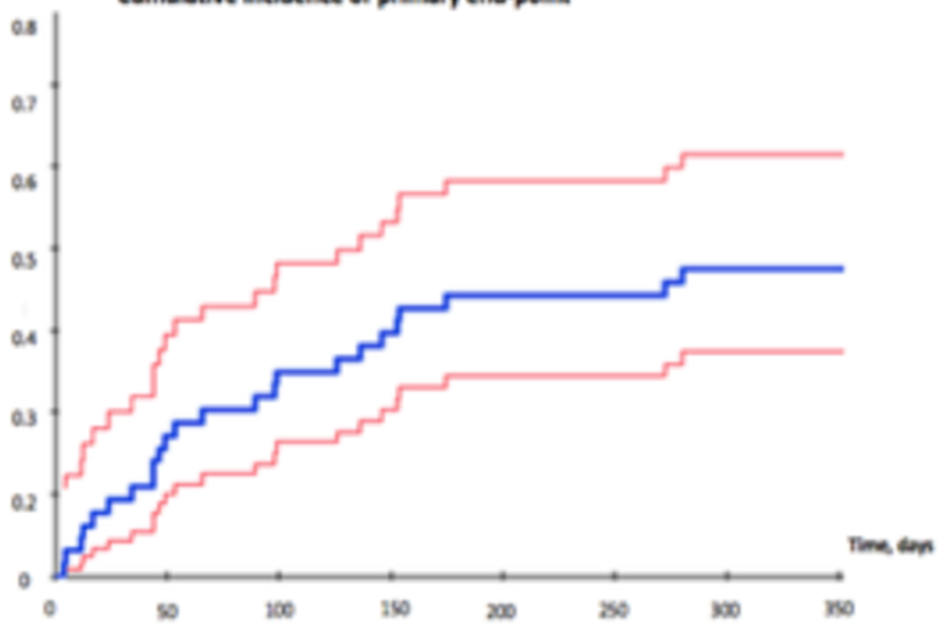
Major cardiac events according to the 18-FDG PET/CT findings in the PVE and NVE groups. Abbreviations. HR: hazard ratio. 18-FDG PET/CT: 18-fluorodeoxyglucose Positron Emission/ Computerized Tomography; NVE: native valvular endocarditis.


Patients with definite IE with 18-FDG PET/CT (n=367)
Definite right-sided IE and CDRIE (n=122)
Definite left-sided IE (n=245)
18-FDG PET/CT performed > 14 days after antibiotic regimen (n=65)
Uninterpretable 18-FDG PET/CT (n=7)
Study population (n=173)
PVE (n=109)
NVE (n=64)

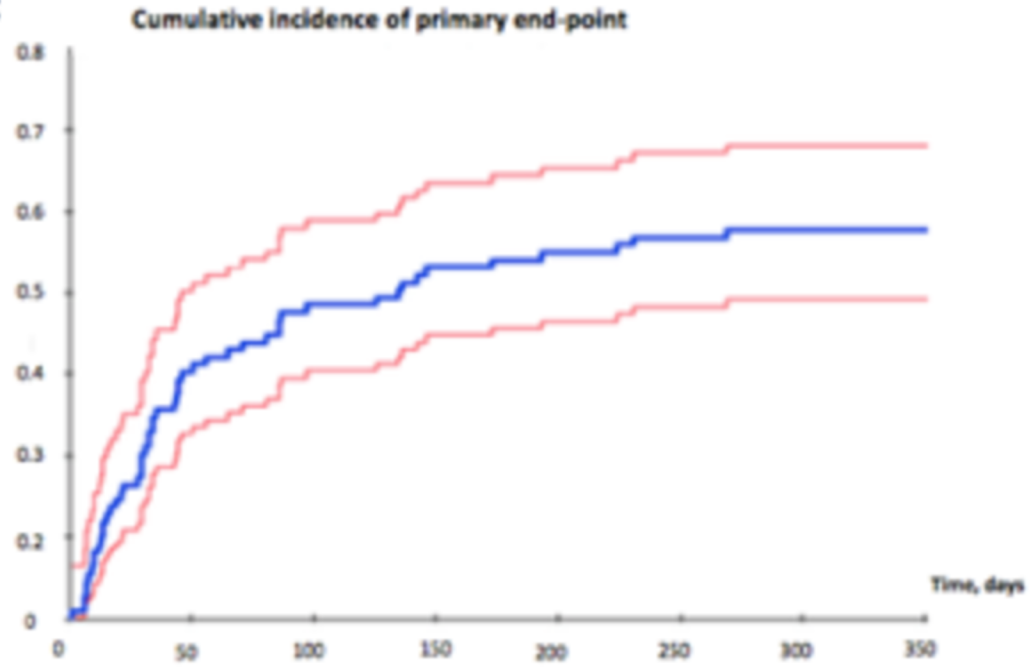
A

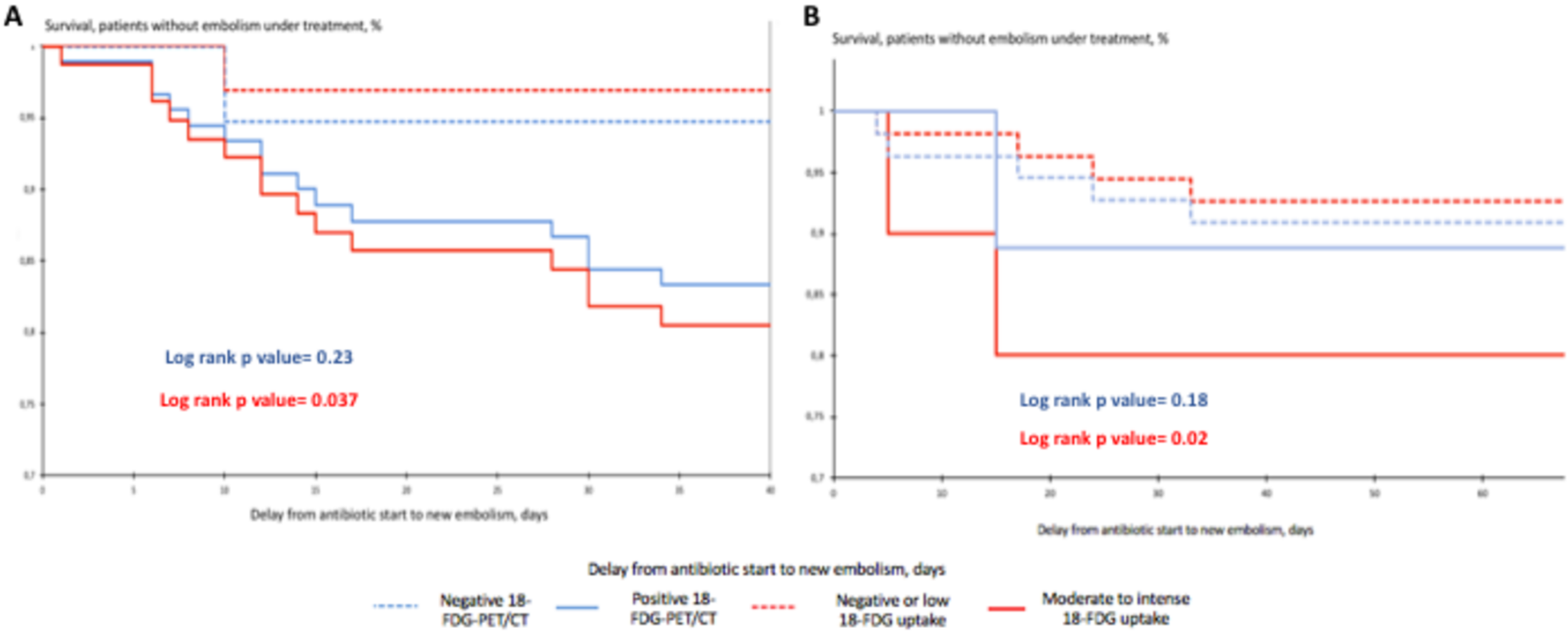

Cumulative incidence of primary end-point
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0
Time, days
0
50
100
150
200
250
300
350

B


Cumulative incidence of primary end-point
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0
Time, days
0
50
100
150
200
250
300
350

C


Cumulative incidence of primary end-point
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0
Time, days
0
50
100
150
200
250
300
350


A
Survival, patients without embolism under treatment, %
Log rank p value= 0.23
Log rank p value= 0.037
Delay from antibiotic start to new embolism, days
B
Survival, patients without embolism under treatment, %
Log rank p value= 0.18
Log rank p value= 0.02
Delay from antibiotic start to new embolism, days
Delay from antibiotic start to new embolism, days
Negative 18-FDG-PET/CT
Positive 18-FDG-PET/CT
Negative or low 18-FDG uptake
Moderate to intense 18-FDG uptake