Impact of systematic whole-body 18F-fluorodeoxyglucose PET/CT on the management of patients suspected of infective endocarditis: the prospective multicenter TEPvENDO study

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Xavier Duval [a, b, c, d], Vincent Le Moing [e], Sarah Tubiana [a, b, c], Marina Esposito-Farèse [a, b, f], Emila Ilic-Habensus [a, b], Florence Leclercq [g], Aurélie Bourdon [h], François Goehringer [i], Christine Selton-Suty [j], Elodie Chevalier [k], David Boutoille [l], Nicolas Piriou [m, n], Thierry Le Tourneau [m], Catherine Chirouze [o], Marie-France Seronde [p], Olivier Morel [q], Lionel Piroth [r], Jean-Christophe Eicher [s], Olivier Humbert [t], Matthieu Revest [u, v], Elise Thébault [v], Anne Devillers [w], François Delahaye [x], André Boibieux [y], Bastien Grégoire [z], Bruno Hoen [i], Cédric Laouenan [a, b, c, d, f] *, Bernard Iung [a, b, c, d] *, François Rouzet [a, b, c, d, aa] * and the AEPEI-TEPvENDO study group

*These authors contributed equally.

[a] Inserm CIC 1425, Paris, France

[b] AP-HP, university hospital of Bichat, Paris, France

[c] Inserm UMR-1137 IAME, Paris, France

[d] University Paris Diderot, Paris 7, UFR de Médecine-Bichat, Paris, France

[e] Department of Infectious Diseases, university hospital of Montpellier, France

[f] Unité de Recherche Clinique, AP-HP, HUPNVS, Hôpital Universitaire Paris Nord-Val de Seine, Paris, France

[g] Department of Cardiology, university hospital of Montpellier, France

[h] Department of Nuclear Medicine, university hospital of Montpellier, France

[i] Department of Infectious Diseases, university hospital of Nancy, Nancy, France

[j] Department of Cardiology, university hospital of Nancy, Nancy, France

[k] Department of Nuclear Medicine, university hospital of Nancy, Nancy, France

[l] Department of Infectious Diseases, CIC UIC 1413 INSERM, university hospital of Nantes, Nantes, France

[m] Thorax Institute, INSERM, UMR 1087, university hospital of Nantes, Nantes, France

[n] Department of Nuclear Medicine, Nantes University Hospital, G. et R. Laennec hospital, Nantes, France

[o] University hospital of Besançon, France, UMR CNRS 6249 Chrono-Environnement, Bourgogne university, Franche-Comté

[p] Department of Cardiology, university hospital of Besançon, France

[q] Department of Nuclear Medicine, university hospital of Besançon, France

[r] Department of Infectious Diseases, university hospital of Dijon, Inserm CIC 1432, CHU Dijon, France, University of Burgundy

[s] Department of Cardiology, university hospital of Dijon, France

[t] Department of Nuclear Medicine, university hospital of Dijon, France

[u] Infectious Diseases and intensive care unit, university hospital of Rennes France; Inserm U1230 CHU Rennes, France

[v] Inserm CIC 1414, university hospital of Rennes, France

[w] Department of Nuclear Medicine, university hospital of Rennes, France

[x] Department of Cardiology, university hospital of Lyon, France

[y] Department of Nuclear Medicine, university hospital of Lyon, France

[z] Department of Infectious Diseases, university hospital of Lyon, France

[aa] Department of Nuclear Medicine, AP-HP, university hospital of Bichat, Paris, France

Address for correspondence

Xavier Duval, MD,
Infectious diseases Department,
Bichat Hospital
46 rue Henri Huchard
75018 Paris, France
Tel: +33 1 40 25 71 48
Fax : +33 1 40 25 67 76
e-mail: xavier.duval@aphp.fr

Summary : In 140 patients suspected of having prosthetic or native valve infective endocarditis, systematic whole body ^{18}F-FDG-PET/CT modified diagnosis classification in 15% of and/or care in 26% of them. Both prosthetic valve and native valve patients benefit from this systematic ^{18}F-FDG-PET/CT.

Abstract:

Background: Diagnostic and patients' management modifications induced by whole-body ^{18}F-FDG-PET/CT had not been evaluated so far in prosthetic valve (PV) or native valve (NV) infective endocarditis (IE)-suspected patients.

Methods: 140 consecutive patients in 8 tertiary care hospitals underwent ^{18}F-FDG-PET/CT. ESC-2015-modified Duke criteria and patients' management plan were established jointly by two experts before ^{18}F-FDG-PET/CT. The same experts reestablished Duke classification and patients' management plan immediately after qualitative interpretation of ^{18}F-FDG-PET/CT. A 6-month final Duke classification was established.

Results: Among the 70 PV and 70 NV patients, 34 and 46 were classified as definite IE before ^{18}F-FDG-PET/CT. Abnormal perivalvular ^{18}F-FDG uptake was recorded in 67.2% PV and 24.3% NV patients respectively ($p<0.001$) and extracardiac uptake in 44.3% PV and 51.4% NV patients. IE classification was modified in 24.3% and 5.7% patients ($p=0.005$) (net reclassification index 20% and 4.3%). Patients' managements were modified in 21.4% PV and 31.4% NV patients ($p=0.25$). It was mainly due to perivalvular uptake in PV patients and to extra-cardiac uptake in NV patients and consisted in surgery plan modifications in 7 patients, antibiotic plan modifications in 22 patients and both in 5 patients. Altogether, ^{18}F-FDG-PET/CT modified classification and/or care in 40% of the patients (95% CI: 32-48), which was most likely to occur in those with a non-contributing echocardiography ($p<0.001$) or IE classified as possible at baseline ($p=0.04$), while there was no difference between NV and PV.

Conclusions: Systematic ^{18}F-FDG-PET/CT did significantly and appropriately impact diagnostic classification and/or IE management in PV and NV-IE suspected patients.

Keywords: ^{18}F-FDG-PET/CT; infective endocarditis, diagnostic impact; patient management.

ClinicalTrial. Gov identification number: NCT02287792

Introduction

Infective endocarditis (IE) diagnosis is often challenging, particularly when the causative microorganism is difficult to identify and /or when echocardiography is non-contributing [1, 2]. In such situations, guidelines recommend resorting to other imaging techniques to confirm or exclude valve involvement and/or search for clinically silent IE extracardiac manifestations [3, 4]. These investigations may help practitioners establish or rule out the IE diagnosis and adapt also patients' management, especially regarding antibiotic choice and indication for and timing of valve surgery.

Several observational series have reported the diagnostic value of 18-fluorine-fluorodeoxyglucose positron emission tomography coupled with computed tomography (^{18}F-FDG-PET/CT) in prosthetic valve (PV) infection [5-10]. This led the European Society of Cardiology to include, in the ESC-2015 modified-Duke classification ^{18}F-FDG perivalvular uptake as a major criterion of PVIE after 3 months of valve implantation, and extracardiac uptake as a minor criterion for both PV and native valve (NV) patients [4]. The American Heart Association guidelines of the same year, however, argued that "more study was needed to define the utility of ^{18}F-FDG-PET/CT in the diagnosis and management of IE" [3]. Furthermore, the diagnostic value of FDG PET/CT in NV endocarditis has been much less investigated so far [11, 12]. In addition, beyond the diagnostic reclassification associated with ^{18}F-FDG-PET/CT, what seems most important is its impact on patient management, which has not been evaluated to date.

Since the above-mentioned guidelines publications, the specificity of ^{18}F-FDG-PET/CT cardiac uptake has been challenged by the evidence that perivalvular ^{18}F-FDG uptake was frequently present in patients with PV and with no infection, regardless of the time span (< or >3 months) since valve implantation, due to inflammation surrounding a foreign body or use of surgical adhesives [13]. This may lead to false positives in PVIE patients when the perivalvular uptake is considered as a major Duke criterion without taking into account the uptake pattern and the use of surgical adhesive during cardiac surgery [14].

The aim of the TEPvENDO multicenter prospective study was to assess both diagnostic and patients' management modifications induced by ^{18}F-FDG-PET/CT using a qualitative reading of perivalvular uptake in patients suspected of NV IE or PV IE, using systematic whole body ^{18}F-FDG-PET/CT including brain and lower limbs.

Methods

Patients

From April 2015 to March 2016, all adult patients with high clinical suspicion of IE, hospitalized in 8 French tertiary care hospitals having a local IE team (which involved at least a cardiologist, an infectious diseases specialist, a cardiac surgeon, and a microbiologist) were included. The inclusion criteria are detailed in supplementary data. Written informed consent was obtained from all participants. The protocol was approved by the French CPP 1 Ethics committee (IRB n° 2014-sept-13685). ^{18}F-FDG-PET/CT was to be performed within 7 days of inclusion. Transthoracic and/or transoesophageal echocardiography (TTE/TOE) were performed as clinically indicated [15].

IE classifications

IE classification was established three times during the course of IE by two IE experts:

- first, before ^{18}F-FDG-PET/CT scan using Duke classification modified by Li, hereafter referred to as "Duke-Li classification at inclusion" [16];

- second, after ^{18}F-FDG-PET/CT completion using a modified-ESC-2015 IE classification, hereafter referred to as "m-ESC2015 ^{18}F-FDG-PET/CT classification". In the ESC-2015 classification, any valvular uptake is considered as a major Duke criterion only in PV patients, and emboli or aneurysms detected by ^{18}F-FDG-PET/CT as a minor Duke criterion in PV and NV patients [3, 4]. In the present m-ESC-2015 ^{18}F-FDG-PET/CT classification, a positive valvular uptake was also considered as a major Duke criterion in NV patients.

- The third and final IE classification was established at month 6, hereafter referred to as “final classification”.

^{18}F-fluorodeoxyglucose PET/CT

Acquisition procedure

All patients underwent a high-fat low carbohydrate diet followed by >12h fasting in order to suppress physiological myocardial ^{18}F-FDG uptake [17]. Sixty minutes after ^{18}F-FDG injection (3.5 to 4 MBq/kg) without heparin, a low-dose CT was acquired followed by whole-body PET (vertex to toes). An additional cerebral step (8-min single bed position) was acquired 3 hours after ^{18}F-FDG injection. Transverse PET slices were reconstructed into a 256 x 256 matrix with (AC) and without (NAC) attenuation correction.

Qualitative Analysis

Any detectable FDG uptake was considered abnormal on NV. On PV, the peri-prosthetic FDG uptake was qualitatively assessed on images corrected (AC) or not (NAC) for attenuation, on oblique views reoriented so that the plane of the slice coincides with the plane of the PV, and considered normal when absent or homogeneous (i.e. diffuse FDG signal around the PV ring without focal enhancement) regardless of uptake intensity [14] and abnormal when heterogeneous and/or extending beyond the peri-annular area. In order to standardize image interpretation across participating centers, a one-day training session was held before initiation of the study with all nuclear medicine physicians involved in the study.

Quantitative Analysis

In case of positive ^{18}F-FDG-PET/CT, maximal standardized uptake value (SUVmax) was measured. Mean SUV of blood-pool was calculated as the average of mean SUVs in three adjacent axial slices within the right atrium in areas devoid of significant spillover activity from surrounding tissues. Valve-to-background ratio was calculated by dividing the SUVmax of the valve area by the mean SUV of bloodpool.

^{18}F-fluorodeoxyglucose PET/CT diagnostic and management modifications

Within 24 hours before ^{18}F-FDG PET/CT, a cardiologist specialist and an infectious diseases specialist, both experts in IE, visited the patients and filled in a standardized questionnaire. They jointly established Duke-Li classification at inclusion according to the Duke-Li criteria, outlined an antimicrobial therapy plan and, if necessary, a surgery plan (timeline, type of surgery, indications …) [16]. Within 24 hours following ^{18}F-FDG-PET/CT completion, the two experts jointly reassessed IE classification (assessing the modifications related to FDG PET/CT results) and proposed diagnostic and/or therapeutic modifications when appropriate (Figure 1).

IE classification gold standard

The gold standard was the 6-month final classification which took into account all available data except the results of the FDG PET/CT if they were not confirmed by another additional exploration, to avoid tautology.

Statistical analysis

Quantitative variables were presented as median and interquartile range (IQR). Baseline and follow-up characteristics were described by standard methods. Comparisons were performed by Chi-square or Student t test as required, or their non-parametric versions, Fisher exact or Wilcoxon/Mann-Whitney tests as appropriate.

We considered that any modification in the Duke-Li classification due to ^{18}F-FDG PET/CT was a change in diagnosis, whatever the direction of the change (upgrade or downgrade diagnosis). To estimate whether ^{18}F-FDG-PET/CT helped physicians to properly reclassify patients according to the gold standard, we calculated the net reclassification index (NRI) [18] (definite IE versus others). Several diagnostic performances were calculated and expressed with their 95% CI.

Patients' characteristics were compared according to whether they would benefit from ^{18}F-FDG-PET/CT. Patients benefiting from ^{18}F-FDG-PET/CT were defined as those whose Duke-Li classification was correctly reclassified after ^{18}F-FDG-PET/CT according to the gold standard, and/or for whom ^{18}F-FDG-PET/CT revealed a previously unknown IE portal of entry, and/or led to a management modification.

The significant statistical level was two-sided 5%. All statistical analyses were performed using R software v 3.4 (The R Foundation for Statistical Computing Platform). The analyses were performed according to the Standards for Reporting of Diagnostic Accuracy guidelines (STARD initiative)[19].

Sample size

Based on the literature, we assumed that ^{18}F-FDG-PET/CT would detect otherwise undiagnosed complications in 20% of patients. We anticipated that findings in 75% of these patients would lead to a change in their therapeutic management, which corresponded to 15% of all the patients. The enrolment of 150 patients would allow 5.7% (95%CI 9.3 to 20.7) accuracy of the estimated rate of change in patients' management.

Results

Baseline characteristics

One hundred and forty patients were analyzed (70 PV patients and 70 NV patients) (Figure 1, Table 1). At inclusion, according to the Duke-Li classification, IE was classified as definite in 80 patients (34 PVIE and 46 NVIE) (p=0.095), possible in 56 patients (33 PVIE and 23 NVIE) and excluded in 4 patients (3 PV and 1 NV) did not fulfill any of these 2 categories but considered as probable IE by attending physicians (Figure 1, Table S1). In the 70 PV patients, the median time span after the last valve implantation was 5.8 years (IQR [2.9: 9.3]); 62 out of the 70 cardiac surgery reports were collected and 6 (9.7%) indicated the use of surgical adhesive. Median CRP was 78 [IQR: 29 - 146] mg/l.

Follow-up

At M6, the final IE classification (i.e. gold standard) was definite in 95 (67.9%) patients (47 definite PVIE and 48 definite NVIE), possible in 26 (18.6%) patients and excluded in 19 (13.6%) patients (Figure 1; Tables 1, Table 2).

Diagnostic value of perivalvular ^{18}F-FDG-PET/CT

^{18}F-FDG-PET/CT was performed at a median time of 2 days after inclusion (IQR 1-3.25), and of 7 days (IQR 4-10) after antibiotic initiation.

Perivalvular/valvular uptake

Abnormal (peri)valvular uptake was present in 64 (45.7%) patients (47 [67.2%] in PV patients and 17 [24.3%] in NV patients) (p<0.001) (Tables 2). Non-specific homogeneous perivalvular FDG uptake attributed to the presence of a PV was reported in 10 (14.3%) additional PV patients and not considered as a major criterion.

In PV patients, SUVmax of perivalvular uptake and mean SUVmax /blood-pool SUV ratio were not statistically different between patients with definite, possible or excluded PVE according to the final diagnosis. The intensity of perivalvular uptake was independent of the time elapsed since

the valve implantation and of the time span between initiation of IE antibiotic therapy and ^{18}F-FDG-PET/CT scan.

Comparison of perivalvular ^{18}F-FDG-PET/CT uptake with echocardiographic findings

Table 1 summarizes the echocardiographic findings according to the final classification at 6 months. Vegetations were found in 71 patients (28 PV patients and 43 NV patients). In patients with vegetations at echocardiography, perivalvular ^{18}F-FDG-PET/CT uptake was considered abnormal in 18 (64.2%) out of the 28 PV patients and in 13 (30.2%) out of the 43 NV patients (p=0.29). In patients with non-contributive echocardiography, perivalvular ^{18}F-FDG-PET/CT was considered as a criterion for IE in 22 of the 29 PV patients and in 4 of the 24 NV patients (p<0.01).

Extracardiac uptake (emboli, distant infection and portal of entry)

Whole-body ^{18}F-FDG-PET/CT identified extracardiac uptake in 69 (49.3%) patients (Table 2). Cerebral acquisitions were performed in 137 (97.9%) patients and were abnormal in 12 (8.8%)(6 patients with cerebral abscess and 6 others with ischemic stroke which were further confirmed by cerebral imaging).

In addition to the 69 patients diagnosed with emboli and/or distant infection, a portal of entry was detected by ^{18}F-FDG-PET/CT in 33 patients (23.6%), which was previously unknown in 12 (8.6%) patients (8 PV and 4 NV patients) (Table 2).

^{18}F-FDG-PET/CT impact on diagnosis and therapy

Diagnostic impact

^{18}F-FDG-PET/CT added at least one Duke criterion (major and/or minor) in 43 (30.7%) (95% CI 23%-39%) patients. This was a major Duke criterion in 23 patients (20 in PV patients and 3 in NV patients) and/or a minor Duke criterion in 21 patients (7 in PV patients and 14 in NV patients (Table S2)). This addition of a Duke criterion led to the modification of the Duke-Li classification in 21 (15%) patients: 17 (24.3%) in PV patients and 4 (5.7%) in NV patients (p=0.004). Duke-Li classification was upgraded

in 18 patients (12.9%): 15 (17%) PV patients and in 3 (4%) NV patients. Duke-Li classification was downgraded in 3 patients (2.1%): 2 (3%) PV patients and in 1 (1.4%) NV patient (Table S2). As compared to final classification at 6 months, upgrading was confirmed as adequate in 16/18 patients (13/15 PV patients and 3/3 NV patients) and downgrading was confirmed as adequate in 1/3 patient (a PV patient). Absolute NRI was 12.1% (20.0% in PV patients and 4.3% in NV patients). The diagnostic performances are presented in Table S1.

Patients' management modification

The therapeutic managment was modified following ^{18}F-FDG-PET/CT scan in 37 of the 140 patients (26.4%; CI 95% 19.1% - 35.5%) corresponding to 15 (21.4%) of the PV patients and 22 (31.4%) of the NV patients (p=0.25) (Tables 3). These modifications were related to antibiotic therapy (modification of duration and/or of type) in 22 patients, surgical management (surgery postponed, advanced, indicated or cancelled) in 7, both in 5 and other aspects in the 3 remaining patients (Table 3). These modifications were mainly due to the presence of a perivalvular uptake in 9 PV patients and due to the presence of an extra-cardiac uptake in 17 NV patients (Figures 2a, 2b).

Characteristics of the patients who benefited from ^{18}F-FDG-PET/CT

Forty percent of the 140 patients (95% CI: 32%-48%) benefited from ^{18}F-FDG-PET/CT as previously defined; they had more frequently non-contributing baseline echocardiography (p<0.001) and/or were more frequently classified as possible IE at inclusion (p=0.04; Table 4). The nature of the cardiac valve (bioprosthesis, mechanical valve or native valve) was not a determinant of the benefit.

Discussion

In this prospective multicenter study evaluating for the first time the diagnostic and patients' management modifications induced by systematic whole body ^{18}F-FDG-PET/CT in patients with a high level of suspicion of IE, we showed that a significant proportion of both PV and NV patients benefited from ^{18}F-FDG-PET/CT.

In this multicenter study, we standardized patient preparation, acquisition protocols and image interpretation through training sessions with specific attention to valve uptake patterns in order to homogenize the classification as non-specific or infection-related [20]. This was all the more worthwhile because of the high prevalence of positive FDG uptake in the perivalvular area regardless of the time span since prosthetic valve implantation when the interpretation of perivalvular uptake was only considered as positive or negative and not combined with qualitative interpretation [14]. This qualitative interpretation led us to consider one-fifth of the PV patients with valvular uptake as non-IE related. Finally, the low number of PV patients with prior use of surgical adhesive does not explain in itself the false positive rates.

Perivalvular ^{18}F-FDG-PET/CT was considered abnormal in some patients with non-conclusive echocardiography (most of them were TOE), but this was observed in a much larger proportion in PV patients. In patients with abnormal echocardiography, concordance with perivalvular ^{18}F-FDG-PET/CT was higher in those with periannular complication than in those with vegetation, in relation with the low content in inflammatory cells of vegetations, the limited spatial resolution of ^{18}F-FDG-PET/CT and the presence of motion artifacts.

As previously reported, peripheral localizations of IE detected by ^{18}F-FDG-PET/CT were frequent, and not previously identified in approximately one-third of patients [5-10]. The rate of peripheral localization was lower in PV patients than in NV patients, as reported in the literature [21]. The possibility for clinicians to identify extra-cardiac locations of IE with ^{18}F-FDG-PET/CT can help them avoid the use of thoraco-abdomino-pelvic CT scan which may favor renal failure [22]. As

previously reported, ^{18}F-FDG-PET/CT enabled the revelation of portal of entry in some patients. For the first time to our knowledge, we showed that cerebral ^{18}F-FDG-PET/CT acquisition may identify asymptomatic lesions despite a high physiological uptake of ^{18}F-FDG.

In the present study population, ^{18}F-FDG-PET/CT improved IE diagnosis in PV and NV patients (up to one patient out of five, approximately), although to a different extent (five times more in PV patients than in NV patients based on net reclassification improvement). The higher impact in PV patients was due jointly to more frequent cardiac abnormal foci detected in these patients and to a lower proportion of patients with definite IE before the ^{18}F-FDG-PET/CT scan as compared to NV patients, making the results of detected lesions by ^{18}F-FDG-PET/CT more likely to impact diagnosis. Of note, the diagnostic impact of perivalvular/valvular uptake was higher than those of extracardiac uptake, as the first is a major criterion and the second is a minor criterion in the m-ESC-2015 ^{18}F-FDG-PET/CT classification. Furthermore, the diagnostic performance of the m-ESC2015 ^{18}F-FDG-PET/CT classification was not improved in the sub-population of patients with CRP ≥ 40 mg/L conversely to what was reported by some authors [13], using as we did a qualitative interpretation of the images.

A low sensitivity of ^{18}F-FDG-PET/CT in patients with NVIE has been reported previously, particularly in the study by de Camargo et al. which enrolled a substantial proportion of patients with NVIE [11]. Histological analysis of infected native valves suggests that extended fibrosis and a low content of polymorphonuclear cells accounted for low FDG uptake. Consequently, there is general agreement that FDG PET/CT is not recommended for the diagnosis of NVIE. However, since the sensitivity of echocardiography is higher in NV patients than in patients with prosthetic valves, the rate of definite IE at baseline as defined by the Duke classification was higher in NV patients than in those with prosthetic valve. Therefore, measuring the diagnostic impact of 18F-FDG-PET/CT through the modification of the Duke classification underestimates the diagnostic impact of 18F-FDG-PET/CT in NV patients.

The present study is the first to assess patients' management modification. It shows that the ^{18}F-FDG-PET/CT cardiac or extracardiac uptakes at the origin of the therapeutic impact was different between NV and PV patients, because more frequent primary or metastatic septic foci were detected by ^{18}F-FDG-PET/CT in the former group, in agreement with previous reports [21]. This led to change both antibiotic and surgery plans. As a result, the overall impact of ^{18}F-FDG-PET/CT in the study population, combining diagnosis and therapeutic management, was independent of the nature of the valve (native or prosthetic).

We must acknowledge several limitations to our study. First, we did not use iodine injection which has been reported to increase ^{18}F-FDG-PET/CT sensitivity in patients with PV [23]. However this was done intentionally to decrease renal toxicity. Second, we did not verify that perivalvular uptake disappeared after patients' cure, which would have been the most accurate way to exclude false positives, but would made patients' care more cumbersome. Third, our experimental design did not assess whether the ^{18}F-FDG-PET/CT-related changes in diagnostic and therapeutic plans improved patient outcomes, or led to unnecessary procedures and increased costs. Fourth, one fifth of the PV patients did not have TOE before ^{18}F-FDG-PET/CT. However, 43% of these patients had had a TTE which revealed vegetation or a perivalvular abscess, giving them a major Duke criterion. Finally, since this study was conducted in reference centers, the proportion of patients with suspected IE on valvular prosthesis was over-represented.

To conclude, this prospective evaluation of the diagnostic and therapeutic impacts of ^{18}F-FDG-PET/CT support its implementation in patients with initial non-definite NVIE as well as PVIE or in case of non-conclusive echocardiography. Despite a lower diagnostic sensitivity in NVIE, therapeutic management is influenced by extra-cardiac findings of whole body staging of the disease. However, ^{18}F-FDG-PET/CT scan must be qualitatively interpreted by trained specialists in order to differentiate abnormal perivalvular uptake related to IE from normal uptake related to prosthetic valve.

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AEPEI TEPvENDO study group

Principal investigator: DUVAL Xavier.

Steering Committee: HOEN Bruno, IUNG Bernard, ROUZET Francois, TUBIANA Sarah.

Clinical centers: Besançon: ALBAYRAK Tubanur, BERNARD Yvette, BOULAHDOUR Hatem, BRIAND Florent, CHIROUZE Catherine, FAUCHER Jean-François, GUIGNIER Alexandre, HUSTACHE-MATHIEU Laurent, ILLES-HAJNAL, Gabriela, MOREAU Joséphine, MOREL Olivier, SERONDE Marie-France, **Dijon** BEHECHTI Niloufar, BLOT Mathieu, BUISSON Marielle, COCHET Alexandre, EICHER Jean-Christophe, HUMBERT Olivier, LECLUSE-BARTH Julien, MAHY Sophie, PIROTH Lionel, ANDRE Philippe; **Lyon**: BOIBIEUX André, DELAHAYE François, DELAHAYE Armelle, Grégoire Bastien; **Montpellier**: BOURDON Aurélie, CADE Stéphane, CASANOVA Marie-Laure, CERUTTI Diane, DE VERBIZIER Delphine, LE MOING Vincent, MARTINEZ Angelina, MORQUIN David, SOLECKI Kamila; **Nancy**: BONAY Stéphanie, CHEVALIER Elodie, CLAUDIN Marine, DJABALLAH Wassila, GOEHRINGER François, HUTTIN Olivier, JEANMAIRE Eliette, MARIE Pierre-Yves, ROCH Véronique, SELTON-SUTY Christine, VAUTHIER Sandrine, VENNER Clément; **Nantes**: ASSERAY Nathalie, BIRON Charlotte, BOUTOILLE David, BROCHARD-LIBOIS Julia, CAVELLEC Morgane, CUEFF Caroline, DELARUE Sandrine, DI PRIZIO Catherine DINC Levent, FELLAH Imen, GUIJARRO Damien, LACHAUD Mathias, LE GLOAN Laurianne, LE TOURNEAU Thierry, LECOMPTE Anne-Sophie, LEFEBVRE Maeva, LUÇON Adrien, MATHIEU Cédric, ORAIN Jérémie, PALLARDY Amandine, PIRIOU Nicolas, POILANE Maxime, SASSIER Jérôme; **Paris**: BEN ALI Khadija, BROCHET Eric, BURDET Charles, CELESTIN Bettia, CIMADEVILLA Claire, DUVAL Xavier, HIAFYL Fabien, ILIC-HABENSUS Emila, IUNG Bernard, LACHATRE Marie, LEPAGE Laurent, LESCURE Xavier, ROUZET François, VINDRIOS William, WOLFF Michel, YAZDAPANAH Yazdan; **Rennes**: DEVILLERS Anne, DONAL Erwan, LACROIX Adèle, LELONG Bernard, REVEST Matthieu, TATTEVIN Pierre, THEBAULT Elise.

Coordination and statistical analyses (Clinical trial unit, Hôpitaux Universitaires Paris Nord Val de Seine, AP-HP, Paris): COUFFIGNAL Camille, ESPOSITO-FARESE Marina, LAOUENAN Cédric, MAKLOUF Sonia, MENTRE France, PREVAULT Margot, ROGIER Ophélie.

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Figure Legends

Figure1: Study Flow chart

Figure 2a: Infective endocarditis of native mitral valve. At admission, the patient had 2 major criteria (vegetation and positive blood cultures (*Rothia aeria*)) and 2 minor criteria (fever and predisposing heart condition (mitral regurgitation))(definite IE). The PET/CT scan showed an FDG uptake localized to the antero-lateral portion of the mitral annulus (red arrows, panel B, oblique reoriented slices) and an large arterial septic aneurysm in the deep femoral artery (yellow arrows, panel C: axial and coronal slices) which was previously not identified. ^{18}F-FDG-PET/CT added a minor Duke criterion (2 major criteria and 3 minor criteria) but did not modify Duke classification which remained definite. Arterial septic aneurysm was treated by an endovascular procedure.

Figure 2b: Infective endocarditis of aortic and mitral bioprosthetic valves in a patient with a pacemaker which has been implanted several years ago. At admission, the patient had 1 major criteria (vegetation on mitral valve on transoesophageal echocardiography without lesion on pacemaker leads) and 4 minor criteria (fever, predisposing heart condition, cerebral emboli, a positive blood culture for *Staphylococcus epidermidis*)(definite IE). The FDG PET/CT scan showed a focal FDG uptake in both aortic and mitral paravalvular areas (red arrows), and a septic emboli in the spleen (green arrows). Extraction of the pacemaker was not initially planned due to the normality of the TEO and the unique positive blood culture. However, an infection of the pacemaker has been suggested by focal FDG uptake located on both atrial and ventricular pacing leads (yellow arrows). The duke classification was not modified (Definite IE) but the patient's management modified and the pacing hardware was extracted.

Table 1: Baseline characteristics of the 140 patients according to the nature of the cardiac valve and to the final Duke-Li IE classification (gold standard) at 6 months

	All patients N=140	**Prosthetic valve patients N=70**				**Native valve patients N=70**				
		Final IE classification (gold standard)				**Final IE classification (gold standard)**				**p-value ‡**
		Definite N=47	**Possible N=17**	**Excluded N=6**	**Total N=70**	**Definite N=48**	**Possible N=9**	**Excluded N=13**	**Total N=70**	
Age (years)	**67**	65.3	69.2	60.7 (24.5)	**65.83**	62.1	67.56	71.31	**64.5**	**0.295**
Male	**74.3**	37 (78.7)	11 (64.71	2 (33.3)	**50 (71.4)**	40 (83.3)	8 (88.9)	6 (46.2)	**54 (77.1)**	**0.562**
Diabetes	**29 (20.7)**	9 (19.1)	2 (11.8)	1 (16.8)	**12 (17.1)**	6 (12.5)	4 (44.4)	7 (53.9)	**17 (24.3)**	**0.404**
History of cancer	**23 (16.4)**	6 (12.8)	4 (23.5)	1 (16.8)	**11 (15.7)**	6 (12.5)	2 (22.2)	4 (30.8)	**12 (17.1)**	**>0.999**
Severe Comorbidity*	**31 (22.1)**	10 (21.3)	5 (29.4)	2 (33.3)	**17 (24.3)**	7 (14.6)	2 (22.2)	5 (38.5)	**14 (20.0)**	**0.684**
Bioprosthetic valve	**39 (27.9)**	25 (53.2)	9 (52.9)	5 (83.3)	**39 (55.7)**	NA	NA	NA	**NA**	**-**
Mechanical valve	**31 (22.1)**	22 (46.8)	7 (41.2)	2 (33.3)	**31 (44.3)**	NA	NA	NA	**NA**	**-**
CRP >= 40mg/L	**93 (67.9)**	31 (67.4)	9 (52.9	2 (33.3)	**42 (60.9)**	36 (78.3)	6 (66.7)	9 (69.2)	**51 (75)**	**0.100**
Causative microorganisms										
Staphylococcus aureus	**26 (18.6)**	7 (14.9)	1 (5.9)	0 (0)	**8 (11.4)**	9 (18.8)	2 (22.2)	7 (53.9)	**18 (25.7)**	0.248
Coagulase-negative staphylococci	**17 (12.1)**	5 (10.6)	1 (5.9)	2 (33.3)	**8 (11.4)**	5 (10.4)	1 (11.1)	3 (23.1)	**9 (12.9)**	
Oral Streptococci	**25 (17.9)**	11 (23.4)	2 (11.8)	0 (0)	**13 (18.6)**	11 (22.9)	1 (11.1)	0 (0)	**12 (17.1)**	
Streptococcus bovis	**11 (7.9)**	6 (12.8)	0 (0)	0 (0)	**6 (8.6)**	4 (8.3)	0 (0)	1 (7.7)	**5 (7.1)**	
Enterococcus	**12 (8.6)**	4 (8.5)	2 (11.8)	0 (0)	**6 (8.6)**	5 (10.4)	1 (11.1)	0 (0)	**6 (8.6)**	
HACEK	**5 (3.6)**	4 (8.5)	0 (0)	0 (0)	**4 (5.7)**	1 (2.1)	0 (0)	0 (0)	**1 (1.4)**	
Others	**23 (16.4)**	8 (17.1)	2 (11.8)	1 (16.7)	**11 (15.7)**	10 (20.8)	2 (22.2)	0 (0)	**12 (17.1)**	
Negative blood cultures	**21 (15.0)**	2 (4.7)	9 (52.9)	3 (33.3)	**14 (20.0)**	3 (6.3)	2 (22.2)	2 (15.4)	**7 (10.0)**	
Echocardiography										
Transthoracic alone †	**36 (25.7)**	10 (21.2)	2 (11.8)	2 (33.3)	**14 (20.0)**	14 (29.2)	3 (33.3)	5 (38.5)	**22 (31.4)**	**0.175**

At least transoesophageal	**104 (74.3%)**	37 (78.7)	15 (88.2)	4 (66.7)	**56 (80.0)**	34 (70.8)	6 (66.7)	8 (61.5)	**48 (68.6)**	**0.175**
Vegetation	**71 (50.7)**	18 (38.3)	6 (35.3)	4 (66.7)	**28 (40.0)**	35 (72.9)	3 (33.3)	5 (38.5)	**43 (61.4)**	**0.018**
Peri annular complication	**16 (11.4)**	8 (17.0)	1 (5.9)	0 (0)	**9 (12.9)**	7 (14.6)	0 (0)	0 (0)	**7 (10.0)**	**0.791**
New partial dehiscence	**13 (9.3)**	9 (19.2)	2 (11.8)	2 (33.3)	**13 (18.6)**	NA	NA	NA	**NA**	**-**
New valvular regurgitation	**34 (24.3)**	7 (14.9)	2 (11.8)	2 (33.3)	**11 (15.7)**	20 (41.7)	3 (33.3)	0 (0)	**23 (32.9)**	**0.029**
Non-contributive echocardiography	**53 (37.9)**	19 (40.4)	9 (52.9)	1 (16.7)	**29 (41.4)**	11 (22.9)	5 (55.6)	8 (61.5)	**24 (34.3)**	**0.486**

*****Underlying disease affecting the vital prognostic or fatal at 5 years**;** values are (%) except for age (mean ± standard deviation); HACEK: *Haemophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*.

† Among the 14 prosthetic valve patients without TOE before ^{18}F-FDG-PET/CT, 5 had vegetation on TTE, 6 had TOE after ^{18}F-FDG-PET/CT and 2 had contraindication to TOE

‡ Statistical comparisons between PV and NV patients

NA: Not applicable; Values are mean (interquartile range) or n (%)

Table 2: Diagnostic value of the Duke-Li criteria at inclusion and after ^{18}F-FDG-PET/CT according to the final Duke-LI IE classification in the 140 patients

	Total	**Prosthetic valve patients N=70**					**Native valve patients N=70**				
	N=140	**Final IE classification (gold standard)**					**Final IE classification (gold standard)**				
		Definite N=47	**Possible N=17**	**Excluded N=6**	**Total N=70**		**Definite N=48**	**Possible N=9**	**Excluded N=13**	**Total N=70**	**P value****
Duke-Li classification at inclusion*											
Definite	**80** (57.1)	32 (68.1)	2 (11.8)	0 (0)	**34** (48.6)		42 (87.5)	0 (0)	4 (30.8)	**46** (65.7)	**0.095**
Possible	**56** (40.0)	15 (31.9)	13 (76.5)	5 (83.3)	**33**		6 (12.5)	9 (100)	8 (61.5)	**23** (32.6)	
Excluded †	**4** (2.6)	0 (0)	2 (11.8)	1 (16.7)	**3** (4.3)		0 (0)	0 (0)	1 (7.7)	**1** (1.4)	
^{18}F-FDG-PET/CT results											
Perivalvular uptake											
Abnormal uptake ‡	**64** (45.7)	38 (80.4)	7 (41.2)	2 (33.3)	**47 (67.1)**		16 (33.3)	1 (11.1)	0 (0)	**17 (24.3)**	**< 0.001**
Non-interpretable	**5** (3.6)	2 (4.3)	2 (11.8)	0 (0)	**4 (5.1)**		1 (2.2)	0 (0)	0 (0)	**1 (1.4)**	**0.282**
Extracardiac uptake											
Peripheral IE complication §	**69** (49.3)	24 (51.1)	7 (41.2)	1 (16.7)	**32 (45.7)**		27 (56.3)	3 (33.3)	7 (53.9)	**37 (52.9)**	**0.381**
Portal of entry											
All	**33** (23.6)	11 (23.4)	4 (23.5)	0 (0)	**15 (21.4)**		14 (29.2)	1 (11.1)	3 (23.1)	**18 (25.7)**	**0.302**
Revealed	**12** (8.0)	6 (12.8)	2 (11.8)	0 (0)	**8 (11.4)**		3 (6.3)	0 (0)	1 (7.7)	**4 (5.7)**	**0.366**
Confirmed	**21** (15.0)	5 (10.6)	2 (11.8)	0 (0)	**7 (10.0)**		11 (22.9)	1 (11.1)	2 (15.4)	**14 (20.0)**	**0.154**
Modification of Duke-Li criteria ‖											
Modification of any Duke criterion	**43 (30.7)**	22 (46.8)	3 (17.7)	1 (16.7)	**26 (37.1)**		14 (29.2)	1 (11.1)	2 (15.4)	**17 (24.3)**	**0.142**
Modification of a Minor Duke criterion	**21** (15.0)	6 (27.3)	0 (0)	1 (100)	**7 (10.0)**		11 (22.9)	1(100)	2 (100)	**14 (20.0)**	**< 0.001**
Modification of a Major Duke criterion	**23** (16.4)	17 (77.3)	3 (100)	0 (0)	**20 (28.6)**		3 (6.3)	0 (0)	0 (0)	**3 (4.3)**	**< 0.001**
Modification of Duke-Li classification ‖											
Any modification	**21** (15.0)	13 (27.7)	3 (17.7)	1 (16.7)	**17 (24.3)**		3 (6.3)	0 (0)	1 (7.7)	**4 (5.7)**	**0.003**
Modification due to a minor Duke	**6** (4.3)	3 (4.6)	0 (0)	1 (16.7)	**4 (5.7)**		1 (2.1)	0 (0)	1 (100)	**2 (2.9)**	**0.544**
Modification due to a major Duke	**16** (11.4)	11 (84.6)	3 (100)	0 (0)	**14 (20.0)**		2 (4.2)	0 (0)	0 (0)	**2 (2.9)**	**0.228**
m-ESC2015 ^{18}F-FDG-PET/CT classification											
Definite	**95** (67.9)	45 (95.7)	1 (5.9)	0 (0)	**46 (65.7)**		45 (93.8)	0 (0)	4 (30.8)	**49 (70.0)**	**0.889**
Possible	**41** (29.3)	2 (4.3)	16 (94.1)	4 (66.7)	**22 (31.4)**		3 (6.3)	9 (100)	7 (53.9)	**19 (27.1)**	
Excluded	**4** (2.9)	0 (0)	0 (0)	2 (33.3)	**2 (2.9)**		0 (0)	0 (0)	2 (15.4)	**2 (2.9)**	

* Duke classification modified by Li [16]

† Not fulfilling the definite and possible IE Duke definition at inclusion

‡ In prosthetic valve patients, peri-prosthetic FDG uptake was considered abnormal when heterogeneous (either focal or diffuse with a focal enhancement) and/or extending beyond the peri-annular area; 10 additional prosthetic valve patients had valvular uptake considered as normal.

§ Excluding sternum, prostate, colon, mouth and skin uptake

‖ Modification of the criteria or the classification of the "Duke-Li classification at inclusion"

¶ see text for m-ESC 2015 ^{18}F-FDG-PET/CT classification definition

** Statistical comparisons between PV and NV patients

Note: Values are n (%)

Table 3: Patients 'management modification following ^{18}F-FDG-PET/CT results according to the final Duke-Li IE classification (gold standard) and cardiac surgery in the 140 patients

	Total N=140	**Prosthetic valve patients N=70**				**Native valve patients N=70**				P value †
		Final IE classification (gold standard)				**Final IE classification (gold standard)**				
		Definite N=47	**Possible N=17**	**Excluded N=6**	**Total N=70**	**Definite N=48**	**Possible N=9**	**Excluded N=13**	**Total N=70**	
Modification of patients' management following ^{18}F-FDG PET/CT*										
	37 (26.4)	10 (21.3)	4 (23.5)	1 (16.7)	**15** (21.4)	13(27.1)	4 (44.4)	5 (38.5)	**22** (31.4)	**0.25**
Antibiotic treatment ‡	18	3 (6.3)	3 (17.6	1 (16.7)	7	5 (10.4)	3 (33.3)	3 (23.1)	11	
Cardiac surgery	6 (4.3)	3 (6.3)	0 (0)	0 (0)	3 (4.3)	3 (6.2)	0 (0)	0 (0)	3 (4.3)	
Anticoagulation	1 (0.7)	1 (2.1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	
Specific treatment of an IE abdominal localization §	1 (0.7)	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.7)	1 (0.3)	
Antibiotic and surgery	5 (3.6)	1 (2.1)	0 (0)	0 (0)	1 (1)	3 (6.2)	1 (11.1)	0 (0)	4 (5.7)	
Antibiotic treatment and anticoagulation	1 (0.7)	0	0 (0)	0 (0)	0 (0)	1 (2.1)	0 (0)	0 (0)	1 (0.3)	0.476
Antibiotic treatment and specific treatment of an IE abdominal localization	2 (1.4)	1 (2.1)	1 (2.1)	0 (0)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	
Surgery and specific treatment of an IE abdominal localization	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.1)	0 (0)	0 (0)	1 (0.3)	
Antibiotic treatment, anticoagulation and specific treatment of an IE abdominal localization	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.8)	1 (0.3)	
Cardiac surgery										

Cardiac surgery during initial hospitalization	**41 (29.3)**	12 (25.5)	4 (23.5)	1 (16.7)	**17** (24.3)	21 (43.7)	3 (33.3)	0 (0)	**24** (34.3)	0.265
Cardiac surgery during the 6 first months following inclusion	**53 (37.9)**	14 (29.8)	5 (29.4)	1 (16.7)	**20 (28.6)**	28 (58.3)	4 (44.4)	1 (7.7)	**33 (47.1)**	0.036

* The duration of antibiotic therapy was reduced in 6 patients due to the exclusion of IE diagnosis by 18F-FDG PET/CT which was in favour of an alternative diagnosis, prolonged in 4 patients. An antibiotic with a better diffusion in bone, joints or prostate gland was added in 11 patients and the dose of an antibiotic was reduced in one patient due to the exclusion of IE diagnosis

† Statistical comparisons between PV and NV patients

‡ Including 2 patients with detection of IE portal of entry;

§ Including 1 patient with detection of IE portal of entry

Note: Surgery modifications include surgery cancellation, surgery indication or modification of surgery timing, or valve substitute. Anticoagulation modifications include interruption of modification of anticoagulation level. Values are n (%).

Table 4: Comparison of the characteristics of the patients according to whether or not they benefited from the **^{18}F-FDG-PET/CT**.

	Patients who did not benefit from ^{18}F-FDG-PET/CT	**Patients who benefit from ^{18}F-FDG-PET/CT**	**p**
	n=84	n=56	
Age (median (IQR))	67 (56.75-76.25)	66.5 (56.75-78.25)	0.79
Male, n (%)	61 (72.6)	43 (76.8)	0.69
Diabetes, n (%)	14 (16.7)	15 (26.8)	0. 20
Nature of the cardiac valve			0. 63
Native valve**, n (%)**	43 (51.8)	27 (50.0)	
Bioprosthesis valve**, n (%)**	24 (28.9)	13 (24.1)	
Mechanical valve**, n (%)**	16 (19.3)	14 (25.9)	
Causative microorganisms			0.51
Staphylococcus aureus	16 (19.1)	10 (17.9)	
Coagulase-negative staphylococci	10 (11.9)	7 (12.5)	
Oral streptococci	12 (14.3)	13 (23.2)	
Streptococcus bovis	5 (5.9)	6 (10.7)	
Enterococcus	8 (9.5)	4 (7.1)	
HACEK	3 (3.6)	2 (3.6)	
Others	13 (15.5)	10 (17.9)	
Negative blood cultures	17 (20.2)	4 (7.1)	
Echocardiography			
Non-contributing echocardiography †	22 (26.2)	34 (60.7)	**< 0.001**
Duke-Li classification at inclusion			
Definite	55 (65.5)	25 (44.6)	
Possible	27 (32.1)	29 (51.8)	**0.04**§
Excluded ‡	2 (2.4)	2 (3.6)	

* Trans-thoracic and trans-oesophageal echocardiography not fulfilling the definition for a major Duke criteria [16]

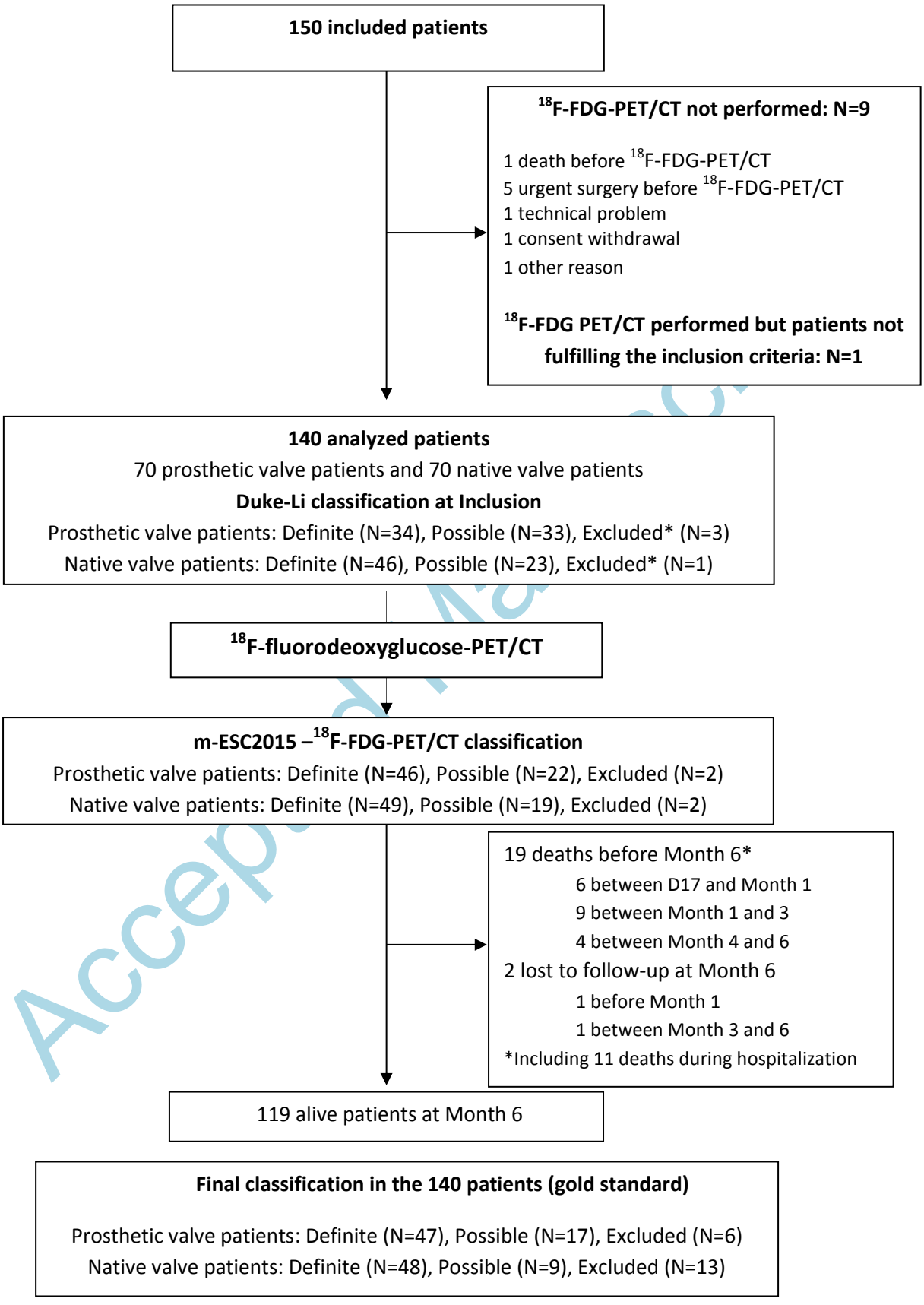
† Duke classification modified by Li [16]

‡ Not fulfilling the definite and possible IE Duke-Li definition at inclusion

§ Comparison possible versus definite or excluded

Note: Patients who benefit from ^{18}F-FDG-PET/CT were those whose Duke-Li classification was correctly modified by 18-FDG-PET/CT, and/or portal of entry discovered and/or therapeutic plan modified.

Figure 1: Study Flow chart



*not fulfilling the definite and possible IE Duke-Li definition at inclusion

Figure 2a

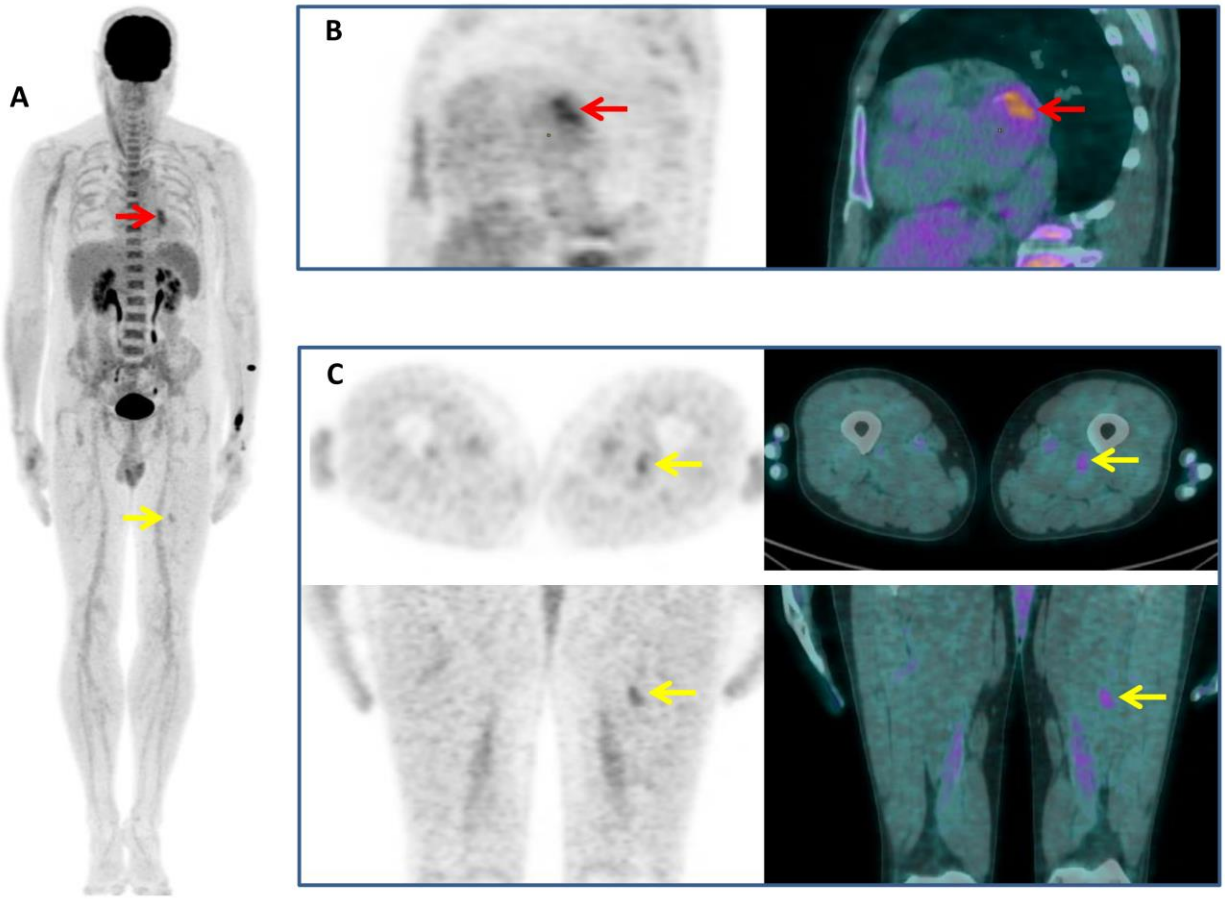


Figure 2b