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Short Report

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Comparison of somatostatin receptor PET with [^{18}F]FDG PET for detecting infective endocarditis: a pilot study

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Abstract

Purpose: Somatostatin-receptor positron emission tomography (PET) may detect myocarditis by targeting macrophages and lymphocytes with minimal physiological myocardial uptake. We assessed whether it could serve as an alternative to [^{18}F]fluorodeoxyglucose (FDG) PET for diagnosing infective endocarditis (IE).

Methods: Fourteen Duke-Li definite IE patients underwent [^{18}F]FDG PET followed 24 h later by [^{68}Ga]Ga-DOTATOC PET.

Results: Fifteen valves were classified as infected (10 prosthetic, 5 native). Twelve showed [^{18}F]FDG uptake (80%), whereas only six showed significant [^{68}Ga]Ga-DOTATOC uptake (40%, $p = 0.031$). None of the 41 non-infected valves showed abnormal uptake with either tracer (specificity, 100%). Myocardial uptake was observed in 11 patients with [^{68}Ga]Ga-DOTATOC and four with [^{18}F]FDG ($p = 0.008$), with colocalized myocardial uptake in three patients.

Conclusion: [^{68}Ga]Ga-DOTATOC PET showed lower sensitivity than [^{18}F]FDG PET for IE detection, likely reflecting the limited targeting of neutrophil-rich inflammatory infiltrates in IE, but revealed remote myocardial uptake that sometimes colocalizes with increased [^{18}F]FDG uptake, suggesting associated myocardial inflammation.

Key words: infective endocarditis, PET, [^{18}F]FDG, [^{68}Ga]Ga-DOTATOC, somatostatin receptors.

Introduction

[^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) / computed tomography (CT) is an established imaging modality for the diagnosis of infective endocarditis (IE), particularly in patients with prosthetic valves, while also enabling detection of extracardiac infectious foci that may influence subsequent clinical management [1–3]. However, physiological myocardial uptake may persist despite appropriate patient preparation, thereby limiting image interpretation [3,4]. Since somatostatin receptor PET has shown promising results for imaging myocarditis by targeting macrophage-rich inflammatory infiltrates while exhibiting minimal physiological myocardial uptake [5–7], we investigated whether it could serve as an alternative imaging modality for the diagnosis of IE.

Materials and Methods

This prospective pilot study included consecutive patients hospitalized at Nancy University Hospital with a definite diagnosis of infective endocarditis according to the modified Duke-Li criteria [8]. All patients underwent an [^{18}F]FDG PET scan following standard metabolic preparation (≥12-h fasting after a low-carbohydrate evening meal), followed 24 h later by a second PET acquisition performed 1 h after intravenous injection of [^{68}Ga]Ga-DOTATOC.

In these patients with Duke-Li definite IE, individual valves were classified as infected based on a retrospective review of all available imaging data, including echocardiography, cardiac CT, and [18F]FDG PET. Valvular involvement was defined by structural abnormalities consistent with IE (e.g., vegetation, abscess, or other valvular or perivalvular abnormalities),

and [18F]FDG PET contributed to the identification of only one infected valve that was not otherwise identified by structural imaging.

The study was approved by a French institutional ethics committee (CPP Sud-Est II) on the 8th March 2022 and by the National Agency for the Safety of Medicines and Health Products (ANSM), on the 21 January 2022. All participants provided written informed consent. The protocol was registered at ClinicalTrials.gov (NCT05183555).

PET image acquisition and reconstruction

PET/CT examinations were performed on a digital PET/CT system (Vereos, Philips Healthcare, Cleveland, OH, USA). Images were acquired 1 h after intravenous injection of 3 MBq/kg of either [^{18}F]FDG or [^{68}Ga]Ga-DOTATOC. Each examination consisted of a low-dose whole-body CT acquisition, followed by a whole-body PET acquisition (1.5 min per bed position) and a dedicated 10-min cardiac PET acquisition centered on the heart. Only the dedicated cardiac acquisitions were analyzed in the present study.

Both [^{18}F]FDG and [^{68}Ga]Ga-DOTATOC images were reconstructed using the same protocol with 2-mm isotropic voxels and an OSEM algorithm (3 iterations, 3 subsets), including a deconvolution of the point spread function and corrections for attenuation, scatter, and random coincidences [9].

PET image analysis

[^{18}F]FDG and [^{68}Ga]Ga-DOTATOC PET images were analyzed independently using the same predefined analysis method by two experienced observers, blinded to all clinical data, on a MIM workstation (MIM Software Inc., Cleveland, Ohio).

First, the presence of IE was assessed visually at each of the four cardiac valves. A valve was considered positive when focal tracer uptake clearly exceeded blood-pool activity at the corresponding valve [4,10]. Inter-observer discrepancies were resolved by consensus.

Second, according to a methodology previously described in detail [5,6,11], quantitative SUV parameters were measured by one observer within tracer uptake regions exceeding 150% of the right atrial blood-pool SUVmax. This quantitative analysis was performed for each of the four valvular regions, as well as for the entire extra-valvular myocardium.

Statistical analyses

Continuous variables were expressed as median [interquartile range] and categorical variables as counts (percentages). Paired comparisons were performed using the Wilcoxon signed-rank test for quantitative variables and the McNemar test for categorical variables. Comparisons of quantitative variables between independent groups were performed using the Mann–Whitney U test. All tests were two-sided, and P values < 0.05 were considered statistically significant.

Results

Fourteen patients with definite IE were prospectively included. Their baseline characteristics are summarized in Table 1. Ten patients (71%) had prosthetic heart valves, and 5 (36%) had a cardiac implantable electronic device. The median duration of antibiotic therapy before [^{18}F]FDG PET was 7.0 [5.5-11.5] days.

IE involved pacemaker leads alone in one patient and one (n = 11) or two (n = 2) cardiac valves in the remaining patients. Overall, 15 of the 56 cardiac valves (4 per patient) were classified

as infected, including 10 prosthetic and 5 native valves. The affected valves were aortic (n = 10), mitral (n = 4), and tricuspid (n = 1).

As detailed in Figure 1, visual analysis identified significant uptake in 12 of the 15 IE lesions with [^{18}F]FDG PET (sensitivity, 80%), but in only 6 with [^{68}Ga]Ga-DOTATOC PET (sensitivity, 40%, p = 0.031). No IE was detected exclusively by [^{68}Ga]Ga-DOTATOC PET. None of the 41 non-infected valves showed abnormal uptake with either tracer, yielding a specificity of 100% for both.

The six IE lesions detected only by [^{18}F]FDG PET exhibited [^{18}F]FDG uptake comparable to that of the six IE lesions detected by both tracers (for SUVmean, FDG+DOTA-: 4.3 [3.8–5.9] vs. FDG+DOTA+: 4.2 [3.5–4.5]), but significantly lower [^{68}Ga]Ga-DOTATOC uptake (SUVmean: 1.1 [0.0–1.5] vs. 2.2 [1.7–2.4], p = 0.026), consistent with the visual analysis findings.

None of the clinical and imaging characteristics listed in Table 1 differed significantly between the FDG+DOTA− and FDG+DOTA+ groups. All six [^{68}Ga]Ga-DOTATOC-positive IE lesions involved prosthetic valves, whereas this was the case for only 50% of the IE lesions detected by [^{18}F]FDG PET. This difference was not statistically significant (p = 0.18).

Finally, total cardiac tracer uptake volume was larger on [^{68}Ga]Ga-DOTATOC PET than on [^{18}F]FDG PET (99 [2–167] cm³ vs. 8 [1–28] cm³, p = 0.019). This finding was consistent with the observation that extra-valvular left ventricular myocardial uptake was visually detected in 11 patients on [^{68}Ga]Ga-DOTATOC PET, compared with only 4 patients on [^{18}F]FDG PET (p = 0.008). In one of these four patients, [^{18}F]FDG uptake was diffuse and intense, consistent with inadequate metabolic preparation. In the remaining three patients, myocardial [^{18}F]FDG uptake colocalized with a corresponding increase in [^{68}Ga]Ga-DOTATOC uptake (see patients #7–9 in Figures 2 and 3).

Representative PET images illustrating these findings are shown in colour in Figure 2 and in grayscale in Figure 3.

Discussion

The present study demonstrates that [^{68}Ga]Ga-DOTATOC PET is less sensitive than [^{18}F]FDG PET for detecting IE, while demonstrating substantially more extensive extra-valvular myocardial uptake. These findings indicate that somatostatin receptor PET cannot be considered an alternative to [^{18}F]FDG PET for the diagnosis of IE.

Activated macrophages, together with subsets of activated monocytes and lymphocytes, express somatostatin receptors [12]. These cell populations are also found in histopathological specimens from patients with infective endocarditis, although in much lower numbers than neutrophils, which constitute the predominant inflammatory cell population [13]. In contrast, [^{18}F]FDG is a more ubiquitous inflammation tracer, being taken up not only by monocytes, macrophages, and lymphocytes, but also by activated neutrophils [14] and activated resident tissue cells [15]. This difference in cellular targeting likely explains the higher sensitivity of [^{18}F]FDG observed in the present study.

As expected, significant extra-valvular myocardial [^{18}F]FDG uptake was observed in four patients. In one of them, this uptake was diffuse and intense, consistent with inadequate metabolic preparation. In the remaining three patients, myocardial [^{18}F]FDG uptake colocalized with areas of increased [^{68}Ga]Ga-DOTATOC uptake (patients #7–9 in Figures 2 and 3). This observation raises the possibility that a substantial proportion of myocardial [^{18}F]FDG uptake observed in patients with IE represents true inflammation rather than physiological myocardial uptake.

This interpretation is supported by previous histopathological studies demonstrating myocardial inflammatory infiltrates associated with IE, even in the absence of direct myocardial extension from the valvular lesion [13,16]. Such myocardial inflammatory involvement may also explain the more extensive extra-valvular myocardial uptake observed with [^{68}Ga]Ga-DOTATOC PET. One possible explanation is that this remote myocardial inflammatory process contains a relatively greater macrophage component than the neutrophil-predominant inflammatory infiltrates of IE lesions, consistent with the prominent [^{68}Ga]Ga-DOTATOC myocardial uptake observed in common myocarditis [5,6].

Another possible explanation is myocardial involvement secondary to silent septic embolization. This hypothesis is particularly plausible in one of the three patients with colocalized myocardial uptake, who had aortic valve endocarditis (patient #7 in Figures 2 and 3).

Therefore, although somatostatin receptor PET cannot be considered an alternative to [^{18}F]FDG PET for the diagnosis of infective endocarditis because of its limited sensitivity, it provides complementary insights into the myocardial inflammation associated with the disease.

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Statements and Declarations

Competing interests: The authors declare that they have no competing interests.

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Ethics approval: The study was approved by the French institutional ethics committee CPP Sud-Est II (March 8, 2022) and by the French National Agency for the Safety of Medicines and Health Products (ANSM; January 21, 2022).

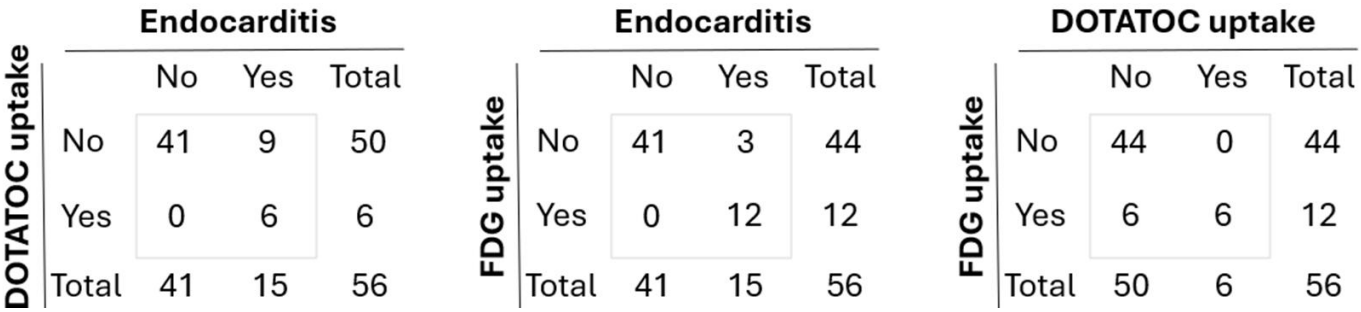
Consent to participate: Written informed consent was obtained from all participants.

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Data Availability : The datasets generated and analyzed during the current study are not publicly available due to patient confidentiality and data protection regulations. Requests for access to de-identified data may be addressed to the corresponding author and will be considered subject to institutional approval and applicable regulations.

Author Contributions : Study conception and design were performed by Caroline Boursier, Pierre-Yves Marie, Elodie Chevalier, Thomas Larive, Benjamin Lefèvre, Nicolas Véran, Laetitia Imbert, Nathalie Pace, Francois Goehringer, Antoine Fraix. Data collection and image interpretation were performed by Pierre-Yves Marie, Thomas Larive, Veronique Roch. Statistical analysis was performed by Pierre-Yves Marie. The first draft of the manuscripts was written by Pierre-Yves Marie, Thomas Larive. All authors reviewed and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Figure 1: Contingency tables showing the associations between definite infective endocarditis and significant valvular uptake on [^{68}Ga]Ga-DOTATOC PET (left panel) or [^{18}F]FDG PET (middle panel), and between significant valvular uptake on both PET tracers (right panel).



DOTATOC uptake	Endocarditis: No	Endocarditis: Yes	Total
No	41	9	50
Yes	0	6	6
Total	41	15	56

FDG uptake	Endocarditis: No	Endocarditis: Yes	Total
No	41	3	44
Yes	0	12	12
Total	41	15	56

FDG uptake	DOTATOC uptake: No	DOTATOC uptake: Yes	Total
No	44	0	44
Yes	6	6	12
Total	50	6	56

Figure 2: Representative PET images illustrating infective endocarditis (IE) visually detected with: (1) both [^{18}F]FDG and [^{68}Ga]Ga-DOTATOC on prosthetic valves (FDG+DOTA+) in patients #1–4; (2) [^{18}F]FDG only on native or prosthetic valves (FDG+DOTA−) in patients #5–7; and (3) neither tracer on native valves (FDG−DOTA−) in patients #8–10. Extra-valvular myocardial uptake was generally more extensive with [^{68}Ga]Ga-DOTATOC than with [^{18}F]FDG. In patients #7–9, colocalized intense myocardial uptake with both tracers suggests associated myocardial inflammation.

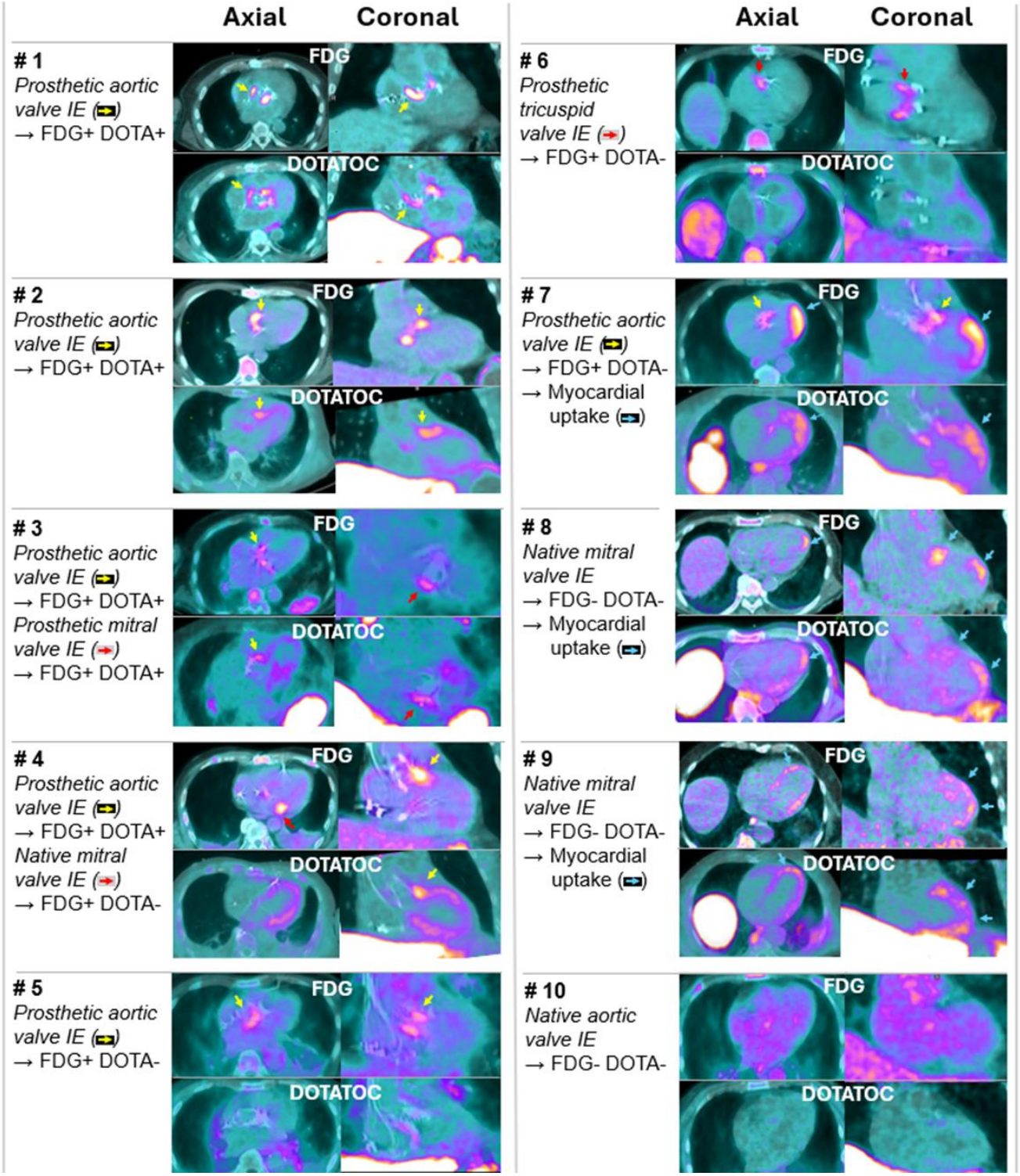


Figure 3: Same legend as Figure 2, but with PET images displayed in grayscale.

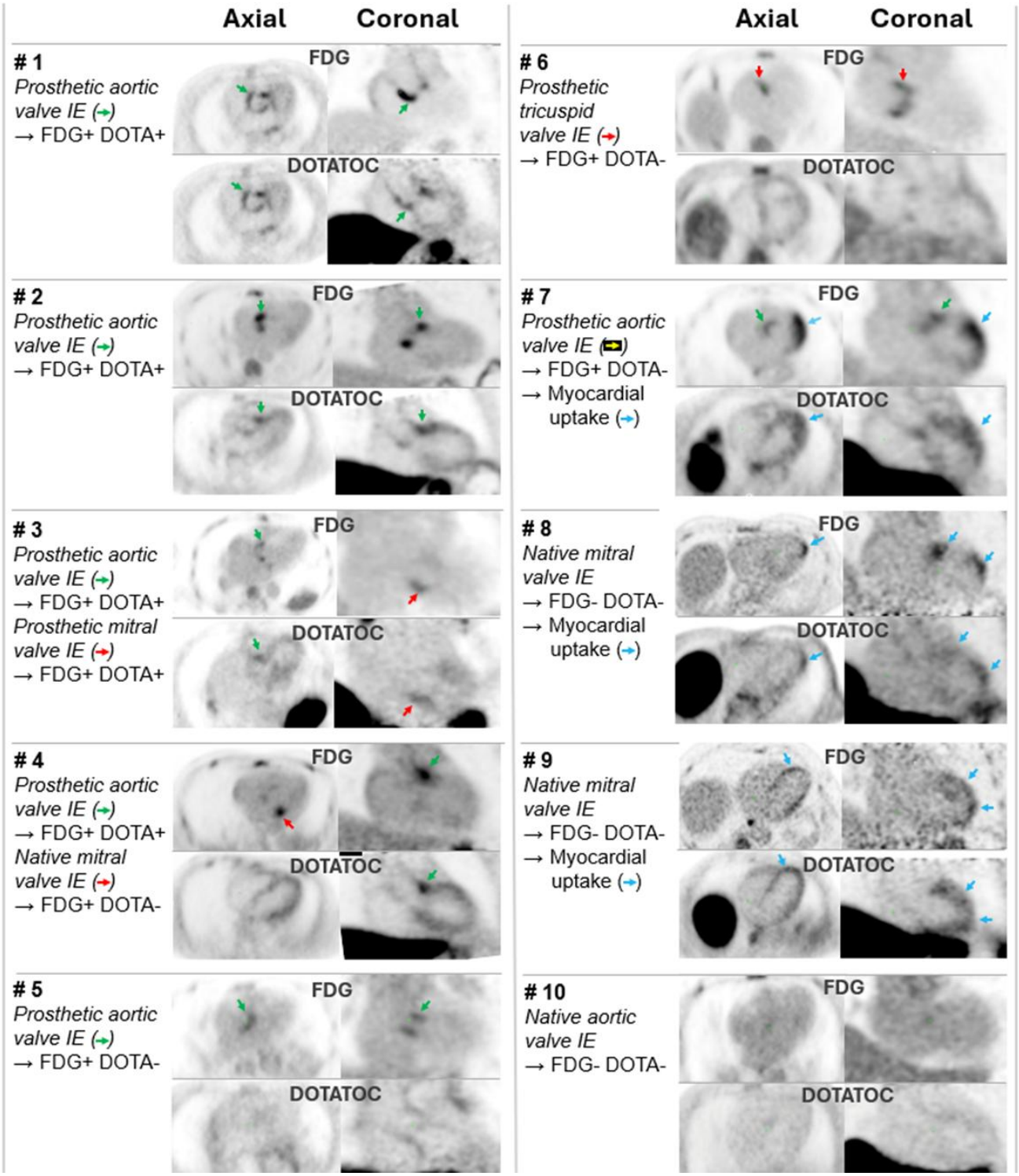


Table 1. Main characteristics of the 14 study patients.

Men	12 (86%)
Age (years)	74 [68-77]
Diabetes	3 (21%)
Body mass index ($kg.m^{-2}$)	24 [23-26]
- obese (> 30 $kg.m^{-2}$)	1 (7%)
Cardiac implants	10 (71%)
- valve	10 (71%)
- pacemaker	5 (36%)
- time from valve implantation to PET (years)	5 [2-10]
Causative microorganism	
- *Streptococcus gallolyticus*	*3*
- *Streptococcus mitis/oralis*	*2*
- *Staphylococcus aureus*	*2*
- *Staphylococcus epidermidis*	*2*
- *Enterococcus faecalis*	*4*
- *Enterobacter cloacae*	*1*
Perivalvular abscess	2 (14%)
Vegetations	13 (93%)
- Multiple and/or ≥ 10 mm	8 (57%)
Time from antibiotic start to FDG-PET (days)	7.0 [5.5-11.5]