




# Procedural recommendations of cardiac PET/CT imaging: standardization in inflammatory-, infective-, infiltrative-, and innervation- (4Is) related cardiovascular diseases: a joint collaboration of the EACVI and the EANM: summary

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**4Is Cardiovascular Imaging: a joint initiative of the European Association of Cardiovascular Imaging (EACVI) and the European Association of Nuclear Medicine (EANM)**

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With this summarized document we share the standard for positron emission tomography (PET)/(diagnostic)computed tomography (CT) imaging procedures in cardiovascular diseases that are inflammatory, infective, infiltrative, or associated with dysfunctional innervation (4Is) as recently published in the European Journal of Nuclear Medicine and Molecular Imaging. This standard should be applied in clinical practice and integrated in clinical (multicentre) trials for optimal standardization of the procedural and interpretations. A major focus is put on procedures using [<sup>18</sup>F]-2-fluoro-2-deoxyglucose ([<sup>18</sup>F]FDG), but 4Is PET radiopharmaceuticals beyond [<sup>18</sup>F]FDG are also described in this summarized document. Whilst these novel tracers are currently mainly applied in early clinical trials, some multicentre trials are

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underway and we foresee in the near future their use in clinical care and inclusion in the clinical guidelines. Diagnosis and management of 4Is related cardiovascular diseases are generally complex and often require a multidisciplinary approach by a team of experts. The new standards described herein should be applied when using PET/CT and PET/magnetic resonance, within a multimodality imaging framework both in clinical practice and in clinical trials for 4Is cardiovascular indications.

**Keyword** Cardiac PET/CT • Joined procedurals • 4Is • cardiovascular diseases

## Introduction

Nuclear imaging plays a pivotal role in cardiac infectious, inflammatory, infiltrative, and innervation disorders. Cardiac amyloidosis, sarcoidosis, large vessel vasculitis (LVV), infective endocarditis (IE), infected cardiac implantable electronic devices (CIEDs), vascular graft infection (VGI), and myocardial innervation dysfunction are the main indications for the use of nuclear medicine procedures in both diagnosis and response assessment.

Positron emission tomography/computed tomography (PET/CT) and PET/magnetic resonance (MR) imaging (MRI) are non-invasive diagnostic tools that allows detection of radiopharmaceutical accumulation in tissues with high sensitivity and provides precise quantification of their local concentration. The most commonly used tracer at present is the fluorine-18 labelled glucose analogue [<sup>18</sup>F]-2-fluoro-2-deoxyglucose ([<sup>18</sup>F]FDG). [<sup>18</sup>F]FDG accumulation in tissues is proportional to their glucose utilization and reflects the glucose metabolism of cells. This glucose metabolism is increased in cancer, but also in infectious and inflammatory processes.<sup>1</sup> Anatomical and morphological information derived from the combination with CT (PET/CT) can be used to improve the localization, extent and characterization of lesions detected by [<sup>18</sup>F]FDG PET. Beyond [<sup>18</sup>F]FDG, several other PET radiopharmaceuticals are available for imaging cardiovascular diseases as described further in this document. The recently established joint cardiovascular imaging group (4Is joint collaboration group) between the European Association of Nuclear Medicine (EANM) and the European Association of Cardiovascular Imaging (EACVI) focuses on Infiltrative, Inflammatory, Infectious, and Innervation dysfunctional (4Is) cardiovascular diseases. This 4Is joint collaboration group is working on recommendations for imaging procedures in the field of 4Is cardiovascular diseases.

The purpose of this review is to assist in performing PET/CT and PET/MR for cardiovascular imaging in the field of 4Is, starting from the selection of the proper radiopharmaceutical based on the specific patients' clinical condition and extending to the correct use of imaging acquisition protocols, post-processing, interpretation and reporting, as recently published in the European Journal of Nuclear Medicine and Molecular Imaging.<sup>2</sup> Proposing a standardized imaging procedure will promote the appropriate use of PET/CT and PET/MRI in clinical practice, increase the quality of investigator driven clinical trials and allow comparison between studies thereby contributing to evidence-based medicine.

## Clinical indications in cardiovascular diseases

[<sup>18</sup>F]FDG PET/CT and PET/MR have an increasingly relevant role in inflammation and infection imaging; they are a rapidly evolving imaging

modalities.<sup>1</sup> However, no appropriateness criteria have been developed to date for these indication in cardiovascular diseases. It must be emphasized that the level of evidence available at this time for using PET/CT and PET/MRI with either [<sup>18</sup>F]FDG or novel PET radiopharmaceuticals varies for many of the indications described in this document but randomized controlled trial data (as with most forms of cardiovascular imaging) are consistently lacking.

General indications for 4Is cardiovascular PET/CT include: Non-invasive diagnosis, imaging-guided biopsy diagnosis, therapy response, monitoring, and prognosis.

Specific routine clinical practice and clinical research applications: Prosthetic and native valve infective endocarditis (IE) (clinical),<sup>3,4</sup> cardiac implantable electronic (CIED) and left ventricular assist devices (LVAD) (clinical),<sup>3,4</sup> vascular graft infection (VGI) (clinical),<sup>5</sup> cardiac sarcoidosis (clinical),<sup>6</sup> large vessel vasculitis (LVV) (clinical),<sup>7,8</sup> cardiac amyloidosis (clinical research),<sup>9,10</sup> atherosclerosis and valvular disease (clinical research),<sup>11</sup> myocardial innervation (clinical research).<sup>12</sup>

## Radiopharmaceuticals

Most PET radiopharmaceuticals are labelled with <sup>18</sup>F, but some are labelled with the shorter living <sup>11</sup>C ( $T_{1/2}$  20 min), or are generator produced <sup>68</sup>Ga ( $T_{1/2}$  68 min). The most promising radiopharmaceutical developments include the application of existing tracers such as [<sup>18</sup>F]NaF in atherosclerosis, and the use of radiolabelled compounds for detection of cardiac amyloidosis ([<sup>18</sup>F]florbetaben, [<sup>18</sup>F]florbetapir, [<sup>18</sup>F]flutemetamol, and [<sup>11</sup>C]PiB). [<sup>68</sup>Ga]DOTA conjugated peptide ([<sup>68</sup>Ga]DOTATOC, DOTATATE, DOTANOC) compounds with affinity to SSRs, and [<sup>18</sup>F]FLT, hold promise in detecting cardiac sarcoidosis with the advantage of having no physiological myocardial uptake which is the main disadvantage of [<sup>18</sup>F]FDG. The [<sup>18</sup>F]-labelled sympathetic nerve PET radiopharmaceuticals [<sup>18</sup>F]LMI1195 (generic name [<sup>18</sup>F]flubrobenguane) are promising with potential to aid clinical decision-making e.g. for optimal selection of patients requiring an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (Supplementary data online, S1).

## PET/CT technical procedures

This background information of cardiovascular imaging in the 4Is field can be found in the main technical manuscript<sup>2</sup> and Supplementary data online, S1. The technical background exists of patients' preparation, camera acquisition, data reconstruction, and data analysis for the [<sup>18</sup>F]FDG- and non-[<sup>18</sup>F]FDG PET/CT procedurals. Additionally, an overview is given of contrast-enhanced CT and PET/MR procedurals, and PET/CT pitfalls (Supplementary data online, S2) in 4Is cardiovascular imaging.

## **[<sup>18</sup>F]FDG PET/CT data assessment, interpretation, and reporting 4Is**

Adapted from Jamar et al.<sup>1</sup>

### **[<sup>18</sup>F]FDG suppression in normal myocardium**

To suppress physiological [<sup>18</sup>F]FDG uptake in the normal myocardium, it is recommended to use patient preparation protocols including high-fat-enriched diet lacking carbohydrates for 12–24 h prior to the scan combined with a prolonged fasting period of 12–18 h, with or without the use of intravenous heparin of 50 IU/kg approximately 15 min prior to [<sup>18</sup>F]FDG injection.<sup>4,13,14</sup> In addition, strenuous exercise should be avoided for at least 12 h prior to the exam.

### **General assessment of [<sup>18</sup>F]FDG PET**

At the end of the PET acquisition and before image interpretation, image quality should be verified.

The level of noise should be low.

In the presence of high [<sup>18</sup>F]FDG uptake in peripheral muscles, patients should be asked about carbohydrate consumption and/or insulin injection in the 6 h preceding [<sup>18</sup>F]FDG injection. In the presence of high residual blood signal, blood glucose at the time of [<sup>18</sup>F]FDG injection should be checked. It is recommended to inject [<sup>18</sup>F]FDG when the blood glucose is <11 mmol/L, or <180 mg/dL.

Suppression of [<sup>18</sup>F]FDG signal in the myocardium should be evaluated. In absence of adequate myocardial suppression of the [<sup>18</sup>F]FDG signal, the compliance of the patient to the preparative procedures should be checked and this information included in the report.

### **General visual analysis**

Data can be evaluated with commercially available software systems. Both CT-attenuation corrected and non-corrected PET images have to be evaluated in the coronal, transaxial, and sagittal planes, as well as in tridimensional maximum intensity projection (MIP) cine mode. FDG-PET images are visually analysed by assessing increased myocardial [<sup>18</sup>F]FDG uptake, taking into consideration the pattern (focal, focal on diffuse, linear, diffuse), intensity, and relationship to areas of physiologic distribution in the near surroundings. PET information should always be compared with morphologic information available on CT, including CT scans where available. It must be kept in mind that the sensitivity of [<sup>18</sup>F]FDG for infection and inflammation is not absolute and that even in the case of negative PET results, a thorough interpretation of the CT scan is essential.

### **General quantitative analysis (SUV)**

In contrast to its use in oncology, standardized uptake value (SUV) has only been partly validated in inflammation and infection. Therefore, SUV metrics should be used with caution in clinical practice, particularly regarding the use of specific SUV cut-off values. In a [<sup>18</sup>F]FDG PET study in IE, a SUV cut-off >3.3 was suggested to avoid false-positive findings.<sup>15</sup> However, extrapolation of this cut-off value to other cardiovascular disease states is difficult, in part due to differences in the underlying pathophysiology and the intensity of

inflammation. Moreover, care has to be taken when extrapolating absolute SUV cut-off values acquired between different hospitals and scanners because of the variation in these values related to differences in the scanner and reconstruction methods used.

### **General interpretation criteria**

To evaluate *clinical* [<sup>18</sup>F]FDG PET-CT imaging, the following should be taken into consideration:

- Clinical question
- Clinical history: fever, infection, inflammatory/auto-immune symptoms
- Prior imaging findings
- Brief treatment history, with particular regards to the presence of cardiac/vascular devices, date of implantation/extraction, surgical/post-surgical complications
- Concomitant treatment including date of initiation/withdrawal of antimicrobial therapy, steroids, statins, beta-blockers, etc.
- Biomarkers: CRP/ESR value at the time of imaging, results of blood cultures (number of positive blood culture, germ type)
- Scanning protocol [ $\pm$ cardiac gating, CT angiography (CTA)]
- Adequate patient preparation
- Physiologic distribution of [<sup>18</sup>F]FDG, and evaluation of its individual variations in the specific patient
- Localization of abnormal uptake according to anatomic imaging data
- The presence and aspect of the [<sup>18</sup>F]FDG signal (focal/diffuse and homogeneous/heterogeneous) and persistence of PET signal on non-attenuation corrected (NAC) images. The presence of a focal, heterogeneous [<sup>18</sup>F]FDG signal that persists on NAC PET images is an imaging aspect in favour of an infectious process.
- Intensity of [<sup>18</sup>F]FDG uptake (e.g. SUVmax)
- Correlation with data from previous clinical, biochemical, and morphologic examinations
- Presence of potential causes of false-negative results (lesion size, low metabolic rate, hyperglycaemia, lesions masked by adjacent high physiologic uptake, concomitant drug use interfering with uptake, such as ongoing steroid therapy in systemic disorders)
- Presence of potential causes of false-positive results (injection artefacts and external contamination, reconstruction artefacts from attenuation correction, use of surgical glue in previous operations, normal physiologic uptake, pathologic uptake not related to infection or inflammation)

## **Specific scoring, interpretation and reporting criteria for 4IS disorders**

### **Prosthetic and native valve endocarditis and cardiac devices**

IE comprises native valve endocarditis (NVE) and infection of intracardiac prosthetic material. The latter includes prosthetic valve endocarditis (PVE, covering all types of prosthetic valves, clips, annuloplasty rings, intracardiac patches, and shunts), and IE related to CIED, which include pacemakers, ICDs, and LVADs.

## Prosthetic valve endocarditis

### Study indication

Suspected PVE, and/or septic embolisms, spread of infection, portal of entry (POE).

### Image analysis and interpretation

The location, pattern, and intensity of the [ $^{18}\text{F}$ ]FDG signal at the valve: intra-valvular (in the leaflets), valvular (following the supporting structure of the valve) or peri-valvular (next to the valve).<sup>16</sup> A peri-valvular signal is in favour of infection, but infection cannot be excluded in the presence of intra-valvular or valvular [ $^{18}\text{F}$ ]FDG signal. Focal and heterogenous uptake is consistent with an infected valve. A typical location for abscesses in PVE is the aorto-mitral trigon, but abscesses can develop in any region in contact with prosthetic material. The probability of infection increases with the intensity of the [ $^{18}\text{F}$ ]FDG signal at the valves/prosthesis. The previous use of surgical adhesives can result in false positive scan findings soon after valve surgery. Post-operative inflammation can also lead to a false positive scan, but depending on the level of risk for infection<sup>15</sup> and a non-complicated valve surgery, scans <3 weeks surgery can be considered.

Several metrics have been tested to quantify the [ $^{18}\text{F}$ ]FDG signal in PVE. The easiest semiquantitative parameter to measure is the highest SUV (SUVmax) in the valvular region. Another semiquantitative parameter that has been proposed is the prosthetic to background ratio that takes into account the variability of the signal related to residual blood pool activity and image noise, by correcting valve SUV values by background activity in remote non-affected myocardium.

Whole-body [ $^{18}\text{F}$ ]FDG PET imaging is particularly useful in patients with a suspicion or proven PVE to identify septic embolism, mycotic aneurysms, and the POE.

[ $^{18}\text{F}$ ]FDG PET is less suited to detect cerebral septic embolism and mycotic aneurysms of intra-cerebral arteries owing to the high physiological uptake of [ $^{18}\text{F}$ ]FDG in the brain. In these cases, CT or MRI is the exam of choice.

Septic emboli appear as focal areas of [ $^{18}\text{F}$ ]FDG uptake and are typically located in the spleen, the liver, the lungs, and the kidneys. Uptake at the inter-vertebral disks and/or the vertebral bone (spondylodiscitis) suggests metastatic infection, which can also be observed in muscles and joints (septic arthritis). Embolic events can be clinically silent in 20% of cases, especially those affecting the spleen or brain. Septic emboli appear typically on CTA as hypodense lesions. [ $^{18}\text{F}$ ]FDG PET is more sensitive and specific than CTA for the detection of septic emboli.<sup>4,17</sup>

[ $^{18}\text{F}$ ]FDG PET imaging in IE is also useful to identify the POE. Typical portals of entry that can be identified are dental abscesses, sinusitis, infected central catheters, skin infection, and colonic cancers/polyps.<sup>4,17</sup>

In order to facilitate the interpretation of [ $^{18}\text{F}$ ]FDG PET images, we suggest classification of the [ $^{18}\text{F}$ ]FDG findings as follow:<sup>3,18,19</sup>

#### Typical findings

- presence of focal, heterogeneous, valvular/peri-valvular [ $^{18}\text{F}$ ]FDG uptake persisting on NAC images and corresponding to an area of suspected infection on echocardiography or CTA (mobile mass,

peri-vascular thickening, aneurysm, or new peri-valvular regurgitation).

- high [ $^{18}\text{F}$ ]FDG signal in the absence of prior use of surgical adhesives.
- presence of focal [ $^{18}\text{F}$ ]FDG uptake in organs with low-background uptake consistent with septic embolism, mycotic aneurysms or the POE.

#### Atypical findings

- diffuse, homogeneous, valvular [ $^{18}\text{F}$ ]FDG signal that is absent on NAC images
- low [ $^{18}\text{F}$ ]FDG signal

ECG-gated cardiac FDG PET acquisitions may improve detectability of IE.<sup>20,21</sup> In all cases correlation with clinical features echocardiography and CT findings is mandatory. In doubtful cases, white blood cell single-positron emission tomography (WBC-SPECT) can further help define the presence/absence of infection at PVE.<sup>3</sup>

In patients who present with suspected NVE, the use of [ $^{18}\text{F}$ ]FDG-PET/CT is less well established. The relatively low sensitivities of FDG PET/CT reported in the literature for evaluation of NVE can be accounted for by both physiological and technical factors.<sup>22</sup> The more frequent presence of isolated valve vegetations, rare paravalvular involvement, lower predominance of polymorphonuclear cells, and increased fibrosis in NVE compared with PVE results in reduced inflammatory response and subsequently lower FDG uptake.<sup>23</sup> Notably, the lower sensitivity of FDG PET/CT is offset by a near perfect specificity for detection of NVE and its unrivalled ability to identify septic emboli.<sup>22</sup> Thus, FDG PET/CT might provide clinically useful information and beneficially impact management in a subset of patients with suspicion of NVE, and the application of gated-PET may further improve it.<sup>21</sup> The *study indication, image analysis and interpretation* are in general comparable with PVE.

## Infection of cardiac implantable electronic devices

### Study indication

Suspected infection of CIED.

Defining the extent of infection in a proven CIED infection.

Positive blood culture in a patient with CIED.

### Image analysis and interpretation

Presence and aspect of the [ $^{18}\text{F}$ ]FDG signal (focal/linear) and persistency on NAC images. The presence of a focal or linear [ $^{18}\text{F}$ ]FDG signal that is located on or alongside a lead on CT and persists on NAC images are characteristics in favour of an infectious process. Late PET acquisitions might prove particularly useful in case of persistent high blood signal on PET images acquired at 1 h p.i.

CIED infection might be confined to the leads, the pocket or involve both sites. From a clinical perspective, it is important to differentiate superficial incisional infection which does not require CIED system extraction, from infection limited to the pocket, and those extending to the leads which are commonly associated with systemic infection and/or IE.<sup>24,25</sup> In CIED infections, the presence of [ $^{18}\text{F}$ ]FDG uptake should be described as pertinent to generator pocket (superficial or deep) and/or to the leads (intravascular or intracardiac

**Table 1** Interpretation of contrast-enhanced CT scans acquired alongside PET/CT imaging in 4Is

Disease	Contrast application	Advantages and scoring methods	Comments
Infective endocarditis and cardiac device infection	++	<ul style="list-style-type: none"> <li>– Visualization of abscesses</li> <li>– Visualization of thrombi/vegetations on valves/probes</li> <li>– Visualization of septic embolism as infarcts in terminal vessels (e.g. spleen, kidney, brain)</li> <li>– Detailed examination of valves (potentially important in surgical procedures)</li> </ul>	Some imaging centres do not deem the administration of contrast medium to be mandatory.
Cardiac sarcoidosis	+/-	Superior morphological allocation of the PET signal (e.g. myocardial vs. lung uptake; organ involvement)	Contrast agent generally not required if perfusion study (PET and SPECT) is available.
Large vessel vasculitis	++	Visualization of the vessels to exclude relevant stenosis and score wall thickness: 0 = no mural thickening 1 = slight mural thickening 2 = mural thickening 3 = long and strong circumferential mural thickening OR as measurement: >2–3 mm	In the presence of a recent angiographic scan (CT/MRT), a low-dose CT is sufficient.
Atherosclerosis	+++	Visualization and quantification of calcium, vascular stenosis and plaque composition <ul style="list-style-type: none"> <li>– Agatston score is mainly applied for calcium burden and risk assessment in coronary artery disease</li> <li>– Vascular stenosis is evaluated on CTA and categorized as non-obstructive or obstructive</li> </ul>	CTA is clinically recommended and aids in the interpretation of the PET scans particularly in the coronary arteries.
Vascular graft infection	+++	<ul style="list-style-type: none"> <li>– Visualization of peri-graft gas and fluid.</li> <li>– Aneurysm expansion/pseudo-aneurysm formation</li> <li>– Detailed examination of vascular graft</li> </ul>	The sensitivity and specificity of CT is moderate and variable.
Cardiac amyloidosis	-	<ul style="list-style-type: none"> <li>– Assessment of thickness of the left ventricular myocardium</li> </ul>	Only patients with a clinical suspicion receive this specific examination (septum thickness usually already available).

-, no contribution;  
 +/-, some contribution;  
 ++, good contribution;  
 +++, excellent contribution.

portion of the leads). In addition, signs of cardiac (valvular or pericardial) involvement as well as systemic signs of infections (septic embolism), in particular in the lung parenchyma and POE should be carefully assessed and reported.

The presence of [<sup>18</sup>F]FDG uptake along pacing leads, in particular in the same location as mobile elements on echocardiography and in association with septic pulmonary emboli appearing as multiple focal [<sup>18</sup>F]FDG spots, is highly suggestive of pacing lead infection.<sup>26</sup> The contrast between [<sup>18</sup>F]FDG signal along the pacing lead and residual blood signal is usually improved with delayed PET acquisitions (3 h p.i.).<sup>27</sup> In addition, every positive blood culture should be carefully evaluated and prompt active exclusion of CIED infection with other diagnostic techniques.<sup>28</sup>

The pattern and intensity of [<sup>18</sup>F]FDG uptake should be described considering that:

- Moderate [<sup>18</sup>F]FDG uptake in relation to post-operative residual inflammation can be found up to 2 months after CIED implantation but is usually of lower intensity than in case of infection.
- A focal [<sup>18</sup>F]FDG signal is often present at the point of entry of the lead into the subclavian vein that resembles a focal inflammation. The semi-quantitative ratio of maximum activity concentration of the pocket device over mean count rate of lung parenchyma<sup>26</sup> or normalization of SUVmax around the CIEDs to the mean hepatic or blood pool activity<sup>29</sup> might help in differentiating mild post-operative residual inflammation up to 2 months after device implantation vs. infection.

**Table 2** Interpretation of combined rest perfusion and [<sup>18</sup>F]FDG imaging in cardiac sarcoidosis

Rest perfusion	[ <sup>18</sup> F]FDG	Interpretation
<i>Normal perfusion and metabolism</i>		
Normal	No uptake	Negative for cardiac sarcoidosis
Normal	Diffuse	Diffuse (usually homogeneous) [ <sup>18</sup> F]FDG most likely due to suboptimal patient preparation
Normal	Isolated lateral wall uptake	May be a normal variant
<i>Abnormal perfusion or metabolism</i>		
Normal	Focal	Could represent early disease or false positive
Defect	No uptake	Perfusion defect represents scar from sarcoidosis or other etiology
<i>Abnormal perfusion and metabolism</i>		
Defect	Focal in area of perfusion defect	Active inflammation with scar in the same location
Defect	Focal on diffuse with focal in area of perfusion defect	Active inflammation with scar in the same location with either diffuse inflammation or suboptimal preparation
Defect	Focal in area of normal perfusion	Presence of both inactive scar and inflammation in different segments of the myocardium or inactive scar and false positive physiological [ <sup>18</sup> F]FDG uptake

Adapted from Slart et al.<sup>5</sup>

- The presence and location of the signal and its persistency on NAC PET images should be described according to the signal intensity and its location.

For CTA analysis and interpretation, see *Table 1*.

The evaluation of remote septic emboli should be performed similar to cases of PVE, but with close attention also paid to the lung parenchyma.

In doubtful cases, WBC-SPECT can further help define the presence/absence of infection at PVE.<sup>3,4,28</sup>

## Left ventricular assist device infection

### Study indication

- Suspected infection of LVAD.
- Evaluation of the extent of infection of LVAD.
- Positive blood culture in a patient with LVAD.

### Image analysis and interpretation

LVADs are generally subdivided into five regions that have to be assessed separately: driveline exit site, driveline within the subcutaneous tissues, LVAD pump, LVAD inflow cannula, and LVAD outflow cannula.

- The presence, intensity and location of the [<sup>18</sup>F]FDG signal across the different components of the device and the persistency of the signal on NAC images should be described.<sup>30,31</sup>
- The analysis of the FDG signal in the pump and cannula is more complex because of the artefacts caused by the device. The persistence of [<sup>18</sup>F]FDG uptake on NAC and its association with infiltration around the pump on the non-enhanced CT is highly suggestive of infection. In doubtful cases, WBC-SPECT can help define the presence/absence of infection of the pump and cannula.<sup>32</sup>

Infection of the driveline can be treated by re-implantation of a new driveline in another site, whereas infection of the pump and cannula usually requires long-term antibiotic therapy.

## Vascular graft infection

VGI is a rare but severe complication after vascular surgery, associated with high morbidity and mortality rates.<sup>33</sup> Early diagnosis of VGI is important for correct and early surgical and/or antibiotic treatment, which improves the outcome. Aortic graft are frequently used at the time of valve surgery, with infection of valves and grafts often co-existing.

Recently, the European Society for Vascular Surgery (ESVS), in collaboration with the EANM, published clinical practice guidelines for the care of patients with vascular graft/endograft infection.<sup>5</sup>

### Study indication

Diagnosis of suspected VGI.

### Image analysis and interpretation

The following aspects need to be carefully considered:

Vascular graft uptake pattern: focal [<sup>18</sup>F]FDG uptake is more consistent with infection than diffuse low level activity. The exact location of the focal uptake, its distribution and intensity should be recorded as well as [<sup>18</sup>F]FDG uptake in regional lymph nodes.

The intensity of [<sup>18</sup>F]FDG accumulation can be assessed visually using a scoring system of 0-4: Grade 0, [<sup>18</sup>F]FDG uptake similar to the background; Grade I, low [<sup>18</sup>F]FDG uptake, comparable with that by inactive muscles and fat; Grade II moderate [<sup>18</sup>F]FDG uptake, clearly visible and higher than the uptake by inactive muscles and fat; Grade III, strong [<sup>18</sup>F]FDG uptake, but distinctly less than the physiologic urinary uptake by the bladder; and Grade IV, very strong [<sup>18</sup>F]FDG uptake, comparable with the physiologic urinary uptake by

the bladder. Focal uptake, with an intensity grade >II is suspected of VGI.<sup>34</sup> However, in addition to visual assessment, [<sup>18</sup>F]FDG uptake should also be quantified with SUVmax for all arterial graft territories and normalized for background activity in the liver or blood pool usually in the caval vein. Diffuse, homogeneous and low intensity [<sup>18</sup>F]FDG uptake can be observed in the majority of non-infected vascular graft prostheses particularly shortly after surgery. This is related to the body's response to foreign material, and should be considered to avoid misinterpretation of PET/CT studies in patients referred for suspected prosthetic infection.<sup>35</sup>

Whole-body imaging: describe remote locations in the body with abnormal increases in [<sup>18</sup>F]FDG uptake. Mycotic aneurysm appears typically as a focal [<sup>18</sup>F]FDG signal in a region corresponding to the arterial wall of the aorta or a peripheral artery, and should be confirmed with CTA.

Comparison with prior [<sup>18</sup>F]FDG PET scans: if the scan is performed to determine response to therapy, then the distribution and intensity of the signal should be compared to prior scans: increase in uptake, no change in uptake, decrease in uptake.

Abnormalities on low dose CT should also be described. For CTA analysis and interpretation, see *Tables 1 and 3*. In doubtful cases, WBC-SPECT can further help define the presence/absence of infection at the vascular graft.<sup>36</sup>

## Cardiac sarcoidosis

The role of [<sup>18</sup>F]FDG PET for the diagnosis of extra-cardiac sarcoidosis is well established. The assessment of cardiac sarcoidosis is more complex but is now recommended for clinical use by international guidelines.<sup>6,37</sup> Serial assessment of the inflammatory status using [<sup>18</sup>F]FDG PET might be helpful for monitoring therapy efficacy and for deciding treatment continuation, tapering or change of treatment.

### Study indication

Suspicion of cardiac sarcoidosis according to the Heart Rhythm Society (HRS) guidelines.<sup>37</sup>

Monitoring of treatment in patients with established cardiac sarcoidosis.

### Image analysis and interpretation

Left ventricle: uptake pattern (i—no [<sup>18</sup>F]FDG uptake, ii—diffuse [<sup>18</sup>F]FDG uptake, iii—focal [<sup>18</sup>F]FDG uptake, iv—focal on diffuse [<sup>18</sup>F]FDG uptake; exact location of the focal uptake; extent of the uptake; intensity of the uptake).

Right ventricle: uptake pattern (grades 1–4), exact location of the focal uptake, extent of the uptake, intensity of the uptake.

Combination of [<sup>18</sup>F]FDG and perfusion imaging (MPI): Perfusion defects in patients with cardiac sarcoidosis can represent areas of scar or inflammation. However, perfusion defect in combination with abnormal [<sup>18</sup>F]FDG uptake represents focal inflammation (*Table 2*) and can help differentiate pathological from physiological [<sup>18</sup>F]FDG activity. [<sup>18</sup>F]FDG and MPI patterns have been described as 'early' (only [<sup>18</sup>F]FDG-positive), 'progressive inflammatory' ([<sup>18</sup>F]FDG positive without major perfusion defects); 'peak active' (high [<sup>18</sup>F]FDG uptake with small perfusion defects), 'progressive myocardial impairment' (high [<sup>18</sup>F]FDG uptake with large perfusion defects), or 'fibrosis-predominant' ([<sup>18</sup>F]FDG negative, but with perfusion defects).<sup>6</sup> In

patients with areas of increased [<sup>18</sup>F]FDG uptake but no clear perfusion defects, this may represent either early cardiac sarcoid beyond the resolution of perfusion imaging, or false positive physiological [<sup>18</sup>F]FDG uptake.

As an alternative to MPI, [<sup>18</sup>F]FDG PET can be compared with CMR late gadolinium enhancement images. Areas of increased [<sup>18</sup>F]FDG that correspond to non-infarct areas of late gadolinium enhancement are highly suggestive of active cardiac sarcoidosis. Areas of typical late gadolinium enhancement with no [<sup>18</sup>F]FDG uptake are consistent with scarred, non-active sarcoid regions. Regions of [<sup>18</sup>F]FDG uptake without late enhancement either representing early sarcoidosis beyond the sensitivity of CMR or false positive physiological [<sup>18</sup>F]FDG activity. Myocardium with neither increased [<sup>18</sup>F]FDG nor late enhancement is considered as normal.<sup>38</sup>

Whole-body imaging: describe extra-cardiac locations with increased [<sup>18</sup>F]FDG uptake.

Comparison with prior [<sup>18</sup>F]FDG PET scan: if scan is performed in the context of assessing therapy response, then both the distribution and intensity should be compared to prior scans (increase, equal or decreased uptake).

SUV quantification can be applied in cardiac sarcoidosis diagnosis, which may provide prognostic information.<sup>39</sup>

Abnormalities on low dose or on diagnostic CT scan should be described (*Table 1*).

Comparison with other (hybrid) imaging modalities: cardiac (PET)/MRI<sup>40</sup> and echocardiography. CMR has limited value to assess treatment response because the majority of these patients receive intra-cardiac devices that may preclude CMR or produce artefacts when MR compatible ICD is implanted.

[<sup>68</sup>Ga]DOTA conjugated peptides maybe promising as alternative cardiac sarcoidosis, with the benefit of no physiological myocardial uptake. [<sup>68</sup>Ga]DOTA conjugated peptides can either be scored visually for intensity and distribution, or semi-quantitatively using SUVs.<sup>41</sup>

## Large vessel vasculitis

LVV is defined as a disease mainly affecting the large arteries, with two major variants, Takayasu arteritis (TA) and giant cell arteritis (GCA). Vasculitis can be distributed locally in the branches of the external carotid artery or the aorta and its main branches more centrally in the thorax. Recent recommendations and statements have been provided, based on the available evidence and consensus of experts in the field, describing patient preparation, as well as [<sup>18</sup>F]FDG PET/CT(A) acquisition and interpretation for the diagnosis and follow-up of patients with suspected or diagnosed LVV.<sup>7,8</sup>

In circumstances where there may be cardiac involvement, patients with LVV should be further investigated (additional myocardial perfusion imaging, CMR, CT coronary angiography). This includes the risk of cardiovascular toxicity related to drug therapy used in LVV.<sup>42</sup>

### Study indication

Diagnosis of LVV.

Monitoring of LVV activity.

**Table 3** Recommended [<sup>18</sup>F]FDG PET/CTA interpretation criteria in LVV

LVV visual grading (GCA and TA)		
[ <sup>18</sup> F]FDG	Grade 0	No vascular uptake ( $\leq$ mediastinum)
	Grade 1	Vascular uptake $>$ mediastinum and $<$ liver uptake
	Grade 2	Vascular uptake = liver uptake, may be PET-positive
	Grade 3	Vascular uptake $>$ liver uptake, considered PET-positive

Adapted from Slart et al.<sup>6</sup>

GCA, giant cell arteritis; LVV, large vessel vasculitis; TA, Takayasu arteritis.

### Image analysis and interpretation

Large vessels as well as the cranial and extra-cranial arterial structures.

Uptake pattern: diffuse circumferential [<sup>18</sup>F]FDG uptake around the vessel, that is different from the more regional and focal uptake observed in atheroma. The exact location of the uptake, its distribution across the vascular system, and its intensity (vascular scoring 0–3 against the liver) should be documented (Table 3).

Whole-body imaging: describe extra-vascular locations with increased [<sup>18</sup>F]FDG uptake.

Comparison with prior [<sup>18</sup>F]FDG -PET scans: if the scan is performed to assess response to therapy, then extent and intensity should be compared to prior scans: increase in uptake, equal uptake, decrease in uptake.

Abnormalities on low dose CT should be described.

Comparison with other imaging modalities: CTA or MRA if available.

For CTA analysis and interpretation, see Table 1.

### Cardiac amyloidosis

Most cases of cardiac amyloidosis result from two protein precursors: amyloid immunoglobulin light chain (AL), in which the mis-folded protein is a monoclonal immunoglobulin light chain typically produced by bone marrow plasma cells, and amyloid transthyretin (ATTR) amyloidosis, in which the misfolded protein is transthyretin (TTR), a serum transport protein for thyroid hormone and retinol that is synthesized primarily by the liver. [<sup>18</sup>F]FDG PET is mainly applied in AL cardiac amyloidosis, and may be supportive of the usual diagnostic tests in differentiating between systemic amyloidosis (no increased FDG uptake at the amyloid site) and localized amyloidosis (increased FDG uptake at the amyloid site).<sup>43</sup> However, other more specific PET radiopharmaceuticals such as [<sup>11</sup>C]PIB, [<sup>18</sup>F]florbetapir, and [<sup>18</sup>F]florbetaben, have demonstrated promise in clinical research studies as recently described in the Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis.<sup>9</sup> In general, AL demonstrates a higher retention of these specific PET compounds as compared with ATTR cardiac amyloidosis.<sup>44,45</sup> SPECT imaging with bone tracers is generally preferred for the assessment of ATTR amyloidosis, although some preliminary research data have suggest [<sup>18</sup>F]NaF PET

might provide similar results to SPECT bone agents but with the opportunity for tracer quantification.<sup>9,46</sup>

### Study indication

Mainly research.

### Image analysis and interpretation

Left ventricle: uptake pattern (i—no [<sup>18</sup>F]FDG uptake (none), ii—diffuse [<sup>18</sup>F]FDG uptake (diffuse), iii—focal [<sup>18</sup>F]FDG uptake (focal), iv—focal on diffuse [<sup>18</sup>F]FDG uptake (focal on diffuse), exact location of the focal uptake, extent of the uptake, intensity of the uptake.

Right ventricle: uptake pattern (grades 1–4), exact location of the focal uptake, extent of the uptake, intensity of the uptake.

Whole-body imaging: describe extra-cardiac locations with increased [<sup>18</sup>F]FDG uptake.

Abnormalities on low dose or diagnostic CT scan should be described.

Comparison with prior [<sup>18</sup>F]FDG-PET scan: if scan is performed in the context of assessment therapy response, then extent and intensity should be compared to prior scan: increase in uptake, equal uptake, decrease in uptake.

Comparison with other imaging modalities: echocardiography, MRI, and with specific PET amyloid compounds that have been evaluated in patients with AL and ATTR cardiac amyloidosis.

For [<sup>11</sup>C]PIB, [<sup>18</sup>F]florbetapir, [<sup>18</sup>F]florbetaben, and [<sup>18</sup>F]flutemetamol, see [Supplementary data](#) online, S1.

So far, the evidence for using clinical PET/MRI in 4Is is very limited, but some overview papers have been published in the field of cardiovascular diseases.<sup>47–50</sup>

### The 4Is-team

A multidisciplinary team approach has been proposed as the model in oncology in many hospitals and medical centres. More recently, this approach has been extended to cardiology with the successful introduction of the heart valve team for the assessment of patients being considered for transcatheter aortic valve implantation.<sup>51</sup> In the field of IE, a multidisciplinary approach for evaluating patients with IE has also been introduced in order to improve management and outcome. This example can be extended to all complex disease states including the 4Is. We would therefore advocate creation of a 4Is-team of experts to improve clinical assessment of decision-making for these complex patients.

To be effective, the structure of a 4Is-Team has to be modelled on the local health systems, including cultural and socio-economic aspects. Its success is contingent upon knowledge of one's own area of expertise as well as that of the team members, flexibility of roles, and comfort and skills in supplying and receiving interdisciplinary education. To promote effective collaboration, the team must address issues of group dynamics, including clarification of individual roles, team unity, communication, and patterns of decision-making and leadership. The clinical imager plays an active role in the teamwork programme and in the global educational planning, developing 'capabilities' and 'competencies', core skills, knowledge and attitudes to facilitate inter-specialist communications. The challenge of the clinical imager within the 4Is-team is to establish a new professional



perspective: a new vision of the imager, no longer thinking as an individual, but rather as an integral player and contributor to the team, translating the image content into clinical planning and a decision-making process that enhance the quality of patient care.

## Conclusions

With this summarized document we provided a standard for PET/CT imaging in inflammatory, infective, infiltrative, and innervation dysfunctional (4Is) cardiovascular diseases. It can be applied in clinical practice and integrated in (multicentre) clinical trials for optimal procedural standardization. 4Is related cardiovascular diseases are generally complex and often require wide ranging expertise and a multidisciplinary approach for optimal diagnosis and management. New PET 4Is radiopharmaceuticals beyond [<sup>18</sup>F]FDG are available, but are currently mainly in the clinical research phase. Further clinical evaluation of the most promising PET tracers is warranted before their implementation in routine clinical practice.

## Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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## Compliance with ethical standards

### Ethics approval

These guidelines do not contain any studies with human participants or animals performed by any of the authors.

### Liability statement

This guideline summarizes the views of the EANM Cardiovascular and Infection & Inflammation Committees and the EACVI. It reflects recommendations for which the EANM and the EACVI cannot be held responsible. The recommendations should be taken into context of good practice of nuclear medicine & cardiology imaging and do not substitute for national and international legal or regulatory provisions.

**Conflict of interest:** none declared.

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