European Heart Journal - Cardiovascular Imaging (2023) **24**, 1489–1490
https://doi.org/10.1093/ehjci/jead175

EDITORIAL

The power of negative metabolic imaging: negative FDG-PET/CT predicts infective endocarditis resolution

Patrizio Lancellotti [1]* and Yun Yun Go [2]

[1]Department of Cardiology, Heart Valve Clinic, GIGA Cardiovascular Sciences, University of Liège Hospital, CHU Sart Tilman, Domaine Universitaire du Sart Tilman, B.35, Liège 4000, Belgium; and [2]Department of Cardiology, National Heart Research Institute Singapore, National Heart Centre Singapore, Singapore, Singapore

Online publish-ahead-of-print 18 July 2023

This editorial refers to 'Absence of infective endocarditis relapse when end-of-treatment fluorodeoxyglucose positron emission tomography/computed tomography is negative', by C. Régis *et al.*, https://doi:10.1093/ehjci/jead138.

Infective endocarditis (IE) is a systemic disease with a myriad of possible complications. The initial presentation can be elusive, and the prognosis is varied, depending on the organ involved, the microorganisms, and patient factors. Multi-modality imaging techniques play complementary roles in the workup of patients with IE, especially in those with diagnostic uncertainties, e.g. possible or rejected IE by Duke criteria, but of high clinical suspicion, or those with intra-cardiac devices or prostheses. A metabolic imaging technique, fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), enables early identification of infection due to its ability to detect subclinical inflammatory activity before structural changes manifest. While the whole-body tomographic imaging aspect enables assessment of extra-cardiac complications, which can often be clinically silent.[1,2]

The 2015 ESC Modified Diagnostic Criteria included abnormal FDG-PET/CT uptake as either a major (around prosthetic valve) or a minor (silent emboli or infectious aneurysms) criterion.[3] While the 2020 ACC/AHA Valvular Heart Disease Guideline gave a Class 2a recommendation for FDG-PET/CT as adjunct diagnostic imaging in patients with 'possible IE' by Modified Duke Criteria.[4] FDG-PET/CT increased the sensitivity of Modified Duke Criteria, especially in patients with suspected prosthetic valve endocarditis (PVE) or cardiac implantable electronic devices. In native valve endocarditis (NVE), however, FDG-PET/CT has lower sensitivity as vegetation can often be small, below the spatial resolution of PET/CT.[1]

FDG-PET/CT's role in the diagnostic workup of patients with suspected IE at initial presentation has been well recognized in routine clinical practice and the guidelines. However, the literature on the prognostic value of FDG-PET/CT is scarce. One study has shown that in patients with PVE, moderate-to-intense uptake on FDG-PET/CT performed shortly after admission was associated with increased risk of mortality, recurrence of IE, heart failure, embolic events, and re-hospitalization at 1 year.[5] There is a paucity of data on the utility of FDG-PET/CT performed beyond the confines of initial workup of IE.

In this issue of the journal, Régis *et al.*[6] followed 62 patients with IE (42 PVE and 20 NVE) who underwent FDG-PET/CT at the end of antibiotic treatment (EOT). FDG-PET/CT findings were compared against IE relapse, as determined by the endocarditis team. It was a retrospective, single-centred study of conservatively managed patients, of which 58% met the indications for surgery. The novelty of this study is two-fold: (i) FDG-PET/CT's role extends beyond the initial diagnosis to include prognostication of patients at EOT; (ii) negative EOT FDG-PET/CT predicted IE resolution in conservatively managed patients.

EOT FDG-PET/CT had excellent, i.e. 100% sensitivity and negative predictive value (NPV). However, it had a specificity of 52.7% and positive predictive value (PPV) of mere 21.2%. In short, an EOT negative FDG-PET/CT was a true negative, while the significance of an EOT positive FDG-PET/CT was indeterminate due to the high false positive rate. In this study, IE patients who had a negative FDG-PET/CT at the start of antibiotic therapy invariably had a negative FDG-PET/CT at EOT and no IE relapse. While all patients with negative EOT FDG-PET/CT had no IE relapse. Hence, any given negative FDG-PET/CT, either at the initiation or at EOT, predicted IE resolution with 100% NPV, underscoring the power of negative metabolic imaging.

FDG-PET/CT identified all the true positives, i.e. IE relapses. Its Achilles heel, however, was in the false positives. Due to the study design, the FDG-PET/CT readers were blinded to patients' clinical information, except for the date of valvular surgery in PVE. It is uncertain if the false positive rate would reduce had the interpretation been done within the clinical context, e.g. with the knowledge of echocardiogram or computed tomography angiography (CTA) findings, C-reactive protein level and leucocyte count, patient's co-morbidities, surgical history, etc.

Surgical history such as the use of an anti-calcification agent or adhesive glue is known to cause FDG uptake, potentially resulting in false positives. It is also possible that the EOT FDG uptake could represent residual aseptic inflammation that lagged behind clearance of infection. In this study, the endocarditis team adjudicated relapse diagnosis. It is not impossible that some FDG-PET/CT deemed 'false positive' could represent insidious infection that has yet to manifest clinically. The study has shown that with its exquisite sensitivity, FDG-PET/CT was able to identify infection undetected by transoesophageal echocardiography, CTA, and surgical exploration.[2]

The opinions expressed in this article are not necessarily those of the Editors of *EHJCI*, the European Heart Rhythm Association or the European Society of Cardiology.

* Corresponding author. E-mail: plancellotti@chuliege.be

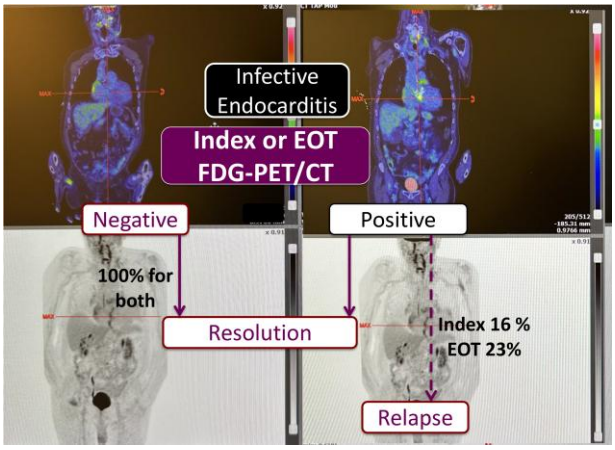

Figure 1 Percentage of infective endocarditis resolution and relapse according to FDG-PET/CT results. Index: first PET/CET examination; EOT: end of antibiotic treatment.

The diagnostic performance, i.e. the PPV, NPV, and accuracy of FDG-PET/CT, is influenced by the prevalence of IE in the study population. In a population with a low IE relapse rate, the test would yield a low PPV and vice versa. The present study population had a relapse rate of 11% within a median follow-up of 10 months. In the literature, the incidence of IE relapse ranged from 4% to 12% at 1 year.[7] To illustrate, the PPV of EOT FDG-PET/CT in the present study was 21.2%. If the incidence of IE relapse was doubled, the PPV would have been 37%. Thus, the diagnostic performance reported in this study is not generalizable to different risk groups.

It is uncertain if EOT FDG-PET value adds to the clinical decision-making above and beyond the current standard of care. In this study, EOT FDG-PET/CT had a high NPV. However, the far majority, i.e. 90% of the study population, had no IE relapse. In such a population, the need for a test with high NPV is less pressing compared with the one with high PPV. Here, a more interesting question would be how to identify the 10% of patients with IE relapse early and with precision. Identification of this high-risk group could change the treatment trajectory, e.g. duration or choice of antibiotic and decision for surgery. In this regard, EOT FDG-PET/CT falls short due to the high false positive rate.

One of the concerns of performing an EOT FDG-PET/CT is that prolonged antibiotic use could decrease the sensitivity of FDG-PET/CT, creating false negatives.[1] This study has shown that all negative EOT FDG-PET/CTs were true negatives and the study population received on average, 61 days of antibiotic prior to FDG-PET/CT (*Figure 1*). In this study, the use of EOT FDG-PET/CT in those with initial negative FDG-PET/CT was guided clinically, i.e. in view of abnormal EOT echocardiography, persistent inflammatory syndrome, etc. The routine use of EOT FDG-PET/CT outside of clinical indications was not studied. Also, in patients with initial positive FDG-PET/CT, the clinical utility of repeating scan at EOT, either to monitor progress or to document clearance, requires further study. In the era of value-based healthcare, the routine use of serial testing, especially advanced imaging, warrants careful cost-effectiveness analysis. This is especially pertinent when the advanced imaging in question has a diagnostic accuracy of 58.6%, which is slightly better than flipping a coin in a population with relatively low disease prevalence.

Suffice it to say that the present study is insufficient to support the routine use of EOT FDG-PET/CT, nor does it advise on the patient groups who are most likely to benefit from such approach. Further, larger studies are needed to bridge these knowledge gaps. The European Infective Endocarditis (Euro-Endo) registry is a prime example of such undertaking.[8] It is a multi-centred, multi-national, prospective registry that provides management and long-term outcomes data on patients with IE.

Funding

None declared.

Conflict of interest: None declared

Data availability

No new data were generated or analysed in support of this editorial comment.

References

1. Erba PA, Lancellotti P, Vilacosta I, Gaemperli O, Rouzet F, Hacker M *et al.* Recommendations on nuclear and multimodality imaging in IE and CIED infections. *Eur J Nucl Med Mol Imaging* 2018;**45**:1795–815.
2. Dilsizian V, Budde RPJ, Chen W, Mankad SV, Lindner JR, Nieman K. Best practices for imaging cardiac device-related infections and endocarditis: a JACC: cardiovascular imaging expert panel statement. *JACC Cardiovasc Imaging* 2022;**15**:891–911.
3. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F *et al.* 2015 ESC guidelines for the management of infective endocarditis. *Eur Heart J* 2015;**36**:3075–128.
4. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F *et al.* 2020 ACC/AHA guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol* 2021;**77**:e25–197.
5. San S, Ravis E, Tessonier L, Philip M, Cammilleri S, Lavagna F *et al.* Prognostic value of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in infective endocarditis. *J Am Coll Cardiol* 2019;**74**:1031–40.
6. Régis C, Thy M, Mahida B, Deconinck L, Tubiana S, Iung B *et al.* Absence of infective endocarditis relapse when end-of-treatment fluorodeoxyglucose positron emission tomography/computed tomography is negative. *Eur Heart J Cardiovasc Imaging* 2023;**24**:1480–8.
7. Alagna L, Park LP, Nicholson BP, Keiger AJ, Strahilevitz J, Morris A *et al.* Repeat endocarditis: analysis of risk factors based on the international collaboration on endocarditis—prospective cohort study. *Clin Microbiol Infect* 2014;**20**:566–75.
8. Habib G, Lancellotti P, Erba PA, Sadeghpour A, Meshaal M, Sambola A *et al.* The ESC-EORP EURO-ENDO (European Infective Endocarditis) registry. *Eur Heart J Qual Care Clin Outcomes* 2019;**5**:202–7.