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A systematic review and meta-analysis of $^{18}$F-FDG-PET interpretation methods in vascular graft and endograft infection

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Short title: $^{18}$F-FDG-PET interpretation methods in VGEI
ARTICLE HIGHLIGHTS

Type of research: Meta-analysis (retrospective analysis of mainly prospectively collected data)

Key findings: As an interpretation method of $^{18}$F-FDG PET/(CT) in diagnosing vascular graft and endograft infection (VGEI), the pattern of uptake showed a pooled sensitivity of 0.94 and a pooled specificity of 0.81 among 431 suspected patients included in the meta-analysis. In contrast, the FDG uptake intensity and SUVmax methods demonstrated less discriminative ability.

Take home message: The pattern of uptake is the most optimal interpretation method of $^{18}$F-FDG PET/(CT) in diagnosing VGEI and should therefore be a structural part of the $^{18}$F-FDG PET/(CT) assessment in patients suspected of VGEI.

TABLE OF CONTENTS SUMMARY

The pattern of uptake as an interpretation method of $^{18}$F-FDG PET/(CT) in diagnosing VGEI showed the highest pooled sensitivity and specificity in this meta-analysis, compared to the FDG uptake intensity and SUVmax methods. Therefore, the pattern of uptake method appears to have the best discriminative ability in diagnosing VGEI.

ABSTRACT

Objective

Vascular graft and endograft infection (VGEI) has high morbidity and mortality rates. Diagnosis is complicated since symptoms vary and can be non-specific. A recent meta-analysis identified the use of $^{18}$F-fluoro-D-deoxyglucose positron emission tomography-computed tomography ($^{18}$F-FDG PET/(CT)) as the most valuable tool for diagnosing VGEI and favorable to computed...
tomography as the current standard. However, the availability and varied use of several
interpretation methods, without consensus on which interpretation method is best, complicates
clinical use. The aim of this study was to evaluate the diagnostic performance of different
interpretation methods of $^{18}$F-FDG PET(CT) in diagnosing VGEI.

Methods

A systematic review was performed according to the PRISMA guidelines. Data sources included
PubMed/Medline, Embase, and Cochrane. A meta-analysis was conducted on the different
interpretation methods for $^{18}$F-FDG PET(CT) in diagnosing VGEI, including visual FDG uptake
intensity, visual FDG uptake pattern, and quantitative SUVmax.

Results

Out of 613 articles, 13 were included—10 prospective and 3 retrospective articles. The FDG
uptake pattern method ($I^2$ 26.2%) showed negligible heterogeneity, while the FDG uptake
intensity ($I^2$ 42.2%) and SUVmax ($I^2$ 42.1%) methods both showed moderate heterogeneity.
The pooled sensitivity for FDG uptake intensity was 0.90 (95% CI: 0.79-0.96), for uptake pattern
0.94 (95% CI: 0.89-0.97), and for the SUVmax method 0.95 (95% CI: 0.76-0.99). The pooled
specificity for FDG uptake intensity was 0.59 (95% CI: 0.38-0.78), whereas for FDG uptake
pattern it was 0.81 (95% CI: 0.71-0.88) and for SUVmax it was 0.77 (95% CI: 0.63-0.87).
The uptake pattern interpretation method demonstrated the best positive and negative post-test
probability—82% and 10%, respectively.

Conclusion

This meta-analysis identified the FDG uptake pattern as the most accurate assessment method of
$^{18}$F-FDG PET(CT) for diagnosing VGEI. The optimal SUVmax cutoff, depending on the
vendor, demonstrated strong sensitivity and moderate specificity.
**Keywords:** vascular graft infection; fluorodeoxyglucose F-18 (FDG); positron emission tomography-computed tomography (PET/CT), meta-analysis; sensitivity and specificity

**FUNDING STATEMENT**

None.

**CONFLICT OF INTEREST**

None.

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**INTRODUCTION**

Although vascular graft and endograft infection (VGEI) is not common, when diagnosed, the complication can have severe consequences, including a mortality rate ranging from 25-88%.\(^1\) Incidence depends on the anatomical region and the technique used for implementation of the graft.\(^2,3,4,5,6\) Studies report an overall incidence between 0.1-6%, whereas the incidence in initial endovascularly treated patients is much lower, at 0.1-1.2%.\(^7,8,9\) Grafts located in the groin appear to be infected most often (6%).\(^10\)
Diagnosis of VGEI is complicated since symptoms vary and can be non-specific.\textsuperscript{11,12} Positive cultures, which can be obtained percutaneously or during surgery, are still considered the reference standard. However, retrieving material for culture is not possible in all patients either because it cannot be obtained percutaneously, the material is contaminated, or because a surgical procedure is too invasive for the patient. Confirming the diagnosis can thus be difficult or impossible.

Although surgical intervention is the preferred treatment, not all patients are in a medical condition conducive to major surgery. Therefore, some patients are treated conservatively with antibiotics. Since surgical treatment is invasive and carries risk, a correct diagnosis or exclusion of graft infection is of great importance.\textsuperscript{13}

Over the last three decades, several imaging modalities have been used to non-invasively diagnose VGEI, with a wide range of sensitivity and specificity.\textsuperscript{14} The current nuclear hybrid imaging techniques are promising for diagnosis of a vascular graft and/or endograft infection. \textsuperscript{18}F-fluoro-D-deoxyglucose positron emission tomography in combination with computed tomography (\textsuperscript{18}F-FDG PET/(CT)) displays metabolic activity combined with the precise anatomic localization of an existing infection and has the ability to tell if the graft is involved in the infectious process.\textsuperscript{14} Early and correct diagnosis is of major importance, since false negatives may be fatal and false positives may result in overtreatment with potentially major consequences. A recent meta-analysis of the diagnostic performance of different imaging modalities used in patients suspected of VGEI described the accuracy of the existing imaging techniques. \textsuperscript{18}F-FDG-PET scans (with or without low-dose CT) yielded high sensitivity and specificity, whereas the
results were marginal for computerized tomography with or without angiography (CT(A)).

For FDG-PET/(CT) in the context of VGEI, no clear interpretation criteria exist; different assessment methods are used to score $^{18}$F-FDG PET/(CT) findings. These assessment methods include visual scoring based on either (i) the uptake intensity of FDG, often assessed by a visual grading scale (VGS); or (ii) the uptake pattern of the FDG, i.e., whether it is focal or diffuse. When the uptake intensity is assessed, the amount of FDG uptake is quantified, often using a five-point VGS. The pattern of FDG uptake can be evenly diffusely distributed (homogeneous) or focally distributed (heterogeneous). VGEI often exhibits higher uptake intensity and a more focal pattern of FDG uptake.

The other assessment methods involve semi-quantitative scoring by (iii) quantifying the maximum standardized uptake value (SUVmax), corresponding with the highest FDG signal; and (iv) calculating the tissue-to-background ratio (TBR) by dividing the SUVmax of the graft by the SUVmean of the reference organ—e.g., the SUVmean of the liver, bladder, or caval vein (blood pool).

The aim of this study is to identify the most optimal interpretation method of $^{18}$F-FDG PET/(CT) for diagnosis of VGEI.

**METHODS**

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2015 statement and the Cochrane Handbook for Diagnostic Test Accuracy Reviews were
followed to conduct this meta-analysis.\cite{16,17}

**Study objective**

The objective of this review was to assess the diagnostic value of the four different assessment methods of $^{18}$F-FDG PET(/CT) used in the diagnostic work-up of patients with suspected VGEI.

**Data sources and search strategy**

A systematic search of MEDLINE, Embase, and the Cochrane library was performed on October 15, 2019, in collaboration with a clinical librarian. Eligible studies published in the last two decades were reviewed. The following Medical Subject Headings (MESH) terms were used for patient identification (vascular grafting, blood vessel prosthesis, bacterial infections, and mycoses) and for diagnostic test and reference standard (FDG, positron emission tomography, PET). Similar search terms were used to search free text.

For the initial search, language restrictions were not used, in order to avoid missing any contributing papers and investigate potential language bias. The details of the search syntax are listed in Supplement 1.

**Study selection**

Pre-specified inclusion and exclusion criteria in our research protocol determined if studies were eligible for full-text analysis. Studies including adult patients suspected of vascular graft or endograft infection were eligible for inclusion. The index tests were specified as the different assessment methods of $^{18}$F-FDG PET(/CT), while the reference standard consisted of either
microbiological assessment or clinical follow-up with biochemical or microbiological assessments or with an imaging modality. Outcome measures had to include the sensitivity, specificity, positive predictive value (PPV), and/or negative predictive value (NPV) of the assessment methods. The observational cohort studies included both prospective and retrospective studies. Studies with fewer than five patients, case reports, abstracts, reviews, or animal studies were excluded. Checks for duplicates and overlapping databases were performed both electronically and manually.

Two reviewers (ERF and RtRS) independently screened all titles and abstracts for relevance to the set inclusion criteria. If either reviewer scored the publication positively in the title/abstract phase, it was included in the full-text review category. Full-text publications were assessed for definitive inclusion independently by two reviewers (ERF, RtRS). If needed, a third reviewer was approached for final consensus (BS). The inclusion process was summarized in a PRISMA flow diagram including the reasons for excluding studies in the full-text phase.

Data extraction
Data extraction was performed by two reviewers (ERF and RtRS) and cross-checked. Study characteristics (year of publication, study design), baseline characteristics of each study (number of patients / number of grafts), \(^{18}\text{F-FDG PET/CT} \) assessment method, reference standard, and outcome data (true positives, false positives, false negatives, true negatives) were extracted. If necessary, authors were contacted to obtain missing data. When data and/or vital information on inclusion criteria was unavailable, that particular study was excluded from the analysis.
Assessment of study quality

Two reviewers (ERF and RtRS) evaluated the methodological quality of the included observational cohort studies. The Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2) was used to assess the applicability and risk of bias. Several categories were labeled as ‘low risk,’ ‘high risk,’ or ‘unclear risk,’ such as patient selection, the index test, the reference standard, and flow and timing.

Data synthesis and analysis

The available data was separated per method of assessment. All assessment methods with sufficient available data were further analyzed during meta-analysis. Sensitivity and specificity forest plots were drawn using RevMan version 5.3.3. Pooled sensitivities and specificities were calculated by using 2x2 contingency tables. The heterogeneity among the studies was evaluated using $\chi^2$ and $I^2$ statistics and drawn in hierarchical summary receiver operating characteristics (HSROC) curves. The $I^2$ statistic was interpreted as follows: 0% to 40% was considered not important, 30% to 60% represented moderate heterogeneity, 50% to 90% represented substantial heterogeneity, and 75% to 100% indicated considerable heterogeneity.

Publication bias was assessed by the linear regression method and funnel plot of Deeks et al. A p-value of $<0.05$ indicated potential publication bias. The pooled diagnostic odds ratios were calculated using a random-effects model, when moderate or considerable heterogeneity was observed in the studies. The diagnostic odds ratio reflects the diagnostic accuracy of the index test and describes the difference in probability of obtaining a positive test result in a diseased rather than a non-diseased person. Weighted estimates for each study were calculated and
illustrated in a forest plot. For the comprehension of the meaning of a negative or positive test result, the pre-test probability and positive and negative post-test probability were calculated and drawn in a bar chart. All tests were two-sided, and a p-value \( \leq 0.05 \) was considered statistically significant. STATA version 13.0 was used to perform the meta-analyses (StatCorp LP).^{22}

**RESULTS**

After excluding duplicate records, the search strategy identified a total of 613 potential studies. Of these, 13 studies met all inclusion criteria for the final analysis (Figure 1).

**Study characteristics**

Most of the included articles were prospective observational cohort studies \( (n = 10) \), while the remaining 3 were retrospective studies. No randomized controlled trials were identified. Study length varied from one to six years. Study size was characterized by either included patients or number of grafts, depending on how it was displayed in the original study.

The included studies investigated the four different assessment methods of \(^{18}\)F-FDG PET/(CT) in the diagnosis of VGEI: (i) visual intensity of FDG uptake, (ii) visual pattern of FDG uptake, (iii) SUV\(_{\text{max}}\), and (iv) TBR. **Table 1** gives an overview of the study characteristics, patient characteristics, index test, and reference standards of the included studies. Only two studies investigated the TBR and therefore we could not perform a meta-analysis of this category.^{23,24}

As a reference standard, microbiological assessment was used for VGEI in all of the studies. Clinical follow-up was used in more than half of the studies and ranged from 4 to 36 months.
Only four studies did not include clinical follow-up, using only microbiological findings or the combination of microbiological findings with other clinical, laboratory, or histopathological findings.\textsuperscript{23,25,26,27}

Patient characteristics

The number and anatomical location of the vascular grafts and endografts are shown in Table 1. Six studies only included patients with central grafts; the other seven studies included peripheral grafts as well. Aortic grafts were classified as thoracic, abdominal, or both.

PET characteristics

An overview of the application of $^{18}$F-FDG PET/(CT) in the selected studies is shown in Supplement 2. Different scanner types (vendors) were used. Most studies used a time interval of 60 minutes after FDG administration before imaging. However, differences in the time interval were found between FDG administration and imaging, as well as in the FDG dose and the preceding hours of fasting. One study excluded patients with diabetes and eight studies measured glucose levels before scanning. Of these eight studies, six studies applied a glucose level threshold, of which two used different thresholds for patients with and without diabetes. $^{18}$F-FDG PET/(CT) images were analyzed by nuclear medicine physicians, radiologists, and/or vascular surgeons.

Study quality

The QUADAS-2 scores of all included studies are shown in Figure 2. Microbiological culture of the infected graft is still considered the gold standard for confirming diagnosis of VGEI and was
used as a reference standard in all of the included studies. Proving the diagnosis by clinical or
laboratory or surgical findings was considered an inferior reference standard. The use of a
reference standard other than microbiological culture, such as follow-up, was considered to
confer a high risk of bias. Therefore, several studies scored as “high risk” of bias in the category
“flow and timing” and “reference standard.”

The general risk of bias and applicability in all studies was deemed to be low in the included
studies.27

Heterogeneity and publication bias

Heterogeneity was evaluated per assessment method and visually drawn in Figure 3. The FDG
uptake intensity method showed a heterogeneity Chi² statistic of 8.69 (p = 0.122) and an I²
statistic of 42.2% and was therefore categorized as moderate heterogeneity. The SUVmax
method had a heterogeneity Chi² statistic of 8.63 (p = 0.125) and an I² statistic of 42.1% and was
also categorized as moderate heterogeneity. The FDG pattern of uptake method had a Chi²
statistic of 8.13 (p = 0.228) and I² statistic of 26.2% and was thus categorized as negligible
heterogeneity.20

Publication bias was also evaluated per assessment method (Figure 4) by using the linear
regression method of Deeks et al. No significant publication bias was observed for any of the
imaging modalities (FDG uptake, p = 0.73; uptake pattern, p = 0.54; SUVmax, p = 0.09).

Pooled outcomes of the different assessment methods
The forest plots of the sensitivities and specificities of the different interpretation methods are shown in Figure 5, with the confidence intervals (CI) given per study. The pooled diagnostic odds ratios are shown in Figure 6.

**FDG uptake intensity.** The estimated pooled sensitivity of the FDG uptake was 0.90 (95% CI: 0.79-0.96) and the pooled specificity was 0.59 (95% CI: 0.38-0.78). The pooled diagnostic odds ratio for the FDG uptake was 10.74 (95% CI: 3.43-33.61).

**FDG uptake pattern.** The estimated pooled sensitivity of the pattern of uptake was 0.94 (95% CI: 0.89-0.97) and the pooled specificity 0.81 (95% CI: 0.71-0.88). The pooled diagnostic odds ratio was 52.37 (95% CI: 19.36-141.63).

**SUVmax.** The studies using SUVmax demonstrated an estimated pooled sensitivity of 0.95 (95% CI: 0.76-0.99) and a pooled specificity of 0.77 (95% CI: 0.63-0.87). The pooled diagnostic odds ratio was 30.86 (95% CI: 7.28-130.79).

FDG uptake intensity exhibits lower specificity, which means a higher number of false negatives. Therefore, the discriminative ability of the FDG uptake pattern and SUVmax appears superior to the FDG uptake intensity method.

**Pre- and post-test probabilities**

To interpret the value of a positive or negative test result of one of the three interpretation methods, the pre- and post-test probabilities were calculated (Figure 7). The pre-test
probabilities of all three interpretation methods are high, as the included studies comprised
patients who were already suspected of VGEI and not a random cohort of patients with a
vascular prosthesis in situ. For example, a patient suspected of VGEI had a risk of 52% of having
VGEI prior to the $^{18}$F-FDG PET(CT) using the uptake pattern interpretation method (pre-test
probability). After a positive scan, the risk of actually having VGEI is 82% (positive post-test
probability). If the test is negative, the risk of having VGEI anyway is 10% (negative post-test
probability).

The uptake pattern interpretation method had the highest positive post-test probability (82%),
followed by the SUVmax method (77%) and FDG uptake intensity method (75%). The uptake
pattern method had the lowest negative post-test probability of 10%, which corresponds with
having the highest pooled specificity (0.81) of the three interpretation methods.

**DISCUSSION**

Vascular graft and endograft infection is a severe complication, resulting in high mortality and
morbidity rates. Rapid and correct diagnosis is of utmost importance to begin optimal therapy as
quickly as possible. The diagnostic accuracy of several interpretation methods of $^{18}$F-FDG
PET(CT) in patients suspected of VGEI was evaluated.

This meta-analysis indicates that all three evaluable interpretation methods (visual FDG intensity
uptake, visual uptake pattern, and SUVmax) have a pooled sensitivity of 0.90 or higher. The
main difference was demonstrated in specificity; the pooled specificity of visual FDG uptake
intensity was the lowest (0.59) and the pooled specificity of the uptake pattern was the highest
(0.81), followed by the SUVmax method (0.77). False positives should be avoided, since this can
result in patients undergoing unnecessary invasive treatment and high-risk surgery. The post-test
probability confirmed this, as the uptake pattern method showed the highest positive post-test
probability and the lowest negative post-test probability.

Although VGS is often used as an uptake intensity interpretation method in diagnosing VGEI,
the pooled outcome demonstrated the lowest accuracy. The pattern of uptake method showed the
highest accuracy of the three interpretation methods and hence appears to have the best
discriminative ability, resulting in fewer missed diagnoses and fewer over-treated patients.

Therefore, FDG pattern of uptake should have a role in the assessment of $^{18}$F-FDG PET(CT)
and should be considered to be implemented as an interpretation criterion in future guidelines on
$^{18}$F-FDG PET(CT) assessment for VGEI.

Since only two articles were available on the TBR, this data could not be pooled and is therefore
not included in the meta-analysis.

A high risk of bias was observed regarding study quality, since several studies did not use
solitary microbiology but rather multiple reference standards. Although there is not absolute
consensus, microbiological confirmation is often regarded as the gold standard. However, most
suspected VGEI patients with a negative imaging result are assigned to follow-up. The included
retrospective studies may be characterized by bias. However, retraction of these studies did not
have a major impact on our results.
The pattern of uptake method group exhibited negligible heterogeneity among the included studies. However, moderate heterogeneity was seen in the FDG uptake intensity and SUVmax groups; therefore, the pooled diagnostic sensitivity and specificity should be interpreted with caution.

Comparing the diagnostic performance of different interpretation methods of $^{18}$F-FDG PET(CT) in suspected VGEI has its limitations. Being a rare complication, the number of patients per included study is limited. Among the included studies, no randomized controlled trials could be included. The ten included studies were all observational cohort studies, of which all but three used prospective methodology. Diagnostic test accuracy reviews often show high heterogeneity among the included studies, since patient and study characteristics differ. Fortunately, only moderate heterogeneity was seen between two groups in this meta-analysis.

Analysis of the $^{18}$F-FDG PET(CT) images was performed by several different medical specialists in the included studies. This may lead to differences in interpretation and quantification. Therefore, assessment by qualified readers of these scans, such as nuclear medicine physicians, is preferred.

Several studies were excluded because $^{18}$F-FDG PET(CT) was performed on both patients suspected and not suspected of VGEI and the results of both groups were combined. Inclusion of these studies would have led to bias in the meta-analysis. Previous reviews on this topic included the study of Berger at al, but in this study nearly half of the included patients were not suspected
Although $^{18}$F-FDG PET/(CT) is a widely used imaging technique, there are limitations in comparing studies of $^{18}$F-FDG PET/(CT) scans in patients suspected of VGEI, due to different scanning protocols. Both the dose of administered $^{18}$F-FDG and the time interval between FDG injection and acquisition varied among the included studies. Guidelines for imaging with $^{18}$F-FDG PET/(CT) scans were developed by the European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) in 2013 to provide more concordance among studies. Further, an initiative was launched by the EANM to harmonize all $^{18}$F-FDG PET/(CT) studies throughout different centers—the EANM Research Ltd (EARL). However, several of the included studies were published before the implementation of these guidelines, resulting in a lack of standardization.

Consequently, and because different vendors were used, the true positives and true negatives of the optimal SUVmax per included study were used, but the absolute value that is optimal per PET/(CT) can vary. The optimal cutoff value demonstrated good sensitivity and moderate specificity.

$^{18}$F-FDG PET/(CT) evaluation can be influenced by other factors, such as diabetes mellitus (DM) and the use of antibiotics. The included studies used different criteria. Some studies measured the glucose level before administering FGD, whereas Fukuchi et al. excluded patients with DM. The exact influence of DM on the uptake and metabolism of FDG remains unclear. However, a recent study showed no change in the number of false negatives when comparing
patients with or without DM or with high or normal serum glucose levels at the time of imaging.\textsuperscript{30}

The influence of antibiotics on the number of false-negatives is a repeatedly discussed dilemma. Due to abundant missing data, an overview of antibiotics used during imaging could not be provided. Long-term antibiotic treatment could result in an increased number of false negatives, resulting in inadequate treatment of patients with VGEI. Not only could \textsuperscript{18}F-FDG PET(/CT) as the index test be influenced by the use of antibiotics, but also the microbiological reference standard. This may lead to missing VGEI diagnosis by culture and maybe even to false positives during \textsuperscript{18}F-FDG PET(/CT) assessment. Saleem et al. found that patients with clinically suspected VGEI but negative cultures were treated with antibiotics significantly longer.\textsuperscript{23}

Since this meta-analysis supports the hypothesis that heterogeneous, focal, and high \textsuperscript{18}F-FDG uptake is associated with infection, the uptake pattern of \textsuperscript{18}F-FDG activity may help identify VGEI with higher diagnostic precision. Another tool for quantifying distribution is textural features (TF) analysis, which may provide valuable information regarding biological heterogeneity. The concept of TF analysis is generally based on the spatial arrangement of voxels in a predefined volume of interest (VOI). Spatial heterogeneity can be depicted from different spatial interrelationships on \textsuperscript{18}F-FDG PET scans. Using TF analysis for VGEI, a sensitivity of 0.80 and a specificity of 1.00 has been reported.\textsuperscript{31}

Whereas TF analysis shows promising results as an interpretation method of \textsuperscript{18}F-FDG PET(/CT) scans in patients with VGEI, the assessment method still needs to be validated in a larger group
and could therefore not be included in this meta-analysis.

CONCLUSION

This meta-analysis indicated that analyzing the pattern of uptake was the most optimal interpretation method of $^{18}$F-FDG PET/(CT) in diagnosing VGEI. FDG uptake pattern should therefore be a structured component of the $^{18}$F-FDG PET/(CT) report for the diagnosis of VGEI. A higher degree of accuracy may be achieved by combining several interpretation methods of $^{18}$F-FDG PET/(CT). Further research to assess each interpretation method separately and determine whether combining the methods leads to increased accuracy is needed. Standardization of $^{18}$F-FDG PET/(CT) assessment methods is warranted to reduce heterogeneity in future studies.
REFERENCES

1  Baddour LM, Bettmann MA, Bolger AF, Epstein AE, Ferrieri P, Gerber MA, et al. Nonvalvular Cardiovascular Device–Related Infections. Circulation 2003;108(16):2015–31.

2  Valentine RJ. Diagnosis and management of aortic graft infection. Semin Vasc Surg 2001;14(4):292–301.

3  Ben Ahmed S, Louvancourt A, Daniel G, Combe P, Chavent B, Duprey A, et al. Cryopreserved arterial allografts for in situ reconstruction of abdominal aortic native or secondary graft infection. J Vasc Surg 2018;67(2):468–77.

4  Chaufour X, Gaudric J, Goueffic Y, Khodja RH, Feugier P, Malikov S, et al. A multicenter experience with infected abdominal aortic endograft explantation. J Vasc Surg 2017;65(2):372–80.

5  Cernohorsky P, Reijnen MMPJ, Tielliu IFJ, Van Sterkenburg SMM, Van Den Dungen JJAM, Zeebregts CJ, et al. The relevance of aortic endograft prosthetic infection. J Vasc Surg 2011;34(2):521–2.

6  Lyons OTA, Baguneid M, Barwick TD, Bell RE, Foster N, Homer-Vanniasinkam S, et al. Diagnosis of Aortic Graft Infection: A Case Definition by the Management of Aortic Graft Infection Collaboration (MAGIC). Eur J Vasc Endovasc Surg 2016;52(6):758–63. Doi: 10.1016/j.ejvs.2016.09.007.

7  Li HL, Chan YC, Cheng SW. Current Evidence on Management of Aortic Stent-graft Infection: A Systematic Review and Meta-Analysis. Ann Vasc Surg 2018. Doi: 10.1016/j.avsg.2018.02.038.
Elens M, Dusoruth M, Astarci P, Mastrobuoni S, Bosiers MJ, Nardella J, et al. Management and Outcome of Prosthetic Vascular Graft Infections: A Single Center Experience. *Vasc Endovascular Surg* 2018;52(3):181–7.

Shukuzawa K, Ohki T, Maeda K, Kanaoka Y. Risk factors and treatment outcomes for stent graft infection after endovascular aortic aneurysm repair. *J Vasc Surg* 2018. Doi: 10.1016/j.jvs.2018.10.062.

Wilson WR, Bower TC, Creager MA, Amin-Hanjani S, O’Gara PT, Lockhart PB, et al. Vascular Graft Infections, Mycotic Aneurysms, and Endovascular Infections: A Scientific Statement from the American Heart Association. *Circulation* 2016. Doi: 10.1161/CIR.0000000000000457.

Schouten LRA, Verberne HJ, Bouma BJ, van Eck-Smit BLF, Mulder BJM. Surgical glue for repair of the aortic root as a possible explanation for increased F-18 FDG uptake. *J Nucl Cardiol* 2008;15(1):146–7.

Orton DF, LeVeen RF, Saigh JA, Culp WC, Fidler JL, Lynch TJ, et al. Aortic prosthetic graft infections: radiologic manifestations and implications for management. *Radiographics* 2000;20(4):977–93.

Chang C, Chang C, Shih C, Yang B, Cheng C, Chang C, et al. Added value of dual-time-point 18 F-FDG PET/CT with delayed imaging for detecting aortic graft infection. *Med (United States)* 2015;94(27):e1124.

Bruggink JLM, Slart RHJA, Pol JA, Reijnen M. MPI, Zeebregts C. J. Current role of imaging in diagnosing aortic graft infections. *Semin Vasc Surg* 2011;24(4):182–90.

Reinders Folmer EI, Von Meijenfeldt GCI, Van der Laan MJ, Glaudemans AWJM, Slart RHJA, Saleem BR, et al. Diagnostic Imaging in Vascular Graft Infection: A Systematic
Review and Meta-Analysis. *Eur J Vasc Endovasc Surg* 2018;**56**(5):719–29.

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2016;**20**(2):148–60.

Deeks J, Wisniewski S, Davenport C. Guide to the contents of a Cochrane Diagnostic Test Accuracy Protocol. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0.0. 2013. pp. 1–15.

Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;**155**(8):529–36.

The Nordic Cochrane Centre. Review Manager. *Cochrane Collab* 2014:1–43.

Higgins JPT, Green S, (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2011.

Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol* 2005;**58**(9):882–93.

StataCorp. Stata Statistical Software: Release 13. *2013* 2013.

Saleem BR, Berger P, Vaartjes I, De Keizer B, Vonken EJPA, Slart RHJA, et al. Modest utility of quantitative measures in 18F-fluorodeoxyglucose positron emission tomography scanning for the diagnosis of aortic prosthetic graft infection. *J Vasc Surg* 2015;**61**(4):965–71.

Zogala D, Rucka D, Ptacnik V, Cerny V, Trnka J, Varejka P, et al. How to recognize stent graft infection after endovascular aortic repair: the utility of 18F-FDG PET/CT in an
infrequent but serious clinical setting. *Ann Nucl Med* 2019;33(8):594–605. Doi: 10.1007/s12149-019-01370-9.

25 Bruggink JLM, Glaudemans AWJM, Saleem BR, Meerwaldt R, Alkefaji H, Prins TR, et al. Accuracy of FDG-PETeCT in the diagnostic work-up of vascular prosthetic graft infection. *Eur J Vasc Endovasc Surg* 2010;40(3):348–54.

26 Sah BR, Husmann L, Mayer D, Scherrer A, Rancic Z, Puippe G, et al. Diagnostic performance of 18F-FDG-PET/CT in vascular graft infections. *Eur J Vasc Endovasc Surg* 2015;49(4):455–64.

27 Mitra A, Pencharz D, Davis M, Wagner T. Determining the Diagnostic Value of 18F-Fluorodeoxyglucose Positron Emission/Computed Tomography in Detecting Prosthetic Aortic Graft Infection. *Ann Vasc Surg* 2018;53:78–85.

28 Bowles H, Ambrosioni J, Mestres G, Hernández-Meneses M, Sánchez N, Llopis J, et al. Diagnostic yield of 18F-FDG PET/CT in suspected diagnosis of vascular graft infection: A prospective cohort study. *J Nucl Cardiol* 2018;25:1–9.

29 Fukuchi K, Ishida Y, Higashi M, Tsunekawa T, Ogino H, Minatoya K, et al. Detection of aortic graft infection by fluorodeoxyglucose positron emission tomography: Comparison with computed tomographic findings. *J Vasc Surg* 2005;42(5):919–25.

30 Rabkin Z, Israel O, Keidar Z. Do Hyperglycemia and Diabetes Affect the Incidence of False-Negative 18F-FDG PET/CT Studies in Patients Evaluated for Infection or Inflammation and Cancer? A Comparative Analysis. *J Nucl Med* 2010;51(7):1015–20.

31 Saleem BR, Beukinga RJ, Boellaard R, Glaudemans AWJM, Reijnen MMPJ, Zeebregts CJ, et al. Textural features of 18F-fluorodeoxyglucose positron emission tomography scanning in diagnosing aortic prosthetic graft infection. *Eur J Nucl Med Mol Imaging*
2017;44(5):886–94.
| Author               | Study design     | Study size             | Grafts                                      | PET/(CT) assessment method       | Reference standard                                      |
|----------------------|------------------|------------------------|---------------------------------------------|----------------------------------|--------------------------------------------------------|
| Fukuchi et al. (2005)| Prospective cohort | 33 patients            | Aortic (thoracic / abdominal)               | FDG uptake intensity (VGS)       | Microbiological and surgical findings                   |
|                      |                  |                        |                                             |                                  | Follow-up > 4 months                                    |
| Keidar et al. (2007) | Prospective cohort | 39 patients 40 grafts | Aortic (abdominal), peripheral and axillofemoral | Uptake pattern                  | Microbiological (surgery) and histopathological (surgery) findings |
|                      |                  |                        |                                             |                                  | Follow-up > 12 months                                   |
| Spacek et al. (2009) | Prospective cohort | 69 patients 96 grafts | Aortic and peripheral                       | Uptake pattern                  | Microbiological (surgery), histopathological (surgery) and surgical findings |
|                      |                  |                        |                                             |                                  | Follow-up > 6 months                                   |
| Bruggink et al. (2010)| Prospective cohort | 25 patients            | Aortic (thoracic / abdominal) and peripheral | FDG uptake intensity (VGS)       | Microbiological findings (culture graft or culture perigraft fluid) |
| Karaca et al. (2014) | Retrospective cohort | 17 patients            | Aortic (abdominal) and peripheral           | Uptake pattern                  | Microbiological (surgery) and histopathological (surgery) findings |
|                      |                  |                        |                                             |                                  | Follow-up > 36 months                                   |
| Chang et al. (2015)  | Prospective cohort | 29 patients            | Aortic (thoracic / abdominal)               | SUVmax                           | Microbiological (surgery or image-guided drainage) and surgical findings |
|                      |                  |                        |                                             |                                  | Follow-up > 11 months                                   |
| Sah et al. (2015)    | Prospective cohort | 34 patients            | Aortic (thoracic / abdominal)               | FDG uptake intensity (VGS)       | Microbiological (culture graft or culture perigraft tissue (surgery)), clinical, laboratory and histopathological findings |
|                      |                  |                        |                                             |                                  | Follow-up > 11 months                                   |
| Saleem et al. (2015) | Prospective cohort | 37 patients            | Aortic (thoracic / abdominal)               | FDG uptake intensity (VGS)       | Microbiological findings (surgery / percutaneous)       |
|                      |                  |                        |                                             |                                  | SUVmax                                                  |
| Bowles et al. (2018) | Prospective cohort | 49 patients            | Aortic (thoracic/abdominal) and peripheral | Uptake pattern                  | Microbiological, surgical, radiologic and clinical findings |
|                      |                  |                        |                                             |                                  | Follow-up > 6 months                                   |
| Mitra et al. (2018)  | Prospective cohort | 21 patients            | Aortic (thoracic/abdominal)                | SUVmax                           | Microbiological findings (culture graft or culture perigraft fluid) |
| Husmann             | Prospective      | 23                     | Aortic                                     | Uptake pattern                  | Microbiological findings                               |
| Authors          | Study Type          | Patients | Imaging Parameters | Follow-up                                                                 |
|------------------|---------------------|----------|-------------------|--------------------------------------------------------------------------|
| et al. (2019)    | Retrospective cohort| 39 patients 96 grafts | SUVmax (combined with clinical, laboratory, histopathological and imaging results) | Follow-up > 12 months |
| Puges et al. (2019) | Retrospective cohort | 16 patients 25 grafts | Aortic (abdominal) | FDG uptake intensity (VGS) Microbiological, clinical and paraclinical findings Follow-up > 12 months |
| Zogala et al. (2019) | Retrospective cohort | 16 patients 25 grafts | Aortic (abdominal) | FDG uptake intensity (VGS) Uptake pattern SUVmax TB-ratio Clinical and laboratory findings, conventional imaging results, microbiological cultures and perioperative findings Follow-up > 5 months |

Computerized Tomography, PET = Positron Emission Tomography, SUVmax = Maximum standard uptake value, TB-ratio = Tissue to background ratio, VGS = visual grading scale
Figure 1 PRISMA flow diagram of study selection

- Records identified through database searching (n = 805)
- Additional records identified through other sources (n = 0)
- Records after duplicates removed (n = 613)
- Records screened (n = 613)
- Records excluded (n = 560)
- Full-text articles assessed for eligibility (n = 53)
- Studies included in qualitative synthesis
- Studies included in quantitative synthesis (meta-analysis) (n = 13)

Full-text articles excluded, with reasons (n = 40)
- Only abstract available (20)
- Study design (review) (6)
- Different endpoints (5)
- Overlapping data (2)
- Full text not available (1)
- < 5 patients (6)
Figure 2 QUADAS-2 tool for quality assessment of the included studies for risk of bias and applicability concerns.
Figure 3 Hierarchical summary receiver operating characteristics (HSROC) per assessment method

a. FDG uptake intensity

b. SUVmax

c. FDG uptake pattern
Figure 4  Deeks’ Funnel Plot Asymmetry test for publication bias
Figure 5  Forest plots of the sensitivities and specificities per assessment method

### a. FDG uptake intensity

| Study            | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|------------------|----|----|----|----|----------------------|----------------------|
| 2005 Fukuchi et al. | 11 | 8  | 0  | 14 | 1.00 [0.72, 1.00]    | 0.64 [0.41, 0.83]    |
| 2010 Bruggink et al. | 12 | 4  | 3  | 6  | 0.80 [0.52, 0.96]    | 0.60 [0.26, 0.88]    |
| 2015 Sah et al.    | 27 | 1  | 0  | 6  | 1.00 [0.87, 1.00]    | 0.86 [0.42, 1.00]    |
| 2015 Saleem et al. | 18 | 6  | 3  | 10 | 0.86 [0.64, 0.97]    | 0.63 [0.35, 0.85]    |
| 2019 Puges et al.  | 16 | 24 | 3  | 53 | 0.84 [0.60, 0.97]    | 0.69 [0.57, 0.79]    |
| 2019 Zogala et al. | 8  | 8  | 1  | 0  | 0.89 [0.52, 1.00]    | 0.00 [0.00, 0.37]    |

### b. SUVmax

| Study            | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|------------------|----|----|----|----|----------------------|----------------------|
| 2015 Chang et al. | 5  | 5  | 0  | 19 | 1.00 [0.48, 1.00]    | 0.79 [0.58, 0.93]    |
| 2015 Sah et al.   | 27 | 1  | 0  | 27 | 1.00 [0.87, 1.00]    | 0.96 [0.82, 1.00]    |
| 2015 Saleem et al.| 14 | 5  | 7  | 14 | 0.67 [0.43, 0.85]    | 0.74 [0.49, 0.91]    |
| 2018 Mitra et al. | 12 | 1  | 1  | 7  | 0.92 [0.64, 1.00]    | 0.88 [0.47, 1.00]    |
| 2019 Husmann et al.| 13 | 5  | 0  | 5  | 1.00 [0.75, 1.00]    | 0.50 [0.19, 0.81]    |
| 2019 Zogala et al.| 8  | 0  | 1  | 8  | 0.89 [0.52, 1.00]    | 1.00 [0.63, 1.00]    |

### c. FDG uptake pattern

| Study            | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|------------------|----|----|----|----|----------------------|----------------------|
| 2005 Fukuchi et al. | 10 | 1  | 1  | 21 | 0.91 [0.59, 1.00]    | 0.95 [0.77, 1.00]    |
| 2007 Keidar et al. | 14 | 2  | 1  | 22 | 0.93 [0.68, 1.00]    | 0.92 [0.73, 0.99]    |
| 2009 Spacek et al.| 54 | 10 | 1  | 31 | 0.80 [0.80, 1.00]    | 0.76 [0.60, 0.88]    |
| 2015 Sah et al.   | 26 | 1  | 1  | 6  | 0.96 [0.61, 1.00]    | 0.86 [0.42, 1.00]    |
| 2015 Saleem et al.| 18 | 6  | 3  | 10 | 0.86 [0.64, 0.97]    | 0.63 [0.35, 0.85]    |
| 2018 Bowles et al.| 14 | 7  | 2  | 26 | 0.80 [0.62, 0.98]    | 0.79 [0.61, 0.81]    |
| 2018 Karaca et al.| 12 | 2  | 0  | 3  | 1.00 [0.74, 1.00]    | 0.60 [0.15, 0.95]    |
Figure 6  Pooled diagnostic risk ratios per imaging modality

a. FDG uptake intensity

b. SUV max

c. FDG uptake pattern
Figure 7 Pre- and post-test probabilities per assessment method

![Graph showing pre- and post-test probabilities per assessment method.](image)
Supplement 1  Search strategy for PubMed, Embase and Cochrane on October 15th 2019

PubMed:
("Blood Vessels"[Mesh] OR blood vessel* [tiab] OR vascular*[tiab] OR aort*[tiab])
AND
("Vascular Grafting"[Mesh] OR "Blood Vessel Prosthesis"[Mesh] OR graft* [tiab] OR prosthesis[tiab] OR prosthet* [tiab])
AND
("Bacterial Infections and Mycoses"[Mesh] OR infect* [tiab] OR q fever* [tiab] OR q-fever* [tiab])
AND
("Positron-Emission Tomography"[Mesh] OR Positron-Emission Tomograph*[tiab] OR Positron Emission Tomograph*[tiab] OR pet* [tiab] OR "Fluorodeoxyglucose F18"[Mesh] OR Fluorodeoxyglucose F18 [tiab] OR fluor-18-deoxyglucose [tiab] OR 18f-fdg [tiab] OR fdg [tiab] OR 18fdg [tiab])

Embase:
('blood vessel'/exp OR 'blood vessel':ab,ti OR vascular*:ab,ti OR aort*:ab,ti)
AND
('blood vessel graft'/exp OR 'blood vessel prosthesis'/exp OR graft*:ab,ti OR prosthesis:ab,ti OR prosthet*:ab,ti)
AND
('infection'/exp OR 'q fever':ab,ti OR 'q-fever':ab,ti)
AND
('positron emission tomography'/exp OR 'positron emission tomograph*':ab,ti OR 'positron-emission tomograph*':ab,ti OR 'fluorodeoxyglucose f 18'/exp OR 'Fluorodeoxyglucose F18':ab,ti OR 'fluor-18-deoxyglucose':ab,ti OR '18f-fdg':ab,ti OR fdg:ab,ti OR 18fdg:ab,ti)

Cochrane
(blood vessel OR vascular*OR aort*)
AND
(graft* OR prosthesis OR prosthet*)
AND
(infect* OR q fever* OR q-fever* )
AND
(positron emission tomograph* OR positron-emission tomograph* OR pet* OR Fluorodeoxyglucose F18 OR fluor-18-deoxyglucose OR 18f-fdg OR fdg OR 18fdg)
### Supplement 2  PET characteristics

| Author          | PET/CT (CT)                                                                 | FDG dose                                                                 | Time interval between FDG administration and scan | Glucose level                                                                 | Readers                                      |
|-----------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------|
| Fukuchi et al.  | ECAT EXACT 47 (Siemens / CTI)                                                | iv injection, 185 MBq                                                   | Scan 60 min after suppletion                     | Patients with DM excluded. 5hrs Fasting before scan.                           | 1 NMPs blinded for previous imaging.         |
| Keidar et al.   | PET/CT (Discovery LS; GE healthcare) a full ring PET with bismuth germanate crystals + 3th generation multislice spiral CT | iv injection, 185-370 MBq                                              | Scan 90 min after suppletion                     | Glucose was measured, no patients removed because of high blood glucose levels. Patients with DM not excluded, normal schedule. 4-6hrs Fasting before scan except glucose-free oral hydration. | 1 NMP, 1 radiologist, 1 vascular surgeon, not blinded for clinical or previous imaging. |
| Spacek et al.   | PET/CT scanner Biograph Duo LSO (Siemens)                                   | iv injection, 256-565 MBq (bodyweight adapted)                          | Scan 40-151 min after suppletion                 | 6hrs Fasting before scan.                                                     | 1 radiologist, blinded for clinical or other diagnostic status. |
| Bruggink et al. | 3D ECAT + scanner (Siemens)                                                   | iv injection, 5 MBq/kg                                                  | Scan 60 min after suppletion                     | Fasted, free access to noncaloric drinks.                                     | 2 independent NMPs, blinded for CTA.         |
| Karaca et al.   | Hybrid PET-CT system (Biograph Sensation 16, Siemens/CTI)                   | iv injection, 7.5 MBq/kg                                                | Scan 45-60 min after suppletion                  | 6hrs Fasting before scan.                                                     | 1 NMP and 1 vascular surgeon.               |
| Chang et al.    | 64-slice PET/CT scanner (GE Healthcare, Waukesha, WI, USA)                  | iv injection, 370 MBq                                                   | Scan 45-60 min after suppletion                  | 6hrs Fasting, glucose of all patients < 8 mmol/l.                             | 2 NMPs, blindly and independently.          |
| Sah et al.      | Integrated PET/CT scanner (Discovery VCT; GE healthcare)                    | Bodyweight adapted                                                     | Scan 60 min after suppletion                     | Glucose ≤8 mmol/l for patients without DM, glucose ≤12 mmol/l for patients with DM. No insulin 4hr prior to scan. 4hrs Fasting before scan. | 2 independent NMPs, blinded for clinical patient data. |
| Saleem et al.   | Philips Allegro PET scanner (Philips Medical Systems) and Biograph mCT scanner (Siemens) | iv injection, 2-3.7 MBq/kg                                              | Scan 60 min after suppletion                     | Glucose measured before scan but not reported. 6hrs Fasting before scan except glucose-free oral hydration. | 2 independent NMPs, blinded for clinical and CTA data. |
| Bowles et al.   | Hybrid PET/CT (SIEMENS Biograph mCT 64S)                                    | iv injection, 4.07 MBq/kg                                               | Scan 60 min after suppletion                     | Glucose levels < 140 mg/dl. 6hrs Fasting before scan.                         | 2 NMPs, disagreements settled by third NMPs. |
| Mitra et al.    | Siemens Biograph PET/CT scanner                                              | iv injection, 370 MBq                                                   | Scan 60 min after suppletion                     | Patients with DM not excluded. 6hrs Fasting before scan (4hrs for type 1 diabetics) | 2 NMPs, independently.                      |
| Husmann et al.  | Discovery VCT (GE Healthcare)/ Discovery MI (GE Healthcare)                 | iv injection, bodyweight adapted                                        | Scan 60 min after suppletion                     | Glucose ≤8 mmol/l for patients without DM, glucose ≤11 mmol/l for patients with DM. No insulin 4hr prior to scan. 4hrs Fasting before scan. | 2 radiologists/NMPs, independently.         |
| Puges et al.    | Integrated PET/CT scanner                                                   | iv injection, bodyweight                                               | Scan 60 min after suppletion                     | Glucose levels < 11 mmol/l.                                                   | 2 NMPs, independently.                      |
| Study | Equipment | Injection Type | Time After Supplementation | Fasting Requirement | NMPs |
|-------|-----------|----------------|---------------------------|-------------------|------|
| Zogala et al. | Integrated PET/CT system (Discovery 690, GE Healthcare) | IV injection, 4.5 MBq/kg of body weight | 64–100 min after supplementation | 6hrs Fasting before scan | 2 NMPs, independently |

CT = Computerized Tomography, PET = Positron Emission Tomography, NMP = nuclear medicine physician
Figure/Table Legends

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Table 1 Study characteristics of the included studies