

SYSTEMATIC REVIEW

Molecular Imaging of Abdominal Aortic Aneurysms with Positron Emission Tomography: A Systematic Review

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WHAT THIS PAPER ADDS

This systematic review summarises the prognostic value of positron emission tomography (PET) with different tracers, including ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) and ¹⁸F-sodium fluoride (¹⁸F-NaF), in abdominal aortic aneurysms (AAA). As current findings on this topic are inconsistent, it is difficult to provide guidance for clinical decision making. Further study should be carried out on how useful PET imaging data are as clinical markers of aneurysm growth and rupture. In addition, more tracers with high sensitivity and specificity are needed, while tracers such as the ¹⁸F-NaF uptake may be a promising predictor for the clinical outcomes of AAA patients.

Objective: Previous studies on the relationship between positron emission tomography (PET) images and abdominal aortic aneurysm (AAA) progression have shown contradictory results, and the objective of this study was to systematically review the role of PET in predicting AAA prognosis.

Data Sources: PubMed, Embase, and Web of Science were searched for studies evaluating the correlation between PET imaging results and AAA growth, repair, or rupture.

Review Methods: Two authors independently performed the study search, data extraction, and quality assessment following a standard method.

Results: Of the 11 studies included in this review, nine used ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET and computed tomography (CT) imaging, whereas the remaining two used ¹⁸F-sodium fluoride (¹⁸F-NaF) PET/CT and ¹⁸F-FDG PET/magnetic resonance imaging (MRI). Findings from the ¹⁸F-FDG PET/CT studies were contradictory. Six studies found no significant association or correlation, and two studies found a significant negative correlation between ¹⁸F-FDG uptake and AAA expansion. Additionally, one study found that the ¹⁸F-FDG uptake was statistically positively related to the expansion rate in a specific AAA subgroup whose AAAs expanded significantly. Two studies suggested that increased ¹⁸F-FDG uptake was significantly associated with AAA repair, while the other studies either found no association between ¹⁸F-FDG uptake and AAA rupture or repair or failed to report the occurrence of clinical events. One PET/CT study that used ¹⁸F-NaF as a tracer showed that an increased tracer uptake was significantly associated with AAA growth and clinical events. Finally, the ¹⁸F-FDG PET/MRI study indicated that ¹⁸F-FDG uptake was not significantly correlated with AAA expansion.

Conclusion: A definitive role for ¹⁸F-FDG PET imaging for AAA prognosis awaits further investigation, and new PET tracers such as ¹⁸F-NaF have the potential to be a promising method for predicting AAA clinical outcomes.

Keywords: Abdominal aortic aneurysm, Positron emission tomography, Systematic review

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INTRODUCTION

Although the prevalence of abdominal aortic aneurysms (AAAs) in subjects over 60 years of age has decreased to 1.2% to 3.3% over the last few decades,^{1–4} it has increased among the more elderly population.⁵ AAAs expand progressively with variable rate, and rupture is the most feared complication, with an incidence of approximately 1% – 5% per year in patients with AAA.^{6,7} Ruptured AAAs have a mortality rate of 81%,⁸ with the majority of patients dying before reaching the hospital and a small percentage arriving in time for emergency repair.^{9,10} Elective repair, the most efficient approach in AAA expansion and rupture prevention, is most often implemented based on AAA diameter (≥ 5.5 cm),^{11,12} expansion rate (>1 cm/year),^{12,13} and symptoms. Of these, aneurysm size is the strongest predictor,^{12,14} and the greater the baseline diameter, the greater the risk of expansion or rupture.^{15,16} However, a proportion of patients with smaller aneurysms (<5.5 cm) also experience rupture,¹⁷ and many patients with larger aneurysms never rupture.^{2,11,18–20} Therefore, it is critical to develop more reliable non-invasive predictors to better identify patients at risk of AAA expansion or rupture.

Chronic inflammation followed by arterial wall proteolysis is believed to play a pivotal role in AAA formation and progression.^{21–23} Novel molecular and cellular imaging techniques that evaluate the inflammatory progress of AAAs have been developed to predict prognosis and provide predictive markers of clinical progression.²⁴ However, none have been used in practice due to a lack of substantial evidence on their effectiveness. Positron emission

tomography (PET), an imaging modality targeting molecular elements of the inflammatory process, including focally increased glucose metabolism and arterial wall microcalcification by means of ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) and ¹⁸F-sodium fluoride (¹⁸F-NaF), respectively,^{25,26} has been used to evaluate a variety of inflammatory conditions including vascular diseases.²⁷ As there is no consensus on the relationship between the PET tracer uptake and AAA expansion or clinical outcomes, a systematic review was conducted to determine the role of PET in predicting the prognosis of AAA.

MATERIALS AND METHODS

Protocol registration

This study was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)²⁸ and a guide on the systematic review and meta-analysis of prognostic factor studies.²⁹ It has been registered on PROSPERO under the registration number CRD42020200055.

Search strategy and selection

PubMed, Embase, and Web of Science were searched for articles published up to 26 October 2020. The search strategies consisted of medical subject headings and text words for abdominal aortic aneurysm, PET, computed tomography (CT), and magnetic resonance imaging (MRI). The detailed search strategies are listed in [Appendix S1](#). Additionally, the

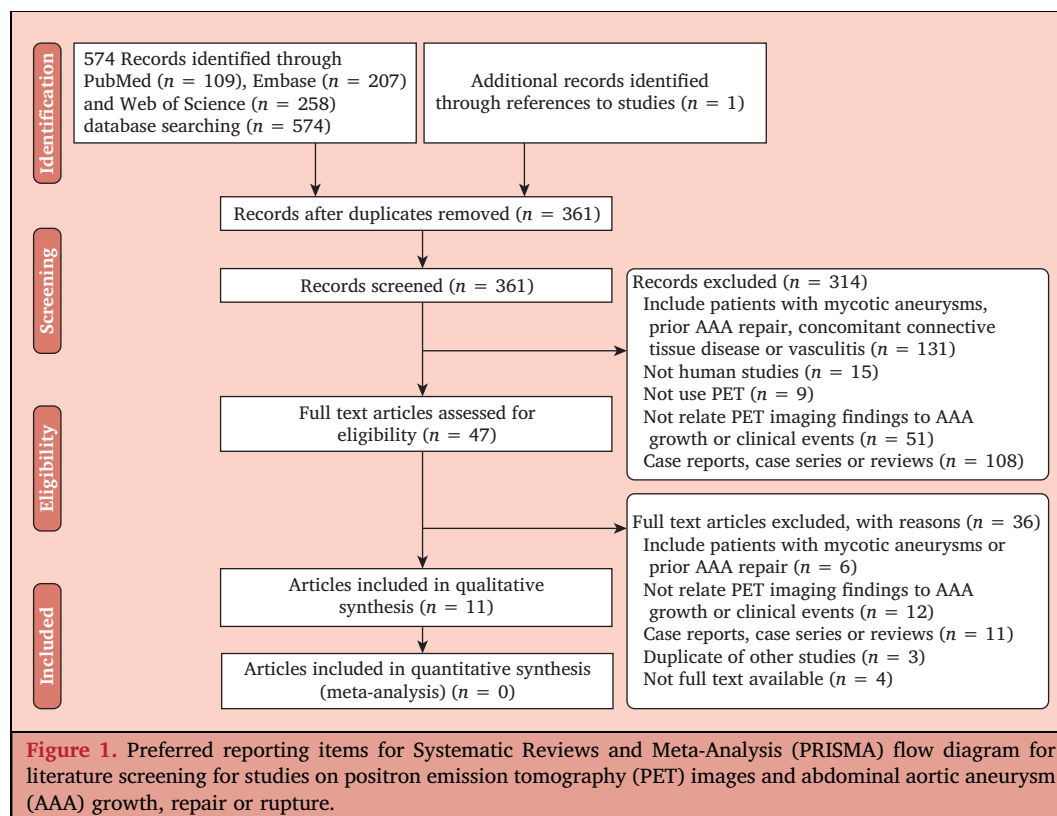


Table 1. The characteristics of 11 studies on positron emission tomography (PET) images and abdominal aortic aneurysm (AAA) growth, repair or rupture

| Author year | Region | Study design | Sample size – n | Imaging outcomes | Follow up time* |
|------------------------------|-------------|---------------------------------------|--------------------|--|-----------------|
| Kuzniar ³³ 2020 | Sweden | Prospective cohort study | 15 | SUV _{max} , TBR _{max} , SUV _{mean} , TBR _{mean} | 12 mo |
| Lee ³⁴ 2018 | South Korea | Retrospective cohort study | 37 | TBR _{max} | 1243 ± 789 d |
| Forsythe ³⁵ 2018 | UK | Prospective cohort study | 72 | TBR _{max} , MDS TBR _{max} , SUV _{max} , corrected SUV _{max} | 510 ± 196 d |
| Morel ³⁶ 2015 | France | Prospective cohort study | 39 | SUV _{max} whole vessel, TBR _{max} | 9 mo |
| Nchimi ³⁷ 2014 | Belgium | Prospective cohort study [†] | 47 | TBR _{max} , SUV _{RL} , SUV _{RV} | 11.4 ± 8.6 mo |
| Kotze ³⁸ 2014 | UK | Prospective cohort study | 40 | SUV _{max} whole vessel, SUV _{max} single site, TBR _{max} | 12 mo |
| Barwick ³⁹ 2014 | UK | Retrospective cohort study | 151 | SUV _{max} whole vessel, TBR _{max} | 18 (8–35) mo |
| Courtois ⁴⁰ 2013 | Belgium | Prospective cohort study [†] | 18 | rSUV, SUV _{max} | NR |
| Kotze ⁴¹ 2009 | UK | Prospective cohort study [†] | 14 | SUV _{max} | 12 mo |
| Reeps ⁴² 2008 | Germany | Prospective cohort study [†] | 15 | SUV _{max} | NR |
| Sakalihan ⁴³ 2002 | Belgium | Cohort study | 26 | ¹⁸ F-FDG uptake (positive or negative) | NR |

SUV_{max} = maximum standardised uptake value; TBR_{max} = maximum target to background ratio; SUV_{RL} = SUV to liver; SUV_{RV} = SUV to venous background; rSUV = aortic SUV_{max}/liver SUV_{max}; MDS = most diseased segment; ¹⁸F-FDG = ¹⁸F-fluorodeoxyglucose; NR = not reported; SUV_{mean} = mean standardised uptake value; TBR_{mean} = mean target to background ratio.

* Presented as mean ± standard deviation or median (interquartile).

† Prospective cohort study with retrospective growth data

references of all selected studies were checked to improve the documented detection rate.

Studies that enrolled adult patients with AAAs and analysed PET in conjunction with CT or MRI imaging to evaluate the molecular characteristics of AAA were included. Studies with insufficient data on the relationship between PET imaging findings and AAA expansion, rupture, or repair; studies that included patients with mycotic aneurysms, prior AAA repair, concomitant connective tissue disease, or vasculitis; and case reports, case series, and reviews were excluded. Two investigators (BL.G and C.C.) independently selected the eligible literature, and any conflicts were resolved by a third investigator (DQ.G or WG.F).

Data extraction

Data from eligible studies were independently abstracted by two researchers (BL.G. and C.C.) using a pre-designed data extraction template, and any disagreements were resolved by discussion or assistance provided by DQ.G. or WG.F. The data extraction template included three parts: (1) study characteristics including author(s), year of publication, study design, inclusion and exclusion criteria, sample size; (2) patient characteristics including age, sex, follow up time, PET imaging techniques, method of measuring tracer uptake, and AAA clinical outcome; (3) PET imaging results, patient clinical outcomes, and the relationship between them.

Risk of bias assessment

The Quality in Prognosis Studies (QUIPS) tool^{30,31} was applied independently by BL.G. and C.C. to assess the risk of bias in the included studies. The tool consists of six domains including study participation, study attrition, prognostic factor measurement, outcome measurement, study

confounding and statistical analysis, and risk of bias can be rated as high, moderate, or low. Studies with ≥5 low risk domains and ≥2 high risk domains were judged as having an overall low and high risk of bias, respectively, and the remaining studies were assessed as having an overall moderate risk of bias.³²

RESULTS

The initial search resulted in 361 articles after duplicates were removed, of which 47 were selected for full text review. Ultimately, a total of 11 articles were retained and included in this review.^{33–43} The study selection process is presented as a PRISMA flow diagram in Figure 1.

Of the 11 studies, four studies^{33,35,36,38} were prospective, four^{37,40–42} were prospective but included retrospective growth data, two^{34,39} were retrospective, and one⁴³ did not clarify its design. Sample sizes ranged from 14 to 151 participants, giving a total sample size of 508 individuals. The proportion of male participants was 91% and the mean or median age ranged from 68 to 78 years. Nine^{33,35,36,38–43} of the 11 studies described AAA baseline diameter, with mean or median values between 4.6 and 6.3 cm. As their imaging analysis approach, nine^{34,36–43} studies used ¹⁸F-FDG PET/CT, one³¹ used ¹⁸F-NaF PET/CT, and one²⁹ used ¹⁸F-FDG PET/MRI. Five^{33,36,37,39,40} of the 10 studies that used ¹⁸F-FDG as a tracer in this review reported pre-scan blood glucose levels: three^{36,37,39} reported that the level varied from 150 to 216 mg/dL, while the other two^{33,40} stated that all patients were within the normal range. The applied injection to scan time interval between the ¹⁸F-FDG injection and PET image acquisition varied from 60 to 180 minutes among the studies included in this review (five studies^{34,35,37,40,43} used 60 minutes, three^{36,39,42} used 90 minutes, and three^{33,38,41} used 180 minutes). Half of these studies^{33,35,36,38,39} used both maximum standard uptake values (SUV_{max}) and

maximum tissue to background ratios (TBR_{max}) as indices of accumulation and metabolic activity of PET tracers in the aortic wall, and five studies selected SUV_{max} ^{41,42} rSUV (AAA/liver),⁴⁰ or TBR_{max} .^{34,37} The remaining study⁴³ did not specify which measurement was used. SUV_{max} , which is calculated as decay corrected tissue radioactivity divided by body weight and injected dose, is a common and validated measure of tissue radiotracer uptake. rSUV is calculated by dividing the aortic SUV_{max} by liver SUV_{max} , while TBR_{max} is calculated by dividing the aortic SUV_{max} by the blood pool SUV. SUV_{max} , rSUV, and TBR_{max} are all dimensionless units, and a higher value suggests higher metabolic activity. All but one study³⁴ came from European countries. Characteristics of the included studies, the AAA patients evaluated, and the imaging techniques used are summarised in Tables 1 – 3 and Supplementary Table S1.

Positron emission tomography imaging and abdominal aortic aneurysm outcomes

Ten studies^{33–38,41–43} investigated the relationship between PET tracer uptake level and AAA expansion. Of these, five^{33,34,38,41,42} related the PET imaging results to multiple AAA growth measurements over a follow up period ranging

from nine to 41 months, and five^{35–37,40,43} reported the association between PET imaging results and AAA diameter at one follow up time point. Five studies used ultrasound (US)^{33,35,38,40,41} to measure growth, and the rest used PET/CT,^{34,37} CT,^{34,38,43} or CT angiography (CTA).³⁶ Additionally, one study⁴² did not state the techniques used for diameter measurement. Of the 11 included studies, five^{34,36,39,41,42} measured the maximum transverse aneurysm diameter, two^{35,38} the maximum anteroposterior diameter, and four^{33,37,40,43} did not specify how the diameter was measured. Furthermore, only three studies^{36,38,39} specified that they had measured the external diameter.

Five studies^{34,35,37,39,43} described the relationship between PET/CT imaging results and the occurrence of AAA clinical events including rupture or repair during follow up, and clinical events occurred in all but one study.³⁷ The key results of all studies are shown in Table 4.

¹⁸F-Fluorodeoxyglucose positron emission tomography/computed tomography

Seven studies^{34,36–38,41–43} used PET/CT to investigate ¹⁸F-FDG uptake as a predictor of metabolic activity in AAA progress. Five studies^{34,37,41–43} found no significant

Table 2. The characteristics of patients enrolled in the 11 studies on positron emission tomography images and abdominal aortic aneurysm (AAA) progression

| Author year | Age – y* | Male | AAA baseline diameter – mm* | Symptomatic AAA | Smoking history | HBP | DM | IHD | APT | Statin |
|------------------------------|---|----------|---|-----------------|-----------------|---------|---------|---------|---------|---------|
| Kuzniar ³³ 2020 | 73 (71–75) | 15 (100) | 54.0 (52.0–62.0) | 0 (0) | 14 (93) | 13 (87) | 1 (7) | 7 (47) | 9 (60) | 10 (67) |
| Lee ³⁴ 2018 | 72 ± 9 | 31 (84) | NR | NR | NR | NR | NR | NR | NR | NR |
| Forsythe ³⁵ 2018 | 73 ± 7 | 61 (85) | 48.8 ± 7.7 | 0 (0) | 67 (93) | 47 (65) | 22 (31) | 22 (31) | 51 (71) | 58 (81) |
| Morel ³⁶ 2015 | 71 ± 12 | 37 (95) | 46.0 ± 3.4 | 0 (0) | 37 (95) | 22 (56) | 5 (13) | 15 (38) | 32 (82) | 28 (72) |
| Nchimi ³⁷ 2014 | 72 ± 8 | 45 (96) | NR | NR | 43 (91) | 32 (68) | 11 (23) | 37 (79) | NR | NR |
| Kotze ³⁸ 2014 | 74 (60–85) | 36 (90) | 49.5 (43.0–53.0) [†] / 51.0 (41.0–55.8) [‡] | 0 (0) | 22 (55) | 31 (78) | 4 (10) | 12 (30) | NR | 28 (70) |
| Barwick ³⁹ 2014 | 74 ± 7 | 123 (81) | 50.0±13.2 | 0 (0) | NR | 77 (51) | 13 (9) | NR | NR | 54 (36) |
| Courtois ⁴⁰ 2013 | 75 (71–80) [§] / 78 (69–81) | 16 (89) | 54.5 (52.8–59.5) [§] / 58.5 (55.3–69.3) | 1 (6) | 6 (33) | 12 (67) | 1 (6) | 8 (44) | NR | 12 (67) |
| Kotze ⁴¹ 2009 | 74 (61–82) | 14 (100) | 54.0 ± 8.0 | 1 (7) | 6 (43) | 6 (43) | 1 (7) | 2 (14) | 6 (43) | 6 (43) |
| Reeps ⁴² 2008 | 68 ± 5 | 13 (87) | 54.0 ± 8.0 [¶] / 59.0 ± 11.0 ^{**} | 12 (80) | 12 (80) | 14 (93) | 6 (40) | 8 (53) | 13 (87) | 6 (40) |
| Sakalihan ⁴³ 2002 | 72 (56–85) | 23 (88) | 63.0 (45.0–78.0) | 11 (42) | NR | NR | NR | NR | NR | NR |

Data are presented as n (%) unless stated otherwise.

HBP = hypertension; DM, diabetes mellitus; IHD = ischaemic heart disease; APT = antiplatelet therapy; NR, not report.

* Presented as mean ± standard deviation, median (interquartile), median (range), or mean (range).

† Measured by ultrasound.

‡ Measured by computerised tomography.

§ Positive tracer uptake.

|| No tracer uptake.

¶ Asymptomatic abdominal aortic aneurysm.

** Symptomatic abdominal aortic aneurysm.

Table 3. The characteristics of imaging technique used in the 11 studies on positron emission tomography (PET) images and abdominal aortic aneurysm progression

| Author year | Imaging technique | Pre-scan blood glucose level* | Injection to scan time – min | Imaging frequency | Diameter measurement technique | Diameter measurement frequency |
|------------------------------|-----------------------------|-------------------------------|------------------------------|-------------------------|--------------------------------|---|
| Kuzniar ³³ 2020 | ¹⁸ F-FDG PET/MRI | Within normal limits | 180 | ×1 | US | ×2: Baseline and follow up |
| Lee ³⁴ 2018 | ¹⁸ F-FDG PET/CT | NR | 60 | ×2.1 ± 1.1 [†] | PET/CT or CT | Unclear: Baseline and follow up |
| Forsythe ³⁵ 2018 | ¹⁸ F-NaF PET/CT | NA | 60 | ×1 | US | ×2: Baseline and the last examination |
| Morel ³⁶ 2015 | ¹⁸ F-FDG PET/CT | <150 mg/dL | 90 | ×2 (baseline and 9 mo) | CTA | ×2: Baseline and 9 mo |
| Nchimi ³⁷ 2014 | ¹⁸ F-FDG PET/CT | <200 mg/dL [‡] | 60 | ×1 | PET/CT | Unclear: Baseline and follow up |
| Kotze ³⁸ 2014 | ¹⁸ F-FDG PET/CT | NR | 180 | ×1 | US and CT | ×3: Baseline, 6 mo, and 12 mo |
| Barwick ³⁹ 2014 | ¹⁸ F-FDG PET/CT | <216 mg/dL | 90 | ×>1 | PET/CT | ×1: Baseline |
| Courtois ⁴⁰ 2013 | ¹⁸ F-FDG PET/CT | Within normal limits | 60 | ×1 | US | Unclear: Baseline and follow up |
| Kotze ⁴¹ 2009 | ¹⁸ F-FDG PET/CT | NR | 180 | ×1 | US | Varying intervals: 3, 6, or 12 mo prior to PET/CT |
| Reeps ⁴² 2008 | ¹⁸ F-FDG PET/CT | NR | 90 | ×1 | NR | Unclear: baseline and follow up |
| Sakalihan ⁴³ 2002 | ¹⁸ F-FDG PET/CT | NR | 60 | ×1 | CT | ×2: Baseline and the last follow up |

¹⁸F-FDG = ¹⁸F-fluorodeoxyglucose; ¹⁸F-NaF = ¹⁸F-sodium fluoride; CT = computerised tomography; MRI = magnetic resonance imaging; CTA = computerised tomography angiography; US = ultrasound; NR = not report; NA = not applicable.

* Blood glucose level of patients preparing to undergo a PET scan.

[†] Presented as mean ± standard deviation.

[‡] Except for one patient with 292 mg/dL.

association or correlation between ¹⁸F-FDG uptake and AAA expansion. One study³⁴ found that ¹⁸F-FDG uptake was statistically positively related to expansion rate in the subgroup with significant growth. Two studies^{36,38} found a significant negative correlation.

Sakalihan *et al.*⁴³ were the first to publish a study concerning the relationship between ¹⁸F-FDG uptake and AAA expansion. They recruited 26 non-consecutive AAA patients (mean diameter 63.0 mm) who had undergone CT scans and complementary PET imaging, and PET results of 10 patients revealed an increased ¹⁸F-FDG uptake in the aortic wall, which was considered positive. Four of the patients with positive PET images suffered from rapid AAA expansion (>5 mm in 6 months), while two of the 16 negative patients' AAAs expanded rapidly ($p = .16$). Only one patient with a positive PET image experienced AAA rupture. The incidence of rupture was similar between subjects in both the positive and negative PET image groups (1/10 vs. 0/16, $p = .39$). Although a significant difference was seen in the proportion of patients who required urgent surgery between the two groups (5/10 vs. 0/16, $p = .018$), the authors did not specify the definition of ¹⁸F-FDG uptake and if all procedures were performed for ruptured AAAs.

Reeps *et al.*⁴² conducted a pilot study which retrospectively analysed the correlation between increased FDG

uptake and AAA growth, comprising 12 asymptomatic and three symptomatic AAA patients. Expanded AAAs were identified in seven patients, of which three were stable (annual expansion rate ≤ 3 mm), and four were unstable (annual expansion rate > 6 mm). The findings revealed no significant correlation between SUV_{max} and AAA annual expansion rates (Pearson correlation coefficient; $p = .15$).

Kotze *et al.*⁴¹ also found no significant correlation between FDG uptake (SUV_{max}) and recent AAA expansion rate ($r = .18$, $p = .60$). They prospectively investigated a total of 14 AAA patients who received US scans with subsequent PET/CT within 14 days at intervals of three, six, and 12 months. The AAAs of 10 patients revealed increased FDG uptake ($SUV_{max} > 2.5$), and recent annual AAA expansions were observed in seven patients, which were ≤ 3 mm (three patients), > 3 mm and < 6 mm (two patients), and > 6 mm (two patients).

Based on a large cohort of patients using ¹⁸F-FDG PET/CT for oncological evaluation, Lee *et al.*³⁴ analysed the association between FDG uptake and long term growth of aneurysms in patients with a diagnosis of AAA. Eighteen of the 37 patients in their study experienced significant AAA expansion over the follow up period, and the average annual expansion rate was 3.49 ± 2.45 mm. There was no significant difference in ¹⁸F-FDG uptake between aneurysms

Table 4. Key results across 11 studies on positron emission tomography (PET) images and abdominal aortic aneurysm growth, repair or rupture

| Author year | Tracer uptake | Growth | | | Clinical events | | | |
|-----------------------------------|---|---|-------|--|--|-------------------|---------------|--------------------|
| | | Growth | r | p | Rupture - n | p | Repair - n | p |
| Kuzniar ³³ 2020 | SUV _{max} for all focal lesions: Mean 3.3 (range 2.1–4.7) | 3 (1–13) mm/y* | -.198 | .48 [†] | NR | NR | NR | NR |
| Lee ³⁴ 2018 | | | NA | .560 [‡] | NR | NR | 11 | .023 [‡] |
| | TBR _{max} (growth/repair): 1.55 ± 0.20/1.76 ± 0.23 | Significant (3.49 ± 2.45 mm/y) [§] : n = 18 | | | | | | |
| | TBR _{max} (no growth/no repair): 1.57 ± 0.14/1.54 ± 0.27 | Non-significant [§] : n = 19 | | | | | | |
| Forsythe ³⁵ 2018 | | | NA | .008 ^{**} ; .042 ^{††} | Rupture or repair: n = 22; no rupture or repair: n = 50; unadjusted HR 2.16, 95 CI 1.03–4.50, p = .041 ; adjusted HR 2.49; 95 CI 1.07–5.78; p = .034 [¶] | | | |
| | MDS TBR _{max} : Low tertile n = 24 | 1.24 (0.52–2.92) mm/y* | | | | | | |
| | MDS TBR _{max} : Medium tertile n = 24 | 1.55 (0.81–3.12) mm/y* | | | | | | |
| | MDS TBR _{max} : High tertile n = 24 | 3.10 (2.34–5.92) mm/y* | | | | | | |
| Morel ³⁶ 2015 | | | NA | .04 [‡] | NR | NR | NR | NR |
| | SUV _{max} : 1.80 ± 0.45 | Significant (≥2.5 mm/9 mo): n = 9 | | | | | | |
| | SUV _{max} : 2.21 ± 0.5 | Non-significant (<2.5 mm/9 mo): n = 30 | | | | | | |
| Nchimi ³⁷ 2014 | | | NA | .30 ^{‡‡} | 0 | NA | 0 | NA |
| | PET (+): n = 13 | Rapid (>1 cm/y): n = 2 | | | | | | |
| | PET (-): n = 34 | Rapid (>1 cm/y): n = 2 | | | | | | |
| Kotze ³⁸ 2014 | SUV _{max} : 1.80 (1.46–2.26) | 2.0 (0.0–4.0) mm/y*; adjusted for baseline size 4.4 (0.0–9.2) | -.383 | .015 [†] | NR | NR | NR | NR |
| Barwick ³⁹ 2014 | | NR | NR | NR | | .61 ^{‡‡} | 20 | NS ^{**} |
| | Increased tracer uptake visually (visual score ≥1): n = 36 | | | | | | 2 | |
| | Increased tracer uptake visually (visual score <1): n = 65 | | | | | | 2 | |
| Courtois ⁴⁰ 2013 | | | NA | .28 ^{‡‡} | NR | NR | NR | NR |
| | PET (+): n = 8 | Significant ^{§§} : n = 3 | | | | | | |
| | PET (-): n = 10 | Significant ^{§§} : n = 1 (8 mm/y) | | | | | | |
| Kotze ⁴¹ 2009 | Increased FDG uptake (SUV _{max} >2.5): n = 10 | Recent annual: n = 7 | .18 | .60 [†] | NR | NR | NR | NR |
| Reeps ⁴² 2008 | NR | AAAs with history of AAA expansion: n = 7 | NR | .15 | NR | NR | NR | NR |
| Sakalihasan ⁴³ 2002 | | | NA | .16 ^{‡‡} | | .39 ^{‡‡} | | .018 ^{‡‡} |
| | PET (+): n = 10 | Rapid (>5 mm in 6 mo): n = 4 | | | | | 1 | 5 |
| | PET (-): n = 16 | Rapid (>5 mm in 6 mo): n = 2 | | | | | 0 | 0 |

Data are presented as mean ± standard deviation, median (range) or median (interquartile range), unless stated otherwise. AAA, abdominal aortic aneurysm; IQR, interquartile range; SUV_{max}, maximum standardised uptake value; TBR_{max}, maximum target to background ratio; MDS, most diseased segment; PET (+), positive tracer uptake; PET (-), negative tracer uptake; NR, not report; NA, not applicable; NS, not significant.

* Growth rate.

[†] Spearman rank correlation.

[‡] Mann–Whitney test.

[§] In case a significant positive correlation was determined on the linear regression of sizes, it was defined as a significant growth of the AAA.

^{||} Kaplan–Meier analysis.

[¶] Cox regression analysis.

^{**} Unadjusted linear regression analysis.

^{††} Adjusted linear regression analysis.

^{‡‡} Fisher's exact test.

^{§§} The definition of significant expansion was not specified in the original study.

^{|||} Pearson correlation coefficient.

with and without significant expansion (1.55 ± 0.20 vs. 1.57 ± 0.14 ; $p = .56$); however, ^{18}F -FDG uptake was positively correlated with AAA expansion rate for the significant growth subgroup ($r^2 = .260$, $p = .031$). Eleven patients received AAA repair, and patients who underwent intervention had a significantly higher TBR_{max} value than those who did not (1.76 ± 0.23 vs. 1.54 ± 0.27 ; $p = .023$).

In the subsequent study of Kotze *et al.*,³⁸ 50 consecutive patients with small AAAs under surveillance were prospectively enrolled and evaluated at baseline using ^{18}F -FDG PET/CT, of which 40 patients completed a one year follow up. The median annual aneurysm growth was 2.0 mm with a relative growth of 4.4% from baseline. Meanwhile, the median AAA SUV_{max} and TBR_{max} was 1.80 and 1.20, respectively. Although the findings revealed a negative correlation between SUV_{max} and growth during follow up ($r = -0.383$, $p = .015$), the correlation between TBR_{max} and growth rate per year was not significant ($r = -.021$, $p = .889$).

Courtois *et al.*⁴⁰ acquired ^{18}F -FDG PET/CT data from 18 AAA patients that had been referred to their department for elective surgery. Of the 18 enrolled patients, a positive and negative ^{18}F -FDG uptake was respectively found in eight and 10 individuals. Superimposed CT and PET images were classified as positive when a focal or segmental ^{18}F -FDG uptake could be observed. The metabolic activity in the AAA expressed as the rSUV (AAA/liver) was significantly higher in the positive uptake patients than in the negative uptake patients. By retrospectively reviewing the follow up growth data, it was found that in the positive and negative ^{18}F -FDG uptake groups, a respective three and one patients experienced significant expansion. The difference between the two groups was not significant ($p = .28$). It should be noted that the definition of significant expansion is not formally defined.

Morel *et al.*³⁶ recruited 39 AAA patients who received ^{18}F -FDG PET and CT angiograms at baseline and nine months later to associate ^{18}F -FDG SUV_{max} with aneurysm expansion. Nine patients' AAA expanded significantly (≥ 2.5 mm) at the follow up time point. Similar to the study of Kotze *et al.*,³⁸ SUV_{max} at baseline decreased as the aneurysm size increased (1.80 ± 0.45 vs. 2.21 ± 0.52 ; $p = .040$) and a trend towards greater change in SUV_{max} was seen at nine months (10.40 ± 0.85 vs. -0.06 ± 0.57 ; $p = .070$) compared with patients whose aneurysms did not grow. Furthermore, it was found that the change in aneurysm size between baseline and nine months was marginally significantly associated with the baseline SUV_{max} of the aortic wall ($p = .049$), and the AAA TBR_{max} of patients with AAA growth was similar to those whose AAAs did not grow.

Nchimi *et al.*³⁷ assessed the relationship between ^{18}F -FDG uptake and clinical events (defined as annual AAA expansion of >1 cm, dissection, rupture, or emergency) in 47 patients with unruptured AAAs. Two of 13 with PET positive (≥ 1 area with >1 cm of ^{18}F -FDG increased signaling) AAAs and two of 34 with PET negative AAAs were observed to experience rapid aneurysm growth after 30 months of follow up ($p = .30$).

Barwick *et al.*³⁹ included 151 patients (135 with tumours) from a PET/CT database of consecutive ^{18}F -FDG PET/CT

studies conducted in a three year period for routine indications and follow up data on AAA rupture or repair were available for 101 patients. Patients who completed or did not complete follow up were comparable on any baseline characteristic. Over a median 1.5 year follow up period, 20 patients received repair and 79 patients did not, and the AAA SUV_{max} values were not significantly different between the intervention and non-intervention groups. Two of four patients with ruptured AAAs exhibited a visible increase in ^{18}F -FDG uptake, while 34 patients without rupture had visibly increased tracer uptake ($p = .61$). However, it should be noted that confounding radiation and chemotherapy related vascular inflammations and alterations in the metabolic milieu may be found among a majority of the patients in the oncology study, with these being related to the underlying malignancy itself.⁴⁴

¹⁸F-Sodium fluoride positron emission tomography/computed tomography

The SoFIA₃ study³⁵ was designed to investigate whether ^{18}F -NaF PET/CT could predict aneurysm growth and clinical outcomes of those affected with AAA. This prospective cohort study recruited 72 AAA patients who had undergone US, and ^{18}F -NaF PET/CT and CTA scans, and selected AAA growth and the composite of AAA repair or rupture as clinical endpoints. After a mean 510 day follow up period, the median AAA annual growth rate was 2.20 mm, and baseline AAA ^{18}F -NaF uptake was associated with growth independent of the quantification method. When stratified by tertiles, the median AAA annual expansion rate in the highest and lowest tertile of ^{18}F -NaF uptake were 3.10 mm and 1.24 mm, respectively, and the difference was significant ($p = .008$). ^{18}F -NaF uptake measured by MDS TBR_{max} (average TBR_{max} across three axial slices centred on the region of the aneurysm with the highest tracer activity) led to AAA expansion adjusted by known risk factors ($p = .042$).

Of the 22 patients who had ruptured AAAs or underwent AAA repair, 19 had elective repair, and three suffered from rupture. ^{18}F -NaF uptake in subjects with clinical events increased significantly compared with those without clinical events (\log_2 MDS TBR_{max} 2.20 ± 0.58 vs. 1.87 ± 0.54 ; $p = .023$). The doubling of ^{18}F -NaF uptake as measured by MDS more than doubled the likelihood of AAA rupture or repair (hazard ratio: 2.16; 95% CI 1.03 – 4.50; $p = .041$), and this risk remained after adjusting for other risk factors (hazard ratio: 2.49; 95% CI 1.07 $p = 5.78$; $p = .034$). AAA patients in the highest tertile of ^{18}F -NaF uptake had an increased rate of repair or rupture (11/24 vs. 4/24; $p = .043$) and a decreased time to clinical events (572 days vs. 709 days; $p = .043$) when compared with those in the lowest tertile over the follow up period.

¹⁸F-Fluorodeoxyglucose positron emission tomography/magnetic resonance imaging

Kuzniar *et al.*³³ conducted a recent study on inflammation assessment by performing ^{18}F -FDG PET/MRI on 15 patients with asymptomatic AAAs. The median baseline AAA

diameter was 54 mm and median growth rate over the past year was 3 mm. Thirty-six FDG hotspots defined as focally increased FDG signals were detected in aneurysm walls against an intra-arterial background uptake, and sizes larger than 7 mm were observed in the aneurysm wall of 13 patients. Additionally, the number of FDG hotspots correlated with recent AAA growth ($r = .62, p = .010$). Late gadolinium enhancement (LGE) in the aneurysm wall was seen in eight of 15 patients, and AAAs with LGE had an increased median growth rate compared with those without (7 mm vs. 2 mm; $p = .030$). Neither SUV_{max} ($r = -0.198, p = .48$) nor TBR_{max} ($r = 0.406, p = .13$) in the aneurysmal wall was significantly correlated with recent AAA growth. MRI results showed corresponding focal mural morphological changes in the aneurysm of three of 13 subjects (23%) with focal FDG uptake, and one with positive overlap displayed the fastest annual growth rate of 13 mm.

Risk of bias assessment

Table 5 presents the risk of bias of each study. One study³⁴ was rated as low risk of bias, three studies^{36,38,39} were rated as moderate, and seven studies^{33,34,37,40–43} were rated as high, and the main risks were biases related to outcome measurement and study confounding.

DISCUSSION

The present systematic review indicates that relationships between tracer (^{18}F -FDG or ^{18}F -NaF) uptake and clinical AAA prognosis are inconsistent in studies using PET/CT. The findings of the ^{18}F -FDG PET/CT studies were contradictory, and more negative than positive findings were reported on the association between ^{18}F -FDG uptake and AAA expansion, rupture, or repair. Additionally, FDG uptake may be correlated positively with AAA growth rate in a specified subgroup with significant aneurysm expansion. The ^{18}F -NaF PET/CT study showed that tracer uptake is positively associated with AAA expansion and clinical events, and the single study that used ^{18}F -FDG combined with PET/MRI suggested that ^{18}F -FDG uptake is not related to aneurysm expansion.

A previous systematic review⁴⁵ which aimed to explore the role of ^{18}F -FDG PET scans in AAA subjects did not establish a credible quantitative cut off value for predicting AAA growth due to conflicting evidence in the included studies. Another systematic review⁴⁶ that included six studies relating ^{18}F -FDG PET uptake to AAA progression also obtained contradictory findings, showing that SUV_{max} either had a negative association or correlation with AAA growth or non-statistically significant associations with AAA expansion. The present review added five additional studies^{33–35,39,40} to the previous review. The additional studies compensated for the insufficient data on the association between ^{18}F -FDG uptake and clinical events including rupture or repair. They also indicate ^{18}F -NaF as a promising PET marker to predict AAA prognosis,³⁵ and suggest that an assessment of AAA with PET/MRI is feasible, opening up new and broad horizons for AAA progression.³³ The replacement of separate PET and CT or MRI by hybrid PET/CT or PET/MRI technology integrates molecular data from PET with anatomical details from CT or MRI,²³ and all but one study⁴³ in this review used these fusion techniques. PET/MRI outperforms PET/CT in terms of improved tracer detectability, due to the excellent morphological characteristics of MRI, and a better spatial matching between the PET and MRI and allowed the depiction of disease activity at low radiation dose.³³ The present review included a newer study³³ on the role of integrated PET/MRI on AAA assessment. However, due to the relatively small sample size of this study,³³ the results may be inconclusive. Furthermore, the study³³ also indicated that FDG hotspots in PET imaging rarely corresponded to MRI findings of inflammatory activity, but patients with LGE and FDG hotspots may experience the worst prognosis, probably because PET and MRI provide information related to glycolysis and phagocytosis, respectively.²⁶

The pathological processes of aortic aneurysms involve inflammation, extracellular matrix degradation, microcalcification, hypoxia, and neovascularisation.^{24,47,48} A variety of PET tracers targeting different stages of diseases exist, and many can be applied to cardiovascular diseases.^{35,49–53} ^{18}F -FDG is a commonly used PET tracer which reflects the glucose accumulation of inflammatory tissues,²⁴

Table 5. Risk of bias assessment of 11 studies on positron emission tomography images and abdominal aortic aneurysm progression using Quality in Prognostic Studies (QUIPS) tool

| Study | Study participation | Study attrition | Prognostic factor measurement | Outcome measurement | Study confounding | Statistical analysis and reporting | Overall risk of bias rating |
|------------------------------|---------------------|-----------------|-------------------------------|---------------------|-------------------|------------------------------------|-----------------------------|
| Kuzniar ³³ 2020 | Moderate | Low | Moderate | High | High | Moderate | High |
| Lee ³⁴ 2018 | Moderate | Low | High | High | High | Moderate | High |
| Forsythe ³⁵ 2018 | Low | Moderate | Low | Low | Low | Low | Low |
| Morel ³⁶ 2015 | Low | Moderate | Low | Moderate | High | Moderate | Moderate |
| Nchimi ³⁷ 2014 | Moderate | Low | Moderate | Moderate | High | Moderate | High |
| Kotze ³⁸ 2014 | Low | Moderate | Low | Low | High | Moderate | Moderate |
| Barwick ³⁹ 2014 | Moderate | Moderate | Moderate | Moderate | High | Moderate | Moderate |
| Courtois ⁴⁰ 2013 | Moderate | Low | Moderate | High | High | Moderate | High |
| Kotze ⁴¹ 2009 | Moderate | Low | Moderate | High | High | Moderate | High |
| Reeps ⁴² 2008 | Moderate | Low | Moderate | High | High | Moderate | High |
| Sakalihan ⁴³ 2002 | High | Low | High | High | High | Moderate | High |

and has been widely investigated during atherosclerotic inflammation.^{25,49,50,54} Since there are common pathological processes involved in both AAA and atherosclerosis,²⁴ inflammation of the aortic wall theoretically can be evaluated by the level of ¹⁸F-FDG uptake. However, the binding of ¹⁸F-FDG is poorly specific for it can accumulate in all cells that metabolise glucose.⁵⁵ ¹⁸F-FDG arterial signal is influenced by local hypoxia and uptake by other resident cell types, thus, the active disease may not be reliably detected in diseases that show mild inflammation, such as when there is atherosclerosis or aneurysm formation.⁵⁵ ¹⁸F-NaF is a promising radiotracer that binds to the hydroxyapatite crystals deposited during microcalcification, and is considered to be able to detect early microcalcification for the identification of necrotic material within the vascular beds that drives further inflammation.²⁴ More recent studies have shown that ¹⁸F-NaF uptake as a predictor predicted the clinical outcomes of patients with coronary artery disease⁵³ and stroke.⁵⁶ This review included a new study³⁵ that focused on the predicted value of ¹⁸F-NaF PET/CT in future AAA progression, and the findings suggested ¹⁸F-NaF uptake has a positive association with AAA expansion or clinical events. One systematic review⁵⁴ on the relationship between carotid plaque PET imaging and cerebral ischaemic disease showed that recent cerebral ischaemia events may be related to an increase in both carotid ¹⁸F-FDG and ¹⁸F-NaF uptake on PET imaging. Another systematic review²⁵ revealed that ¹⁸F-FDG PET visualised various inflammatory stages of carotid atherosclerosis evolution and its complications, whereas ¹⁸F-NaF PET appeared to reflect more long term outcomes through the demonstration of artery wall microcalcification. In patients receiving dual tracer PET scans, it was found that ¹⁸F-NaF PET uptake is likely to be a more sensitive predictor of the evolution of vascular diseases,^{56–59} including AAA.⁶⁰ The dissimilar findings between the ¹⁸F-NaF PET/CT study and ¹⁸F-FDG PET/CT studies may be caused by the use of differing tracer types. More specific PET tracers have been shown to be effective in AAA animal models and have been investigated in other cardiovascular diseases.^{55,61,62} These tracers included those that track inflammation, such as ⁶⁸Ga-DOTA-TATE, ⁶⁴Cu-DOTA-ECL1i, ⁶⁸Ga-pentixafor, and ¹⁸F nanoparticles; those that track neo-angiogenesis, such as ¹⁸F-fluciclatide and ⁶⁸Ga-NOTA-RGD; and those that target hypoxia, such as ¹⁸F-fluoromisonidazole and ¹⁸F-HX4. There is hope for the future that these novel PET tracers can be translated into clinical practice.

Alternatively, there is speculation that contradictory features of inflammation might have led to the varying results. Two polarised subtypes of macrophages (M1 and M2) play different roles in inflammation: M1 is generally pro-inflammatory and induces the destruction of tissues, whereas M2 induces the repair and recovery of tissues. Both M1 and M2 macrophages could lead to an increased uptake of tracers in inflammatory tissues. Increased ¹⁸F-FDG uptake in aneurysms may suggest the activation of M1 or M2 macrophages, resulting in different outcomes.⁶³ In addition, AAA growth is a dynamic process with a specific

period of growth and stability and repeating inflammatory damage and repair processes, and is likely to cause cyclic changes in tracer uptake. Although findings from Morel *et al.*³⁶ and Barwick *et al.*³⁹ support the fact that cyclic changes in metabolic activity in AAAs occur during expansion phases, most of the studies in this review only analysed a single time point. Instead of one single measure, metabolic activity may vary with time and changes in SUV_{max} or TBR_{max}, which may be a better predictor of AAA progression. When evaluating aortic tracer uptake, comparisons of SUV_{max} or TBR_{max} alone between two groups may yield non-significant results, as metabolic activity may remain in the lower range even with increased tracer uptake. An additional point of note is that the multiple inflammatory pathways that are implicated in AAA pathogenesis may account for the contradictory results. Targeting single pathways or cell types might not be effective; something that is supported by the evidence that using only a limited number of drugs with anti-inflammatory properties cannot limit AAA growth.⁶⁴

The ¹⁸F-FDG PET imaging protocols used to assess inflammation in atherosclerosis were variable and uncertain. This raises an important question about the source of this poor reproducibility. It is recommended that patients preparing to undergo a PET scan should maintain a pre-scan blood glucose level below 126 mg/dL (7 mmol/L),⁶⁵ since even moderate hyperglycaemia can lower the ¹⁸F-FDG uptake by inflammatory cells. In the present review, the three studies^{36,37,39} that reported specific values of pre-scan blood glucose levels all had higher thresholds. Moreover, the ¹⁸F-FDG injection to PET scan time interval has not always been confirmed. Some studies suggest that circulation time longer than 90 minutes improves visualization of vessel wall atherosclerosis because vessel walls and lesions are more distinguishable as background activity decreases.⁶⁵ In a dual time point imaging study, delayed ¹⁸F-FDG PET/CT imaging at 180 minutes improved the quantification of atherosclerotic plaque inflammation over imaging at 90 minutes.⁶⁶ Most of the studies in this review applied a circulation time that was shorter than 180 minutes. It may be useful to carry out further study into the relationship between the imaging time point with lesion uptake and clinical and pathological outcomes. Additionally, most of the studies included in this review did not specify the parameters related to the spatial resolution of PET, which directly affects the image quality and is a key factor which restricts the ability of PET to detect lesions. This lack of appropriate reporting prevented a sound comparison of the results, which creates bias among the measurements in small lesions. For the aortic wall ¹⁸F-FDG uptake measurement, most studies applied a variety of approaches such as visual assessment, absolute SUV_{max}, SUV thresholds, and various TBRs, without using a standardised approach.

There are a number of limitations of this study that need to be recognised. All the studies in this review were observational designs with a small sample size, characteristics which can often produce misleading results. Moreover, the majority showed a high risk of bias in study confounding,

probably due to their small sample size, which makes it impossible to perform multivariable analysis to adjust for the impact of confounders on the statistical analysis results. This review had several limitations in regards to methodology: first, in most studies, the AAA diameters were measured by a researcher who was unblinded to the tracer uptake; second, systematic errors in US measurements may be unable to identify small changes in AAA diameters; third, the threshold for SUVs associated with AAA progression cannot be determined for the quantitative assessment of arterial inflammation and varied from study to study; fourth, single time points of the tracer uptake evaluations in most studies were not able to reflect metabolic activity in AAAs undergoing cyclic changes; fifth, the follow up times of most studies were shorter than two years and not long enough to detect all inflammatory phases of the aortic wall and the growth or AAA clinical events; and finally, only three studies mentioned the interobserver variability or difference in diameter measurements. Moreover, studies with dissimilar designs, image acquisition methods, statistical analysis, and interpretations made it impossible to quantitatively synthesise the results of each study.

It is difficult to establish a reliable quantitative cut off of ^{18}F -FDG uptake to predict the risk of rupture based on current evidence; thus, the current inconsistent findings may not be helpful in providing clinical decision making guidance in the near future. However, using ^{18}F -NaF uptake as a predictor may be useful for patients who have difficulty in deciding whether intervention is necessary, such as in those with high risk AAAs that are <55 mm, critically sized, or of larger diameter with uncertain risk benefit profiles.

Conclusion

Currently, there is insufficient evidence on the relationship between PET tracer uptake and AAA growth or clinical events. Neither ^{18}F -FDG PET/CT nor PET/MRI can be used as prognostic tools in common practice in the near future; however, ^{18}F -NaF PET/CT has the potential to be a promising method for predicting clinical outcomes in AAA patients. Much further work remains to be done before establishing the relationship between PET imaging and AAA prognosis.

CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejvs.2021.08.010>.

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