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Fluorine-18–Sodium Fluoride Uptake in Abdominal Aortic Aneurysms
The SoFIA3 Study

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ABSTRACT

BACKGROUND Fluorine-18–sodium fluoride (18F-NaF) uptake is a marker of active vascular calcification associated with high-risk atherosclerotic plaque.

OBJECTIVES In patients with abdominal aortic aneurysm (AAA), the authors assessed whether 18F-NaF positron emission tomography (PET) and computed tomography (CT) predicts AAA growth and clinical outcomes.

METHODS In prospective case-control (n = 20 per group) and longitudinal cohort (n = 72) studies, patients with AAA (aortic diameter >40 mm) and control subjects (aortic diameter <30 mm) underwent abdominal ultrasound, 18F-NaF PET-CT, CT angiography, and calcium scoring. Clinical endpoints were aneurysm expansion and the composite of AAA repair or rupture.

RESULTS Fluorine-18-NaF uptake was increased in AAA compared with nonaneurysmal regions within the same aorta (p = 0.004) and aortas of control subjects (p = 0.023). Histology and micro-PET-CT demonstrated that 18F-NaF uptake localized to areas of aneurysm disease and active calcification. In 72 patients within the longitudinal cohort study (mean age 73±7 years, 85% men, baseline aneurysm diameter 48.8±7.7 mm), there were 19 aneurysm repairs (26.4%) and 3 ruptures (4.2%) after 510±196 days. Aneurysms in the highest tertile of 18F-NaF uptake expanded 2.5× more rapidly than those in the lowest tertile (3.10 [interquartile range (IQR): 2.34 to 5.92 mm/year] vs. 1.24 [IQR: 0.52 to 2.92 mm/year]; p = 0.008) and were nearly 3× as likely to experience AAA repair or rupture (15.3% vs. 5.6%; log-rank p = 0.043).

CONCLUSIONS Fluorine-18-NaF PET-CT is a novel and promising approach to the identification of disease activity in patients with AAA and is an additive predictor of aneurysm growth and future clinical events. (Sodium Fluoride Imaging of Abdominal Aortic Aneurysms [SoFIA]; NCT02229006; Magnetic Resonance Imaging [MRI] for Abdominal Aortic Aneurysms to Predict Rupture or Surgery; The MA3RS Trial; ISRCTN76413758) (J Am Coll Cardiol 2018;71:513–23) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
Aneurysm iron oxide superparamagnetic particles of ultrasmall USPIO = tissue-to-background TBR = standardized uptake SUV = positron emission tomography MDS = most diseased segment PET = positron emission tomography CT = computed tomography CI = confidence interval AAA = abdominal aortic aneurysm FDG = fluorodeoxyglucose CH/09/002, RE/13/3/30183, and RM/13/2/30158; and has received a Wellcome Trust Senior Investigator Award (WT103782AIA). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**STUDY DESIGN.** This was a prospective single-center, case-control, observational cohort study of patients with asymptomatic AAA who were under ultrasound-based surveillance as part of routine clinical follow-up and control subjects with normal-caliber abdominal aortas demonstrated on targeted screening ultrasound. The study (NCT02229006) was conducted with the written informed consent of all subjects, with approval by the research ethics committee, and in accordance with the Declaration of Helsinki.

**STUDY ASSESSMENTS.** Participants underwent a clinical evaluation including documentation of medical history, concomitant medications, and family history as well as an ultrasound evaluation of the maximum anteroposterior abdominal aortic diameter. Ultrasound scans were carried out in an accredited clinical vascular science laboratory using a standardized protocol with known interobserver variability of 3.4% (14). The AAA growth rate was determined using the AAA maximum anteroposterior diameter obtained

**METHODS**

In AAA disease, degradation of the extracellular matrix occurs in response to the accumulation of inflammatory cells, such as macrophages and lymphocytes, and the activation of matrix metalloproteinases. The resulting milieu of cellular inflammation, tissue destruction, and necrosis can lead to cycles of further inflammation (8). Focal “hotspots” of such intense biological activity have been identified in active aneurysm disease and can occur at the site of rupture (9). We have recently demonstrated that the positron-emitting radiotracer $^{18}$F-sodium fluoride ($^{18}$F-NaF) can identify areas of early microcalcification (10) that occur in response to necrotic inflammation in ruptured or high-risk human carotid (11) and coronary (12) atherosclerotic plaques. This tracer has not been assessed in patients with AAA, although loss of tissue integrity and necrotic inflammation may be central to its pathophysiology, underlie aneurysm expansion, and ultimately predict disease progression and outcome (7). We hypothesized that $^{18}$F-NaF uptake on positron emission tomography (PET) would highlight areas of microcalcification and AAA disease activity, representing regions prone to expansion and rupture. The main aims of this study were to determine whether $^{18}$F-NaF uptake on combined PET and computed tomography (CT) is increased in AAA and whether this is associated with aneurysm growth (the primary endpoint) and subsequent rates of AAA repair or rupture.
Forsythe et al. 18F NaF Uptake in AAAs

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FEBRUARY 6, 2018:513-23

at baseline and the last ultrasound examination performed during study follow-up. Abdominal aortic tissue was obtained at postmortem or from patients undergoing elective AAA repair and analyzed by micro-PET-CT and histology (Online Appendix).

18F- NaF PET-CT. Patients were administered a target dose of 125 MBq of 18F-NaF intravenously and after 60 min were imaged on a hybrid 128-detector array PET-CT scanner (Biograph mCT, Siemens Healthcare, Erlangen, Germany) (10). A low-dose attenuation correction CT scan was performed (120 kV, 50 mAs, 3/3 mm), followed by acquisition of PET data, using 3 10-min bed positions to ensure coverage from the thoracic aorta to the aortic bifurcation. An electrocardiographically gated calcium scoring CT scan (120 kV, 120 mAs, 3/3 mm; prospective electrocardiographic gating at 50% of the R-R interval) and contrast-enhanced CT angiography (120 kV, 145 mAs, 3/3 mm, field of view 400; and 1/1 mm, field of view 300; triggered at 181 Hounsfield units) were performed, centered on the AAA (or abdominal aorta in control patients) and extending to the aortic bifurcation (Figure 1).

To estimate 18F-NaF uptake, the maximum standardized uptake values (SUVs) (a validated measure of tissue radiotracer uptake) were quantified from regions of interest (Online Appendix) (15). Maximum tissue-to-background ratios (TBRs) were then calculated, after correction for blood pool activity using the averaged mean SUVs of 3 consecutive regions of interest from the right atrium, according to our previously described technique (16). Although TBRmax was used for our primary analysis (12), we also investigated other methods for quantification, including SUVmax and corrected SUVmax (calculated by subtracting the blood pool activity from SUVmax) (17). Finally, we adopted the “most diseased segment” (MDS) approach, as suggested by others (11,16,18–20). The MDS TBRmax was calculated as the average TBRmax across 3 axial slices centered on the region of the aneurysm with the highest tracer activity (11).

CLINICAL ENDPOINTS AND ADJUDICATION. Clinical data from clinic visits, the research database, electronic health records, primary care contacts, and the General Register Office were reviewed and clinical endpoints adjudicated by the independent Clinical Endpoint Committee (Online Appendix). The committee members were blinded to the findings of PET-CT. Follow-up was censored at January 10, 2017, or at the time of event.

STATISTICAL AND DATA ANALYSIS. Baseline characteristics are reported as number (percentage) for categorical variables and as mean ± SD or median (interquartile range) for continuous variables, as appropriate. We stratified our patient cohort by AAA MDS TBRmax tertiles to assess associations with aneurysm expansion (the primary endpoint) and the clinical outcomes of aneurysm repair or rupture (the secondary endpoint). For the aneurysm growth and outcomes analysis, AAA expansion rate and MDS TBRmax were log-transformed (log2) to normalize the data. One-way analysis of variance was used to compare continuous data across multiple factors, with post hoc analysis using the Bonferroni test as appropriate. The Kruskal-Wallis test was used for nonparametric continuous data and the log-rank test for comparisons of AAA event rate and mortality between tertiles. Categorical data were compared using chi-square or Fisher exact tests, and the unpaired Student’s t-test was used to compare continuous outcomes between 2 independent groups. Two-tailed Pearson correlation and linear regression analysis were performed to investigate the relationship between 18F-NaF uptake and aneurysm expansion. Finally, we performed Kaplan-Meier and Cox regression analysis to investigate time to AAA event by tertile, censored at the date of death. Statistical analysis was undertaken using SPSS Statistics 23 (IBM, Armonk, New York), and significance was taken at the 2-sided 5% level (p < 0.05).

RESULTS

A total of 145 patients with AAA were screened for inclusion: 136 were approached, and 76 patients ultimately attended for the scanning visit. Four patients underwent protocol development scans, had incomplete data, and were excluded from the final analysis, leaving a total of 72 patients with AAA and 20 control subjects (Figure 2). Patients were predominantly elderly (mean age 72.5 ± 6.9 years) men (84.7%) with multiple cardiovascular risk factors, including hypertension (65.3%) and hypercholesterolemia (81.9%) (Table 1). More than 90% were current or ex-smokers (27.8% and 65.3%, respectively), with a mean baseline AAA diameter of 48.8 ± 7.7 mm. Control subjects were younger (mean age 65.2 ± 2.8 years) but also predominantly men (95.0%), and 40% were current (25%) or prior (15%) smokers.

CASE-CONTROL STUDY. Twenty patients with AAA were matched for age, sex, and smoking status with the 20 control subjects (Table 1). Background blood pool activity in the right atrium was similar between groups (log2 SUVmean −0.570 ± 0.517 vs. −0.588 ± 0.531; difference 0.018; 95% confidence interval...
FIGURE 1  Positron Emission Tomographic and Computed Tomographic Images of Abdominal Aortic Aneurysms

(A) Structural image of computed tomographic angiography, (B) $^{18}$F-sodium fluoride uptake on positron emission tomography, and (C) fused positron emission tomographic-computed tomographic images colocalizing $^{18}$F-sodium fluoride uptake with the skeleton and abdominal aortic aneurysm.
Fluorine-18-NaF uptake was higher in the AAA when compared with the abdominal aorta of control subjects irrespective of the method of quantification (e.g., log₂ MDS TBRmax 1.712 ± 0.560 vs. 1.314 ± 0.489; difference 0.398; 95% CI: 0.057 to 0.739; p = 0.023) (Online Table 1). In contrast to control aortic tissue, AAA tissue demonstrated ex vivo ¹⁸F-NaF uptake that correlated with areas of tissue disruption with necrotic debris and active calcification (r = 0.808, p = 0.015) (Figure 3). Areas of ¹⁸F-NaF uptake on PET were distinct from areas of macrocalcification on CT (Online Video 1).

Patients with AAA had more cardiovascular risk factors and higher abdominal aortic CT calcium scores (log₂ Agatston score 11.444 ± 1.760 vs. 7.338 ± 3.811; difference 4.105; 95% CI: 2.013 to 6.198; p = 0.001) (Online Table 1) than control subjects. However, no differences in ¹⁸F-NaF uptake were observed between these groups in either the descending thoracic aorta or the nonaneurysmal abdominal aorta.

**OBSERVATIONAL COHORT STUDY.** Fluorine-18-NaF uptake was again higher in the aneurysm than in the nonaneurysmal portion of the abdominal aorta (log₂ TBRmax 1.647 ± 0.537 vs. 1.332 ± 0.497; difference 0.314; 95% CI: 0.0685 to 0.560; p = 0.004) and almost double the uptake observed in the descending thoracic aorta (log₂ TBRmax 1.647 ± 0.537 vs. 0.881 ± 0.414; difference 0.766; 95% CI: 0.517 to 1.011; p < 0.0001). These differences were consistently observed regardless of the method of PET quantification.

Across the tertiles of AAA MDS TBRmax, there were no differences in most risk factors for AAA disease, including age, sex, smoking habit, aneurysm diameter, hypertension, and hypercholesterolemia. Although there appeared to be some differences with respect to diastolic blood pressure, body mass index, and peripheral arterial disease, the trend was inconsistent across the tertiles (Table 1).

**¹⁸F NaF UPTAKE AND ANEURYSM GROWTH.** During 510 ± 196 days of follow-up, the median AAA
When stratiﬁcation analysis, 18F-NaF activity in the AAA (MDS TBRmax) in the lowest tertile (3.10 mm/year [IQR: 2.34 to 5.92 mm/year]) was associated with future expansion regardless of the method of quantiﬁcation (e.g., log2 MDS TBRmax; log-rank p = 0.006). When stratified by tertiles, aneurysms in the highest tertile expanded 2.5× more rapidly than those in the lowest tertile (3.10 mm/year [IQR: 2.34 to 5.92 mm/year]) vs. 1.24 mm/year [IQR: 0.52 to 2.92 mm/year]; p = 0.008) (Figure 4). Moreover, in multivariate analysis, 18F-NaF activity in the AAA (MDS TBRmax) emerged as a predictor of growth independent of age, sex, baseline diameter, body mass index, blood pressure, smoking, renal function, or peripheral arterial disease (p = 0.042) (Online Table 2). In contrast, the aneurysm Agatston score was not associated with future expansion (r = 0.199; p = 0.141).

18F-NaF UPTAKE AND CLINICAL EVENTS. In total, 22 patients (30.6%) met the composite endpoint of AAA repair or rupture. Of these, 19 (26.4%) underwent elective AAA repair and 3 (4.2%) experienced AAA rupture, all of whom died without repair. Five other patients died during study follow-up, all from non-AAA causes.

Patients with aneurysms in the highest tertile of 18F-NaF uptake were more likely to experience AAA repair or rupture during follow-up (15.3% vs. 5.6%; log-rank p = 0.043) (Table 2). They also had a reduced time to AAA event: 572 days versus 735 days for AAA repair (log-rank p = 0.014) and 572 days versus 709 days for the composite of AAA repair or rupture (log-rank p = 0.043) (Figure 4). In those patients who experienced AAA events, 18F-NaF activity was higher than in those who continued under surveillance (log-rank p = 0.043) (Table 2). In unadjusted analysis, a doubling of 18F-NaF activity in the MDS was associated with a more than 2-fold risk for experiencing AAA rupture or repair (hazard ratio: 2.16; 95% CI: 1.03 to 4.50; p = 0.041) (Table 2). When adjusted for age, sex, baseline diameter, systolic blood pressure, body mass...
Ex vivo micro-positron emission tomography and computed tomography (left) and histology (right) of aortic wall excised (A) at postmortem in a patient without an aneurysm and (B) during open abdominal aortic aneurysm repair. Regions of interest (dashed circle) of 18F-fluoride (18F-NaF) uptake demonstrate atheromatous disease with necrosis (hematoxylin and eosin stain, magnification ×100 [Online Video 1]; B1) and calcification (black, Von Kossa stain, magnification ×200; B2) in the aortic aneurysm tissue that is not apparent in control aorta (A1, A2).
Fourth, this is the largest dedicated study using PET-CT in AAA disease to date and the first clinical study to investigate $^{18}$F-NaF PET-CT in AAA disease progression (21). Finally, this was a prospective clinical cohort study, in contrast with many previous studies of PET-CT in patients with AAA that are based on retrospective data, often obtained from cohorts derived from oncological imaging practice. We previously demonstrated that $^{18}$F-NaF selectively binds to microcalcification in coronary (11) and carotid atherosclerotic (10,11) plaques and that this is associated with plaque vulnerability and rupture. We (11,12) and others (22) have also shown that $^{18}$F-NaF binds to areas of tissue necrosis-associated myocardial and cerebral infarction. In our present study, data from histology and micro-PET-CT indicate that this tracer behaves in a similar fashion in AAA. Increased $^{18}$F-NaF uptake was most marked in AAA tissue with advanced disease and active calcification. We suggest that $^{18}$F-NaF uptake again relates to microcalcification and is particular to the most diseased areas associated with tissue disruption and loss of integrity. Interestingly, we also showed that $^{18}$F-NaF is distinct from AAA macrocalcification detected by CT and that the latter is not associated with expansion or AAA events, suggesting that once established, dense calcified deposits represent a more stabilized biological state.

Most previous clinical studies using PET-CT in AAA disease have focused on the use of $^{18}$F-fluorodeoxyglucose (FDG) to identify inflammation, with variable results and no clear clinical application. Although some groups have suggested a potential role for $^{18}$F-FDG PET-CT in predicting AAA expansion or rupture (23–25), others have disputed this and reported contradictory findings (26,27). This in part relates to the small study sample sizes and whether patients had symptomatic or inflammatory AAAs, but to date there is no clear relationship between $^{18}$F-FDG and aneurysm expansion or clinical outcome (22). Our present study was nested within another larger clinical cohort study, the MA3RS trial. This was a multicenter study of 342 patients with AAA who underwent ultrasmall superparamagnetic particles of iron oxide (USPIO)-enhanced magnetic resonance imaging to identify cellular inflammation within the aortic wall (13). This study recently reported and demonstrated that although USPIO-enhanced magnetic resonance imaging did predict AAA expansion and clinical outcome, the association was modest and was not independent of established clinical factors, including ultrasound AAA diameter (28). This suggests that imaging of cellular inflammation alone, either by $^{18}$F-FDG or USPIO-enhanced magnetic

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**Table 2: Expansion Rate and Clinical Outcomes According to Tertiles of $^{18}$F-Sodium Fluoride Uptake**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Patients With AAA (N = 72)</th>
<th>Tertile 1 (n = 24)</th>
<th>Tertile 2 (n = 24)</th>
<th>Tertile 3 (n = 24)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA expansion rate, mm/yr</td>
<td>2.20 (0.96–3.73)</td>
<td>1.24 (0.52–2.92)</td>
<td>1.55 (0.81–3.12)</td>
<td>3.10 (2.34–5.92)</td>
<td>0.008</td>
</tr>
<tr>
<td>AAA events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite events</td>
<td>22 (30.6)</td>
<td>4 (16.7)</td>
<td>7 (29.2)</td>
<td>11 (45.8)</td>
<td>0.043</td>
</tr>
<tr>
<td>Repair</td>
<td>19 (26.4)</td>
<td>3 (12.5)</td>
<td>5 (20.8)</td>
<td>11 (45.8)</td>
<td>0.014</td>
</tr>
<tr>
<td>Rupture</td>
<td>3 (4.2)</td>
<td>1 (4.2)</td>
<td>2 (8.3)</td>
<td>0 (0.0)</td>
<td>–</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause</td>
<td>8 (11.1)</td>
<td>4 (16.7)</td>
<td>4 (16.7)</td>
<td>0 (0.0)</td>
<td>0.343</td>
</tr>
<tr>
<td>AAA-related</td>
<td>3 (4.2)</td>
<td>1 (4.2)</td>
<td>2 (8.3)</td>
<td>0 (0.0)</td>
<td>–</td>
</tr>
</tbody>
</table>

Values are median (interquartile range) or n (%). *p value for trend across the tertiles. AAA = abdominal aortic aneurysm.

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In this prospective series of clinical studies, we have demonstrated for the first time that $^{18}$F-NaF uptake is specifically increased in AAA and relates to areas of advanced aneurysmal disease. Moreover, $^{18}$F-NaF uptake is a major predictor of aneurysm expansion and clinical outcome that is additive to standard clinical risk factors, including aneurysm diameter. This is the first study to demonstrate that an imaging biomarker of disease activity can add to the risk prediction of AAA and to suggest that this approach might refine clinical decisions regarding the need for surgery and improve patient outcomes (Central Illustration).

Our studies have several major strengths and prominent observations. First, we have shown AAA tissue demonstrates markedly increased levels of $^{18}$F-NaF uptake that far exceed those seen in control volunteers. Perhaps more important, uptake of the AAA also exceeds that observed in the non-aneurysmal aorta within the same patient. Second, we demonstrate that $^{18}$F-NaF uptake localized to areas of AAA disease, highlighting diseased areas of poor tissue integrity that may be susceptible to aneurysm expansion and clinical events. Third, we assessed the potential clinical value of this technique in a cohort of patients with extended follow-up in which the clinicians responsible for the patient’s care were unaware of the findings of PET-CT. It is therefore salient to note that $^{18}$F-NaF uptake predicted expansion and clinical outcomes in addition to clinical risk factors including AAA diameter, especially as the latter drives the decision for elective AAA repair.

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index, and smoking, this risk remained (hazard ratio: 2.49; 95% CI: 1.07 to 5.78; p = 0.034) (Online Table 2).

**DISCUSSION**

In this prospective series of clinical studies, we have demonstrated for the first time that $^{18}$F-NaF uptake is specifically increased in AAA and relates to areas of advanced aneurysmal disease. Moreover, $^{18}$F-NaF uptake is a major predictor of aneurysm expansion and clinical outcome that is additive to standard clinical risk factors, including aneurysm diameter. This is the first study to demonstrate that an imaging biomarker of disease activity can add to the risk prediction of AAA and to suggest that this approach might refine clinical decisions regarding the need for surgery and improve patient outcomes (Central Illustration).

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resonance imaging, is insufficient to provide additive clinical information beyond established clinical risk factors and AAA diameter. In contrast, 18F-NaF PET-CT identifies focal areas of microcalcification indicative of more advanced aneurysm disease and independently predicts both disease progression and clinical events.

We have demonstrated an important clinical application of 18F-NaF PET-CT in AAA disease. Until now, future prediction of aneurysm expansion has relied on the simple morphological parameter of aneurysm diameter. However, it is clear that AAA growth is nonlinear and cannot be predicted accurately from a simple anatomic measure, such as AAA diameter. Although we know that larger aneurysms tend to expand more rapidly and are more prone to rupture, disease evolution is not straightforward. Better AAA disease prediction using 18F-NaF uptake could be particularly useful for patients in whom the decision to intervene is challenging, such as those with high-risk aneurysms smaller than 55 mm, those with borderline aneurysm sizes, and those with larger aneurysms where the balance of risk and benefit is uncertain.

**STUDY LIMITATIONS.** This was a single-center proof-of-concept study with a small number of rupture events, making adjustment for potential confounders and covariates challenging. Although we observed no marked differences in sex across the tertiles of 18F-NaF uptake, our study population had a strong male bias (typical of this disease population), and we cannot be certain that our findings are truly representative of both men and women. The clinical impact of this technique has not been assessed and would require a larger trial in which clinical and surgical decisions would be influenced or dictated by the findings of 18F-NaF PET-CT. The widespread implementation of this technique may be challenging, especially given the relative expense and complexity of PET-CT compared with ultrasound. However, we have demonstrated the feasibility of this technique, which uses a well-established, widely available, and relatively cheap radiotracer. Moreover, with the more widespread use and availability of PET-CT scanners, barriers to implementation are declining. There are also some inherent limitations of 18F-NaF image analysis that merit comment. Being a bone tracer, 18F-NaF is readily taken up by the vertebrae, which lie in close proximity to the abdominal aorta. In our study, it was necessary to exclude some areas of the posterior aorta because of overspill of signal. However, this is not unique to 18F-NaF, with similar issues seen with 18F-FDG uptake in...
regions of interest adjacent to bowel, muscle, or other metabolically active tissues. Finally, further validation of the tissue binding characteristics and time course of change in $^{18}$F-NaF uptake in aneurysmal and nonaneurysmal aortas are needed, and this would be interesting to explore in future studies.

**CONCLUSIONS**

This novel proof-of-concept PET-CT study of patients with asymptomatic AAA demonstrates that $^{18}$F-NaF uptake identifies advanced aneurysmal disease and is associated with aneurysm growth and clinical AAA events independent of established clinical risk factors, including aneurysm diameter. This technique holds major promise for the future management of patients with AAA disease.

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COMPETENCY IN MEDICAL KNOWLEDGE: 18F-Sodium fluoride uptake is specific to abdominal aortic aneurysm tissue, proportional to the rate of aneurysm expansion, and predictive of repair or rupture, independent of aneurysm diameter.

TRANSLATIONAL OUTLOOK: Additional studies are needed to clarify the clinical utility of this imaging biomarker as a guide to selection of patients for elective repair of abdominal aortic aneurysms.

REFERENCES


KEY WORDS abdominal aortic aneurysm, positron emission tomography, repair, rupture

APPENDIX For the supplemental methods, tables, and video, please see the online version of this article.