Native aortic valve disease progression and bioprosthetic valve degeneration in patients with transcatheter aortic valve implantation

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Native Aortic Valve Disease Progression and Bioprosthetic Valve Degeneration in Patients with Transcatheter Aortic Valve Implantation

Running Title: *Kwiecinski, Tzolos, Cartlidge, et al.; ^{18}F-NaF PET Predicts TAVI Degeneration*

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Abstract

Background: There remain major uncertainties regarding disease activity within the retained native aortic valve as well as bioprosthetic valve durability following transcatheter aortic valve implantation (TAVI). We aimed to assess native aortic valve disease activity and bioprosthetic valve durability in patients with TAVI in comparison to subjects with bioprosthetic surgical aortic valve replacement (SAVR).

Methods: In a multicenter cross-sectional observational cohort study, patients with TAVI or bioprosthetic SAVR underwent baseline echocardiography, CT angiography and ^{18}F-sodium fluoride (^{18}F-NaF) positron emission tomography (PET). Participants (n=47) were imaged once with ^{18}F-NaF PET/CT either at one-month (n=9, 19%), 2 years (n=22, 47%) or 5 years (16, 34%) after valve implantation. Subsequently patients underwent serial echocardiography to assess for changes in valve hemodynamic performance (change in peak aortic velocity) and evidence of structural valve dysfunction. Comparisons were made to matched patients with bioprosthetic SAVR (n=51) who had undergone the same imaging protocol.

Results: In patients with TAVI, native aortic valves demonstrated ^{18}F-NaF uptake around the outside of the bioprostheses that showed a modest correlation with the time from TAVI (r=0.36, p=0.023). ^{18}F-NaF uptake in the bioprosthetic leaflets was comparable between the SAVR and TAVI groups (target-to-background ratio 1.3 [1.2-1.7] versus 1.3 [1.2-1.5] respectively, p=0.27). The frequencies of imaging evidence of bioprosthetic valve degeneration at baseline were similar on echocardiography (6% versus 8% respectively, p=0.78), CT (15% versus 14% respectively, p=0.87) and PET (15% versus 29% respectively, p=0.09). Baseline ^{18}F-NaF uptake was associated with subsequent change in peak aortic velocity for both TAVI (r=0.7, p<0.001) and SAVR (r=0.7, p<0.001). On multivariable analysis, ^{18}F-NaF uptake was the only predictor of peak velocity progression (p<0.001).

Conclusions: In patients with TAVI, native aortic valves demonstrate evidence of ongoing active disease. Across imaging modalities, TAVI degeneration is of similar magnitude to bioprosthetic SAVR suggesting comparable mid-term durability.

Clinical Trial Registration: URL: https://www.clinicaltrials.gov/ Unique Identifier: NCT02304276

Key Words: SAVR; TAVI; valve degeneration; ^{18}F-sodium fluoride; PET/CT

Non-standard Abbreviations and Acronyms

CT – Computed tomography
HALT – Hypoattenuated leaflet thickening
HU – Hounsfield units
PET – Positron emission tomography
ROI – Region of interest
SAVR – Surgical aortic valve replacement
SD – Standard deviation
SUV – Standard uptake value
SVD – Structural valve deterioration
TAVI – Transcatheter aortic valve implantation
TBR – Target to background ratio

Clinical Perspective

What is new?

- After transcatheter aortic valve implantation, native aortic valves demonstrate evidence of ongoing disease activity, suggesting that aortic stenosis is an active disease process that is independent of motion and mechanical injury.
- ^{18}F-NaF PET identifies subclinical bioprosthetic degeneration of transcatheter aortic valves, providing prediction of subsequent valvular dysfunction and highlighting patients at risk of valve failure.
- Across three complementary and distinct imaging modalities, bioprosthetic degeneration of transcatheter aortic valves appears to be of similar magnitude to bioprosthetic SAVR suggesting comparable mid-term durability.

What are the clinical implications?

- ^{18}F-NaF PET holds promise in detection of bioprosthetic aortic valve degeneration and prediction of bioprosthesis failure.

Introduction

Transcatheter aortic valve implantation (TAVI) has revolutionized intervention options in aortic valve stenosis (1-4). Although the term TAVI and transcatheter aortic valve replacement (TAVR) are widely used interchangeably, TAVR is a misnomer since the native aortic valve is not replaced but rather displaced and splinted against the wall of the aorta at the time of bioprosthetic valve insertion. As a consequence, the native aortic valve is rendered immobile. Previously, it has been suggested that the impact of repeated valve closure and trauma is fundamental to aortic stenosis (5). Therefore, patients with TAVI present a unique opportunity to investigate the pathophysiology of aortic stenosis in the absence of the ongoing cyclical mechanical trauma of valve closure. Is aortic stenosis simply a disease of 'wear-and-tear' or is it an active regulated pathobiological process that continues despite valve immobilization?

TAVI is rapidly gaining popularity as a treatment option in younger low-risk populations (2-4). With its more widespread use, questions regarding valve durability become increasingly important (6). All bioprosthetic valves are susceptible to degeneration, driven by similar processes to native aortic valve stenosis. Indeed, active calcification appears to be the final common pathway of such degeneration leading to bioprosthetic valve stenosis, leaflet tears and valvular regurgitation (7,8). Whilst transcatheter bioprostheses are similar in structure to surgical valves, it has been suggested that the increased effective orifice area of TAVI will result in improved longevity. However, others have proposed that crimping of TAVI bioprostheses coupled with incomplete asymmetric frame expansion and suboptimal leaflet coaptation may lead to accelerated structural valve deterioration (SVD) (9). Whilst long term hemodynamic valve data are lacking, there is interest in comparing earlier non-invasive markers of valve

durability in patients with TAVI and those with bioprosthetic surgical aortic valve replacement (SAVR).

We have demonstrated that ^{18}F-sodium fluoride (^{18}F-NaF) positron emission tomography (PET) provides a marker of calcification activity and vascular injury across a range of cardiovascular conditions (10-15). In native aortic valve stenosis, ^{18}F-NaF uptake can assess valve calcification activity, providing important pathophysiological insights, a measure of disease severity and act as a predictor of subsequent disease progression and clinical events (10, 11). In bioprosthetic SAVR, ^{18}F-NaF PET uptake is an early and sensitive marker of leaflet degeneration, providing powerful prediction of subsequent valve dysfunction and valve failure (12).

In the present study, we sought to investigate whether the retained native aortic valves in patients undergoing TAVI demonstrate evidence of ongoing disease progression. Additionally, since long-term durability of transcatheter aortic valves is yet to be established, we aimed to establish whether bioprosthetic valve durability or degeneration was appreciably different between patients with TAVI or SAVR at mid-term follow-up.

Methods

Study Design and Patient Population

Patients with aortic stenosis who had undergone previous TAVI (1 month, 2 years or 5 years prior to study inclusion) using a balloon-expandable or self-expanding bioprosthesis were prospectively recruited into an observational cross-sectional cohort study at 3 high-volume TAVI centers between September 2016 and November 2019 (Edinburgh Heart Centre, Cedars Sinai Medical Center and Cambridge University Addenbrooke's Hospital; Figure 1). All participants

were under routine clinical follow-up and did not have established clinical evidence of bioprosthetic valve degeneration (16). Each patient underwent clinical assessment, echocardiography, hybrid ^{18}F-NaF PET and computed tomography (CT) angiography at baseline with annual repeat echocardiography thereafter (Figure 1). We excluded patients unable to give informed consent, with claustrophobia, allergy to iodinated contrast, liver failure, chronic kidney disease (with estimated glomerular filtration rate <30 mL/min/1.73 m^2), Paget's disease, metastatic malignancy, or an inability to tolerate the supine position. Patients with TAVI were compared to patients with SAVR valves undergoing the same research protocol (including multi-modality imaging protocols, image analysis assessments and follow up) (NCT02304276). Patients were recruited prospectively, matching the age of SAVR and TAVI valves (time from valve implantation for aortic stenosis to imaging) in the two groups. Baseline and follow up data from the SAVR cohort in isolation have been reported previously (12). The study (NCT02304276) was conducted in accordance with the Declaration of Helsinki and was approved by NHS Scotland Research Ethics Committee (14/SS/1049), the Administration of Radioactive Substances Advisory Committee and Institutional Review Boards at all sites. Recruitment was prematurely halted due to the onset of SARS-CoV-2 pandemic and the potential vulnerability of our target population. Additionally, we encountered difficulties in recruiting patients at 5 years following TAVI who were both alive and well enough to undergo study procedures. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Aortic Valve Imaging

Echocardiography

Two-dimensional and Doppler echocardiography was performed at baseline and annually

thereafter according to American Society of Echocardiography guidelines (17). Aortic valve Doppler measurements were routinely assessed from the apex, suprasternal notch and right sternal edge to measure the peak aortic jet velocity, the mean gradient and the effective orifice area of the bioprosthesis. Mean values were taken from 3 measurements when subjects were in sinus rhythm and from 5 measurements if in atrial fibrillation. Bioprosthetic valve regurgitation was graded as mild, moderate or severe according to guideline recommendations on the basis of visual appraisal of color Doppler images, measurement of pressure half-time (milliseconds) and assessment for aortic flow reversal in diastole (17).

PET/CT Imaging

All patients underwent ^{18}F-NaF PET at baseline on hybrid PET/CT scanners (128-slice Biograph mCT, Siemens Medical Systems, Knoxville, USA or Discovery 690/710 GE Healthcare, Milwaukee, WI, USA) using harmonized imaging protocols, 60 min after intravenous administration of 125 MBq of ^{18}F-NaF (18) obtained in 3-dimensional mode in a single 30-min bed position centered on the valve. Attenuation-correction CT was performed before acquisition of PET data. Finally, electrocardiogram-gated contrast-enhanced CT angiography was performed on the same scanner with prospective gating in end-expiration. Patients were given beta-blockers if resting heart rate was >65 beats/min and in the absence of clinical contraindications. After co-registration with PET, the CT data served for anatomical reference and facilitated PET tracer uptake quantification (19).

Imaging Analysis

Computed Tomography

Abnormalities on CT angiography were adjudicated using pre-specified criteria. Non-calcific leaflet thickening (hypoattenuated leaflet thickening - HALT) was defined as focal areas of low-

attenuation [30 to 200 Hounsfield Units (HU)] leaflet thickening visualized in at least 2 planes typically thickest at its base and thinning to the tips in accordance with consensus guidelines (20,21). Pannus was defined as circumferential low-attenuation (non-calcific) material with radial thickness ≥2 mm and encroachment on to the valve cusps (12). Leaflet calcification was defined as calcium >500 HU localized to a valve cusp in at least 2 planes and classified according to size as spotty calcification if maximum diameter was <3 mm, or large calcification if maximum diameter was ≥3 mm (22).

Positron Emission Tomography

Reconstructed ECG-gated PET and contrast-enhanced CT images were reoriented, co-registered in orthogonal planes and cardiac motion corrected with automatic algorithm preserving counts from all cardiac phases (supplemental methods) (23-26). Using *en face* images of the bioprosthetic valves, the maximum standard uptake values (SUV) in the native aortic valve was measured between the perimeter of the TAVI bioprostheses and the aorta. Care was taken to avoid regions of activity originating from the TAVI leaflets and nearby coronary arteries. Tissue to background ratio (TBR) values were derived from maximum SUV values corrected for blood-pool activity (mean SUV) measured in the right atrium (1-cm radius 9-mm high cylinder drawn on axial slices, at the level of the right coronary ostium).

With respect to ^{18}F-NaF uptake in the TAVI bioprosthetic valves, PET scans were adjudicated to be abnormal if discernible ^{18}F-NaF uptake originating from the valve leaflets was observed on 3 orthogonal planes. We quantified ^{18}F-NaF uptake according to a previously proposed methodology where a circular (area 1 cm^2) region of interest (ROI) was drawn around the area of maximal uptake originating in the valve cusps (12,27). ROIs were carefully drawn to avoid any uptake originating from outside of the bioprosthetic valve leaflets, in particular uptake

related to surrounding native aortic valve tissue. In subjects with no visible (exceeding blood-pool activity) uptake in the valve leaflets, a 1-cm^2 circular ROI was drawn in the center of the valve (10-12). Maximum SUV values were extracted from these ROIs and divided by the blood-pool activity measured in the right atrium to calculate the TBR values as described above. A similar approach was taken to the analysis of SAVR valves (12).

Clinical Follow up

Patients were invited to return annually for 2 years for repeat clinical assessment and echocardiography to assess for evidence of deterioration in hemodynamic bioprosthetic performance. In particular, change in peak velocity through the valve, change in mean pressure gradient and change in the effective orifice area were recorded. Changes in the grade of aortic regurgitation were documented.

Bioprosthetic valve deterioration was determined at baseline and after follow-up and was categorized as: *stage 1* a morphological abnormality (detected on echocardiography or CT), including HALT, calcification or pannus, in the absence of hemodynamic changes; *stage 2* either moderate valve obstruction, moderate regurgitation or both; stage 3 either severe valve obstruction or regurgitation (9, 16).

Patients were followed up for clinical events with outcome information obtained from local and national healthcare record systems that integrate primary and secondary health care records. The primary clinical endpoint of the study was a composite of bioprosthetic valve failure or repeat TAVI. Categorization of these outcomes was performed blinded to the PET imaging or other study data. Outcome data were collected in September 2020.

***Ex Vivo* Assessment**

To elucidate the pathology of aortic stenosis and TAVI degeneration and to validate our in vivo

imaging findings, we studied surgically explanted native and bioprosthetic aortic valves obtained from patients with dysfunctional degenerated TAVI in the Cardiovascular Tissue Registry at St. Paul's Hospital. E*x vivo* histological (hematoxylin and eosin; Movat's pentachrome), immunohistochemistry (runx2 and osteopontin) and ^{18}F-NaF autoradiography assessments (8) were made on these samples in accordance with the approval of the Research Ethics Board of Providence Health Care (supplemental methods).

Statistical Analysis

We assessed the distribution of data with the Shapiro-Wilk test. Continuous parametric variables were expressed as mean (SD) and compared using Student's t tests. Non-parametric data were presented as median [interquartile interval], compared using Mann-Whitney U test and log transformed to achieve normality prior to inclusion in regression models and correlation. Fisher's exact test or chi-squared test was used for analysis of categorical variables. We assessed correlations with the Pearson's coefficient. Multivariable linear regression modeling was used to assess the change in echocardiographic measures of bioprosthesis performance, clinical characteristics, and ^{18}F-NaF uptake. The multivariable model was constructed with annualised peak velocity change (m/sec) as the dependent variable and age, sex, time after aortic valve replacement, presence of HALT, valve TBR and baseline peak velocity and abnormalities on CT as independent variables, selected on the basis of clinically relevant and plausible mechanisms that may relate to valvular degeneration. Model residuals were checked against fitted values and distributions confirmed with quantile-quantile plots. To assess imaging evidence of bioprosthetic valve degeneration in TAVI or SAVR, we compared the echocardiography, CT and ^{18}F-NaF PET findings in our TAVI population with matched data from a previous study which characterized patients with bioprosthetic SAVR using the same clinical assessments, multi-

modality imaging protocols and image analyses (12). Receiver operating characteristic (ROC) analysis was performed to identify the optimum cut-off for TBR to identify patients at increased risk of structural valve degeneration using Youden J statistic. Statistical analysis was performed with SPSS version 24 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp), R studio and R software version 4.01 (R Foundation for Statistical Computing, Vienna, Austria). We used R packages: dlpyr, ggplot2, magrittr, QuantPsyc, Forestplot, cutpointr and ggpubr. A two-sided $p<0.05$ was considered statistically significant.

Results

Study Populations

We recruited 47 patients with TAVI from 3 high volume centers (81±6 years old, 79% male) who were compared with 51 patients with SAVR from the same institutions (Table 1). Similar to the SAVR cohort, patients with TAVI were imaged once with ^{18}F-NaF PET/CT at either one month (n=9, 19%), 2 years (n=22, 47%) or 5 years (16, 34%) after valve implantation. Twenty-five (53%) subjects were implanted with a balloon expanded bioprosthesis and 22 (47%) received a self-expanding valve.

Calcification Activity in Native Aortic Valve Tissue

Ex Vivo Validation

In five patients with TAVI for severe aortic stenosis, explanted TAVI valves and associated aortic roots were obtained 945 (range 3-2044) days after implantation (Tables I and II in the supplement). Calcified native aortic valve tissue was present around the perimeter of the TAVI bioprostheses (Figure 2) and histologically demonstrated evidence of ongoing calcification

activity with increased staining for both osteopontin and Runx-2 (Figure 2, Figures I and II in the supplement).

^{18}F-Sodium Fluoride Positron Emission Tomography

On contrast CT angiography at baseline, residual calcification from the native aortic valve was seen around the perimeter of the TAVI bioprosthesis in all cases. All subjects demonstrated ^{18}F-NaF uptake surrounding the TAVI bioprostheses that originated from the native aortic valve tissue (TBR range 1.6-5.8; Figure 2). Native valve ^{18}F-NaF uptake was highest in patients imaged 5 years after TAVI (TBR 3.3 [2.6-3.9] versus 2.2 [1.9-2.5] in those imaged one month after TAVI, p=0.023; Figure 2). Overall native valve uptake showed a modest positive correlation with the time from TAVI (r=0.36, p=0.023).

Assessments of Bioprosthetic Valve Degeneration

Ex Vivo Validation

In four explanted TAVI valves with evidence of valve leaflet degeneration, increased ^{18}F-NaF uptake was seen on autoradiography, with co-localization of this signal to regions of calcification within the TAVI valve leaflets as observable on hematoxylin and eosin and Movat's pentachrome staining (Figure 3).

Baseline Echocardiography and Computed Tomography

On echocardiography during their baseline research visit, valve function was normal in all but 3 patients. These 3 patients had 5-year-old TAVI valves and demonstrated increased transvalvular gradients. This had not been appreciated on previous clinical echocardiograms or clinical follow up. No patient had clinically significant valvular regurgitation. Leaflet morphology was assessable in 77% of patients and no abnormalities were detected on baseline echocardiograms.

CT scans had image quality suitable for leaflet assessments in 87% of patients. Only one patient had evidence of TAVI leaflet calcification on CT, demonstrating spotty calcification that was just discernible from the valve struts (Figure 3). Pannus formation was not observed in any of our patients. HALT was found in 6 (13%) patients, 5 of whom were imaged 5 years after TAVI and one patient imaged 1 month after implantation. Four of these patients demonstrated minimal (<25%) leaflet involvement, while 2 patients had pronounced HALT (exceeding 50% of the leaflets) causing restricted single leaflet motion on 4-dimensional CT. One patient with HALT had evidence of hemodynamic valve deterioration on echocardiography (mean pressure gradient 24 mmHg).

Overall, 8 patients had imaging evidence of bioprosthetic TAVI valve degeneration on echocardiography or CT. Seven of these patients were in the cohort of patients imaged 5 years following TAVI, with no differences in their baseline clinical characteristics compared to patients with similar aged TAVI valves but normal imaging (Table III in the supplement).

Baseline ^{18}F-Sodium Fluoride Positron Emission Tomography

All patients had good image quality enabling assessment of ^{18}F-NaF uptake in the bioprosthetic leaflets. There was no difference in ^{18}F-NaF uptake in self-expandable versus balloon-expandable TAVI bioprostheses (TBR: 1.3 [1.2-1.6] versus 1.3 [1.2-1.7], p=0.74). We detected ^{18}F-NaF uptake localized to the TAVI leaflets in 7 patients (15%), all imaged 5 years after TAVI (TBR range 1.6 to 5.9). Valve TBR values were nearly double those in patients without visually apparent leaflet uptake (2.3 [1.7-4.3] versus 1.3 [1.2-1.4], p<0.001). The 3 highest TBR values (range 3.0-5.9) were observed in the patients with evidence of hemodynamic structural valve deterioration on echocardiography (Stage 2 SVD; mean transprosthetic pressure gradients > 20 mmHg). Increased uptake was also observed in patients with structural evidence of valve

degeneration on CT (Stage 1 SVD) compared to valves with normal echocardiographic and CT appearances (Figure 2). One patient had evidence of increased ^{18}F-NaF leaflet uptake in the absence of any changes on CT or echocardiography. Of 6 patients presenting with HALT, 4 showed increased ^{18}F-NaF TAVI leaflet uptake (Figure 3 and Figure III in the supplement).

Disease Progression and Clinical Outcomes

Patients with TAVI underwent repeat echocardiographic evaluation at 15 [12-17] months to assess for evidence of progressive valve dysfunction. A strong correlation was observed between baseline ^{18}F-NaF TBR values in the TAVI leaflets and the subsequent annualized change in bioprosthetic valve peak velocity on echocardiography ($r=0.70$, $p<0.001$; Figure 4). Similar correlations were observed between ^{18}F-NaF leaflet uptake and the change in the mean pressure gradient ($r=0.55$, $p=0.01$) and the change in the effective orifice area ($r=-0.71$, $p=0.007$). On univariable analysis, the only predictors of the annualized change in peak velocity were valve age ($p=0.035$), abnormal CT findings ($p=0.006$) and ^{18}F-NaF leaflet uptake ($p<0.001$; Table 2). On multivariable analysis incorporating age, sex, duration of valve implantation, baseline peak prosthetic valve velocity and abnormal CT findings, ^{18}F-NaF uptake was the only predictor of the annualized change in peak velocity ($p<0.001$; Table 3).

Four patients developed clinical criteria for hemodynamic SVD during the follow up period, with each developing bioprosthetic valve stenosis (mean pressure gradient 27 [24-31] mmHg and peak velocity 3.6 [3.4-4.1] m/s). Three patients had increased ^{18}F-NaF TAVI leaflet uptake at baseline. In the single patient without increased ^{18}F-NaF uptake at baseline, the increased mean pressure gradient normalized after 3 months of anti-coagulation therapy and in retrospect was attributed to valve thrombosis rather than established irreversible structural valve disease. The patient with the highest leaflet ^{18}F-NaF uptake in the TAVI cohort developed

bioprosthesis failure 18 months after baseline PET and underwent a successful TAVI-in-TAVI. Based on the Youden's index, the optimal cut-off TBR value to identify patients at increased risk of structural valve degeneration was 1.59. In our study, the 1.59 TBR threshold had a sensitivity of 86%, specificity of 89%, positive predictive value of 86%, negative predictive value of 97% and accuracy of 89% for prediction of hemodynamic valve degeneration.

Comparison to Patients with Age-matched SAVR Valves

Fifty-one patients with SAVR who underwent the same research imaging protocol were compared to the 47 patients with TAVI. The latter were older (82 [76-86] versus 72 [70-77] years, p<0.001) and had more co-morbidity than patients with SAVR. The time from valve replacement to imaging was similar (24 [24-60] vs 24 [24-60] months, p=0.91) as were the number of SAVR and TAVI patients imaged 1 month, 2 years and 5 years after valve replacement (Table 1). Patients with TAVI had lower peak aortic jet velocity (2.4 [2.0-2.7] vs 2.7 [2.4-3.0] m/s, p=0.03) and larger effective orifice area (1.5 [1.3-1.8] vs 1.1 [1.0-1.5] cm^2, p=0.02, Table 1) than patients with SAVR.

Evidence of bioprosthetic degeneration was similar in TAVI and SAVR groups on echocardiography (6% vs 8% respectively, p=0.78) and CT (15% vs 14% respectively, p=0.87; Figure 5). While the overall prevalence of patients with increased leaflet ^{18}F-NaF uptake appeared to be nearly double in patients with SAVR (29% versus 15% in those with TAVI), this did not reach statistical significance (p=0.09) and in those studied at 5 years, there was no difference in the proportion of patients demonstrating bioprosthetic uptake (40% SAVR vs 44% TAVI patients, p=0.79). Overall ^{18}F-NaF uptake was similar in both TAVI and SAVR valves (TBR: 1.3 [1.2-1.7] vs 1.3 [1.2-1.5], p=0.27).

Discussion

In patients with TAVI, we have demonstrated that ^{18}F-NaF uptake within the native aortic valve is higher with longer duration of implantation suggesting disease activity continues despite immobilization of the valve leaflet. This was further supported by our histological finding of continued activation of pro-calcific markers in explanted native valves after TAVI. We have further shown using 3 complementary and distinct imaging modalities that the prevalence of valve degeneration within TAVI bioprostheses is similar to that of bioprosthetic SAVR valves for up to 7 years after valve replacement. Finally, we have confirmed that ^{18}F-NaF PET of the bioprosthetic valve provides a powerful independent predictor of subsequent hemodynamic bioprosthetic valve degeneration that is applicable to both TAVI and SAVR and outperforms all other traditional risk factors. We conclude that aortic stenosis is an active regulated disease process rather than solely the result of simple wear and tear of the valve, and that TAVI appears to have similar durability to SAVR with comparable modest rates of mid-term bioprosthetic valve degeneration.

We have previously established ^{18}F-NaF PET as a tool for the *in vivo* assessment of calcification activity across multiple different cardiovascular disease states (10-15). In patients with aortic stenosis, valvular ^{18}F-NaF uptake provides an assessment of disease activity and prediction of subsequent disease progression and clinical events (10,11). We have here demonstrated that ^{18}F-NaF uptake continues to occur in the retained native aortic valve of all patients with TAVI. We had hypothesized that ^{18}F-NaF uptake might have transiently increased early following TAVI when native valve calcium has been disrupted, thereby increasing the available surface area for ^{18}F-NaF binding. Thereafter, ^{18}F-NaF uptake would be anticipated to decline as the valve heals and the mechanical trauma of repeated valve closure ceased. However,

we observed the opposite. Native aortic valve ^{18}F-NaF uptake and calcification activity was higher with longer duration of implantation. We observed a modest correlation between native valve uptake and the time from TAVI. This finding was supported by our *ex vivo* data that demonstrated histological evidence of ongoing calcification activity in native aortic valve tissue many years following TAVI. These observations are consistent with the hypothesis that once established, calcification activity in the native aortic valve continues to accelerate in an ongoing pathobiological process with continuing mineralization (the propagation phase) that is not halted even following TAVI (28). Indeed, the fact that it continues several years after TAVI, when mechanical stresses are no longer being exerted on the valve leaflets, confirms that aortic stenosis is an active regulated disease process and not simply the result of valve wear and tear. Therapies focused on slowing this cycle of calcification are required if we are going to develop the medical treatments for aortic stenosis that are so urgently needed. Medications interfering with tissue calcification and ectopic bone formation (alendronate and denosumab) have recently been tested in this context but unfortunately were unable to alter aortic valve calcification or disease progression (5, 29, 30).

In patients with bioprosthetic SAVR, ^{18}F-NaF uptake provides a marker of bioprosthetic valve degeneration and a powerful predictor of subsequent valve dysfunction (12). Our current study extends these findings to patients with TAVI, demonstrating that increased ^{18}F-NaF uptake in the bioprosthetic valve leaflets provides an early indication of valve degeneration and a more powerful predictor of subsequent valve dysfunction than valve age, cardiovascular co-morbidities and imaging assessments provided by echocardiography and computed tomography. Interestingly, the association between baseline bioprosthetic leaflet ^{18}F-NaF uptake and subsequent change in bioprosthetic valve peak velocity was identical in patients with TAVI

(r=0.7, p<0.001) to that previously reported for bioprosthetic SAVR valves (r=0.7, p<0.001). Combined with the existing bioprosthetic SAVR data, this positions ^{18}F-NaF PET as a highly promising marker of early bioprosthetic valve degeneration that might provide important value in the prediction of bioprosthesis failure, particularly as other imaging modalities such as echocardiography and CT are currently limited in this regard. Future trials are now required to assess whether this molecular imaging technique can aid clinical decision making and risk stratify patients with bioprosthetic valves. Based on the findings of this study, one potential strategy would be to perform a 5-year ^{18}F-NaF PET scan after TAVI as a screening tool for identifying those at increased risk of rapid deterioration. This might help the planning of repeat intervention and differentiate patients who require close monitoring from those with no evidence of even early valve degeneration who can be assessed much less frequently.

Given the powerful prediction of valve dysfunction provided by ^{18}F-NaF in both bioprosthetic SAVR and TAVI valves, our dataset provides a unique opportunity to compare early valve degeneration in age-matched bioprosthetic SAVR and TAVI valves, thereby helping address one of the most important current questions in heart valve disease. Are TAVI valves likely to last as long as surgical bioprostheses? In the present study, there were no differences in the proportion of patients with TAVI or SAVR bioprostheses who had echocardiographic or CT evidence of valve degeneration for up to 7 years after replacement. Very similar rates of increased ^{18}F-NaF uptake were observed in patients with SAVR and TAVI valves implanted 5 years previously (40 versus 44 %) despite patients with TAVI having a much higher burden of cardiovascular co-morbidities. Taken together, our data suggest that imaging assessments of valve degeneration are similar between these two types of valve, supporting similar mid-term durability of TAVI and SAVR bioprosthetic valves. If confirmed in larger studies, then this

would help assuage one of the main lingering concerns about performing TAVI as the first line valve replacement method in patients with aortic stenosis.

Our study has several strengths and weaknesses. We have employed a state-of-the-art multi-modality imaging study design and employed the same protocols to image patients with age matched SAVR and TAVI valves thereby providing a unique opportunity to compare imaging findings in these 2 valve types. Moreover, we provide longitudinal data confirming the predictive value of ^{18}F-NaF PET in both SAVR and TAVI valves. Whilst relatively large for a complex molecular imaging study, our overall sample size is modest (47 TAVI and 51 SAVR valves). Our observations therefore require confirmation in larger data sets with longer follow-up. Patients with bioprosthetic SAVR and TAVI were not matched for age nor co-morbidities however, given the different patient populations who currently received these two treatments, this is inevitable, and our results would suggest that these co-morbidities do not greatly influence valve degeneration nor durability. Given the cross-sectional nature of our study, we acknowledge the potential for survivor bias. This could be addressed in future longitudinal cohort studies to ensure prospective capture of all cases of valvular degeneration. Due to the outbreak of SARS-CoV-2 pandemic, we discontinued further recruitment before reaching our pre-defined number of study participants and therefore further studies are needed to confirm our findings. Finally, in our study, we focused on bioprosthetic valves, and our findings should not be extrapolated to mechanical aortic valve prostheses which have better durability than both forms of bioprosthetic valve.

In conclusion, we have demonstrated that native aortic valves after TAVI demonstrate evidence of ongoing disease activity, suggesting that aortic stenosis is an active disease process that is independent of motion and mechanical injury. Across three complementary and distinct

imaging modalities, TAVI degeneration appears to be of similar magnitude to bioprosthetic SAVR suggesting comparable mid-term durability. ^{18}F-NaF PET appears to be a consistent method of detecting early bioprosthetic valve degeneration and predicting subsequent dysfunction for both TAVI and SAVR.

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Disclosures

JAL consults for Heartflow Inc., and Circle Cardiovascular Imaging and provides CT core lab services for Edwards Lifesciences, Medtronic, Boston Scientific, Abbott, PI Cardia, MVRX, for which no direct compensation is received. J. Leipsic has stock options in HeartFlow Inc and Circl CVI. NLC and NGU proctor for Edward Lifesciences.

Supplemental Materials

Expanded Methods

Supplemental Tables I - III

Supplemental Figures I - III

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Table 1. Comparison of patients following transcatheter aortic valve implantation versus patients following surgical aortic valve replacement.

	Patients with transcatheter bioprosthetic valves n=47	**Patients with surgical bioprosthetic valves n=51**	**P value**
Age (years)	82 [76-86]	72 [70-77]	<0.001
Men	29 (62%)	29 (57%)	0.63
Body-mass index (kg/m^2)	24 [20-26]	27 [24-32]	<0.001
Systolic blood pressure (mmHg)	132 [120-146]	156 [142-165]	<0.001
Diastolic blood pressure (mmHg)	68 [60-73]	80 [73-87]	<0.001
Heart rate	63 [59-74]	70 (63-82)	0.03
Bioprosthesis age			
Time since valve replacement (months)	24 [24-60]	24 [24-60]	0.91
5 years post valve replacement	16 (34%)	20 (39%)	0.65
2 years post valve replacement	22 (47%)	22 (43%)	0.68
1 month post valve replacement	9 (19%)	9 (18%)	0.79
Comorbidities			
Hypertension	38 (80%)	38 (75%)	0.45
Hyperlipidemia	24 (51%)	39 (76%)	0.01
Diabetes	15 (31%)	3 (6%)	0.02
Smoking	28 (60%)	25 (49%)	0.31
Coronary Artery Disease	24 (51%)	18 (35%)	0.12
coronary artery bypass grafts	17 (31%)	14 (27%)	0.35
Medication			
Aspirin	27 (57%)	37 (73%)	0.12
P2Y12 antagonist	8 (17%)	7 (14%)	0.65
Warfarin	7 (14%)	4 (8%)	0.27
Direct Oral Anticoagulation	1 (2%)	1 (2%)	0.85
ACE inhibitor/angiotensin receptor blocker	30 (63%)	28 (55%)	0.37
Beta blocker	28 (60%)	24 (47%)	0.21
Statin	35 (74%)	35 (68%)	0.52
Electrocardiogram			
Sinus rhythm	27 (57%)	47 (92%)	<0.001
Paced rhythm	9 (20%)	0	<0.001
Atrial Fibrillation	7 (14%)	2 (4%)	0.06
Left ventricular hypertrophy	5 (11%)	20 (39%)	0.01
Left ventricular hypertrophy – with strain	3 (7%)	12 (24%)	0.02
Echocardiography			
Evidence of valve degeneration	3 (6%)	4 (8%)	0.78
Evidence of valve degeneration in 5-year-old valves	3 (19%)	4 (20%)	0.78
Reduced LV ejection fraction	9 (19%)	8 (16%)	0.65
Vmax (m/s)	2.4 [2.0-2.7]	2.7 [2.4-3.0]	0.03
Mean valve gradient (mm Hg)	12 [9-14]	15 [12-19]	0.18
Effective orifice area (cm^2)	1.5 [1.3-1.8]	1.1 [1.0-1.5]	0.02
Computed Tomography			
CT evidence of valve degeneration	7 (15%)	7 (14%)	0.87
CT evidence of valve degeneration in 5-year-old valves	6 (38%)	4 (20%)	0.42

Spotty calcification	1 (2%)	2 (4%)	0.61
Pannus	0	2 (4%)	0.07
Hypoattenuated leaflet thickening	6 (13%)	4 (8%)	0.42
^{18}F-Sodium Fluoride Positron Emission Tomography			
Increased leaflet ^{18}F-NaF	7 (15%)	15 (29%)	0.09
Increased leaflet ^{18}F-NaF in 5-year-old valves	7 (44%)	8 (40%)	0.79
Target to background ratio	1.3 [1.2-1.7]	1.3 [1.2-1.5]	0.27

Number (%); median [interquartile range]

ACE – angiotensin-converting enzyme; CT – computed tomography; ^{18}F-NaF - ^{18}F-sodium fluoride

Table 2. Factors associated with future deterioration in TAVI function (annualized change in peak velocity after 2 years): univariable analysis.

UNIVARIABLE PREDICTORS OF PROGRESSION IN PEAK VELOCITY				
Variable	**Unstandardized Coefficient (95% Confidence Interval)**	**Standard Error**	**Standardized Coefficient**	**P value**
Sex	0.106 (-0.491 to 0.704)	0.298	0.083	0.72
Age	-0.006 (-0.040 to 0.027)	0.013	-0.086	0.70
Body-mass Index	-0.016 (-0.064 to 0.031)	0.023	-0.169	0.47
Valve Age	0.139 (0.011 to 0.268)	0.064	0.431	**0.035**
Valve Type	-0.021 (-0.050 to 0.010)	0.015	-0.085	0.54
Systolic blood pressure	-0.005 (-0.021 to 0.011)	0.013	-0.153	0.50
Hypertension	0.028 (-1.318 to 1.373)	0.6429	0.010	0.96
Diabetes	0.104 (-0.473 to 0.681)	0.276	0.086	0.71
Dyslipidemia	0.255 (-0.713 to 1.224)	0.463	0.126	0.59
Smoking	-0.865 (-2.096 to 0.366)	0.479	-0.628	0.13
Baseline Peak Velocity	-0.2417 (-0.850 to 0.367)	0.294	-0.173	0.42
Hypoattenuated leaflet thickening on CT	0.4495 (-0.346 to 1.245)	0.383	0.242	0.25
Abnormal CT findings	0.889 (0.277 to 1.501)	0.295	0.540	**0.006**
Native valve TBR	0.032 (-0.218 to 0.282)	0.120	0.058	0.79
TAVI TBR	0.509 (0.348 to 0.669)	0.078	0.813	**<0.001**

CT: computed tomography; TAVI: transcatheter aortic valve implantation; TBR: target to background ratio.

Table 3. Factors associated with future deterioration in TAVI function (annualized change in peak velocity after 2 years): multivariable analysis.

MULTIVARIABLE ANALYSIS: PREDICTORS OF PROGRESSION IN PEAK VELOCITY				
SUMMARY:	**R = 0·760**		**R Square 0.580**	**p = 0.002**
Variable	**Unstandardized Coefficient (95% Confidence Interval)**	**Standard Error**	**Standardized Coefficient**	**P value**
Age	-0.013 (-0.039 to 0.012)	0.012	-0.176	0.287
Sex	0.109 (-0.303 to 0.520)	0.193	0.090	0.447
Valve Age	-0.029 (-0.171 to 0.113)	0.066	-0.088	0.663
Baseline Peak Velocity	-0.09 (-0.552 to 0.366)	0.214	-0.070	0.670
Abnormal CT findings	0.565	0.445	0.330	0.225
TAVI TBR	0.476 (0.244 to 0.727)	0.114	0.628	**<0.001**

TAVI: transcatheter aortic valve implantation; TBR: target to background ratio.

Figure Legends

Figure 1. CONSORT flow diagram of study recruitment, allocation (assessments), follow-up and analysis.

Figure 2. Baseline assessment with ^{18}F-sodium fluoride activity in native aortic valve tissue following transcatheter aortic valve replacement.

A: Hybrid ^{18}F-sodium fluoride positron emission tomography and computed tomography (^{18}F-NaF PET/CT) *en face* and long axis images of native aortic valve tissue uptake. We observed intense tracer activity originating from the native valve tissue around the perimeter of the bioprosthesis in all patients with transcatheter aortic valve replacement (TAVI). **B:** Native aortic valve ^{18}F-NaF uptake in patients with TAVI was higher with longer duration since bioprosthesis implantation suggesting increased calcification activity following intervention. **C:** Representative macroscopic images of explanted TAVI valves (green arrow) surrounded by native aortic valve (red arrow) jailed between the bioprostheses and the aortic root (blue arrow): ventricular aspect (left), aortic aspect (middle) and view of the root with native valve tissue cut and opened out along its perimeter (right). **D:** Histology (Movat's pentachrome staining) and immunohistochemistry of native aortic valves showing morphology, high expression of Runx2 and osteopontin in the native aortic valves explanted a month, 32 and 53-months post-TAVI.

Figure 3. ^{18}F-Sodium fluoride identifies early TAVI bioprosthetic valve degeneration.

A: Top row: a 76-year-old female with hemodynamic valve deterioration on echocardiography imaged 5 years after transcatheter aortic valve replacement (TAVI) implantation. Computed

tomography angiography revealed spotty calcification on the bioprosthetic leaflets. On ^{18}F-sodium fluoride positron emission tomography (^{18}F-NaF PET), we detected very high uptake in the leaflets (target-to-background [TBR] = 5.9). The patient developed bioprosthesis failure 18 months after baseline PET and underwent a successful TAVI-in-TAVI. Second row: an 88-year-old male with hemodynamic valve deterioration on echocardiography imaged 5 years after TAVI. Computed tomography angiography revealed hypoattenuated leaflet thickening. On ^{18}F-NaF PET we detected very high uptake in the leaflets (TBR = 3.8). **B:** There was a stepwise increase in TAVI ^{18}F-NaF uptake according to the presence and severity of valve dysfunction. ^{18}F-NaF uptake was highest in patients with hemodynamic dysfunction, and more pronounced in those with structural valve deterioration (SVD) than normal TAVI valves. **C:** Histological and autoradiography validation of ^{18}F-NaF avidity in a Edwards CE TAVI valve explanted after 86 months: Movat's pentachrome and hematoxylin and eosin staining, demonstrate that leaflet calcification corresponds closely with ^{18}F-NaF binding on autoradiography.

Figure 4. Baseline ^{18}F-sodium Fluoride Uptake Predicts Subsequent Deterioration in TAVI Function.

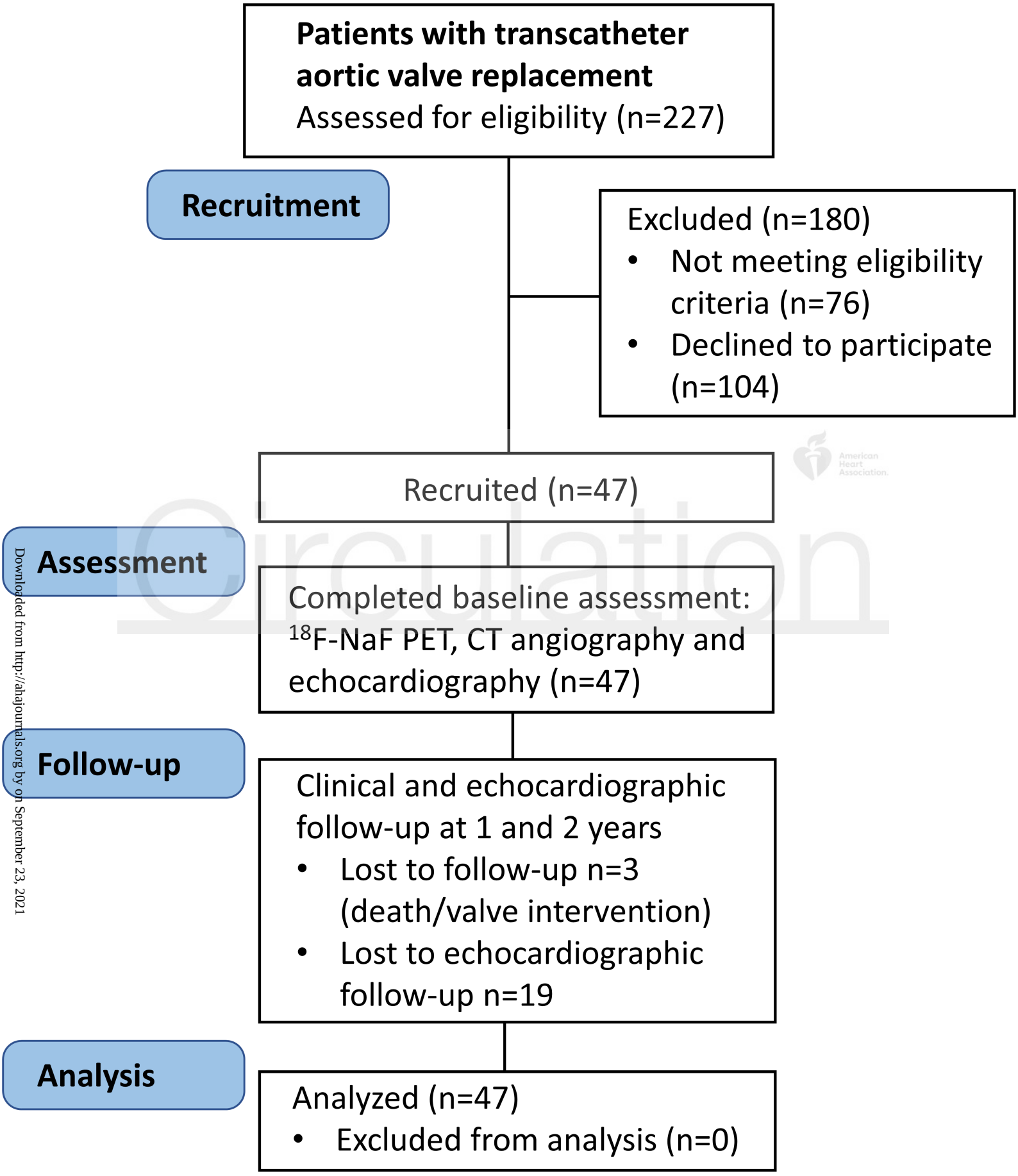
A: Case example of an 84-year-old patient imaged 5 years following transcatheter aortic valve replacement (TAVI). We detected TAVI ^{18}F-sodium fluoride (^{18}F-NaF) leaflet uptake in the absence of abnormalities on echocardiography (mean pressure gradient 11 mmHg) and computed tomography (CT). At follow up, the patient developed moderate bioprosthesis stenosis with mean pressure gradient of 23 mmHg. **B:** A strong correlation was observed between baseline ^{18}F-NaF uptake in the TAVI valves (TBR) and subsequent progression in bioprosthetic valve peak velocity ($r=0.7$; $p < 0.001$). **C:** Forest plot of unstandardized coefficients (95% confidence

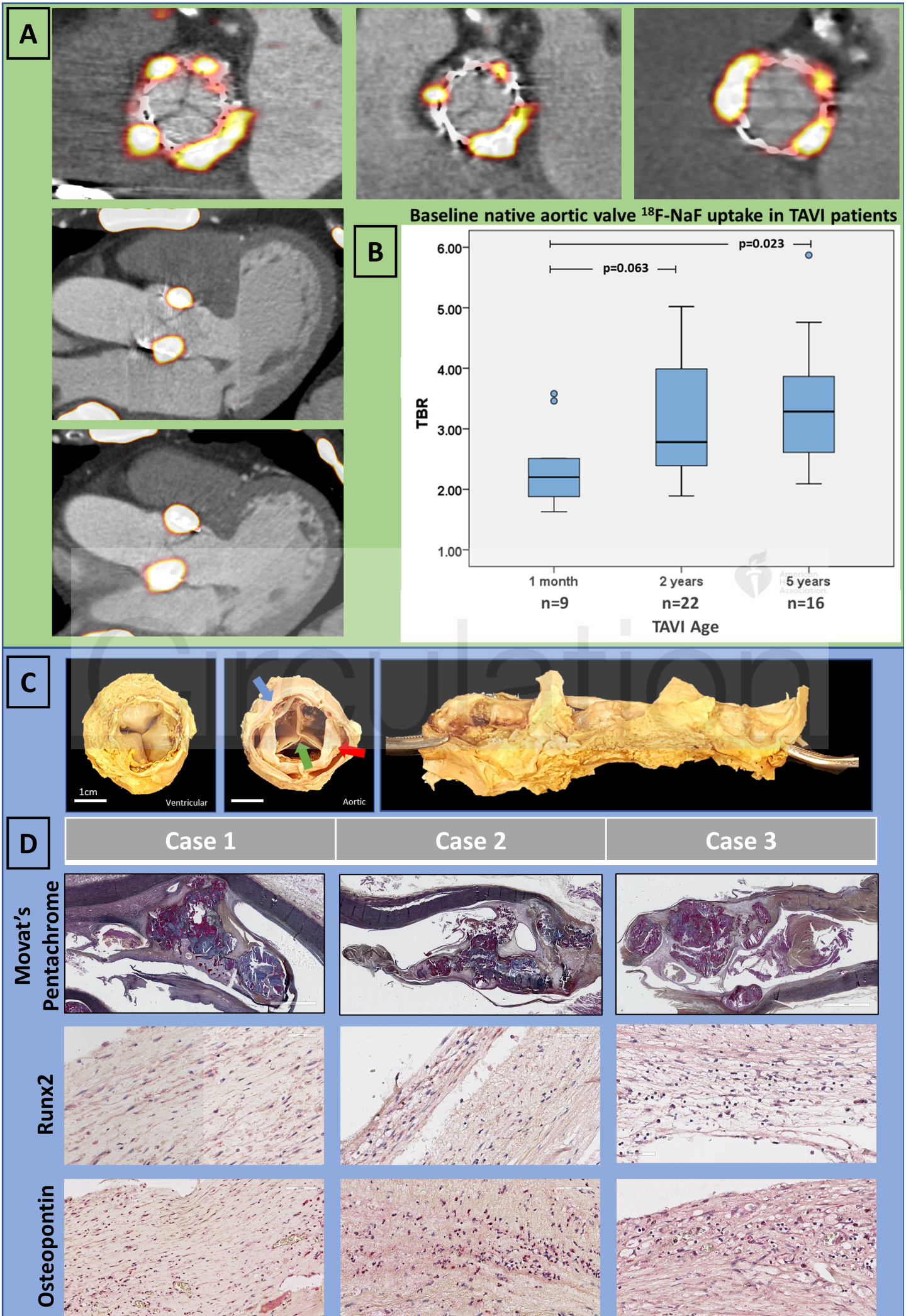
intervals) from a multivariable linear regression analysis predicting change in TAVI valve function (annualized change in peak velocity) during follow-up. When examining all relevant baseline characteristics, ^{18}F-NaF uptake was the only independent predictor of hemodynamic TAVI deterioration.

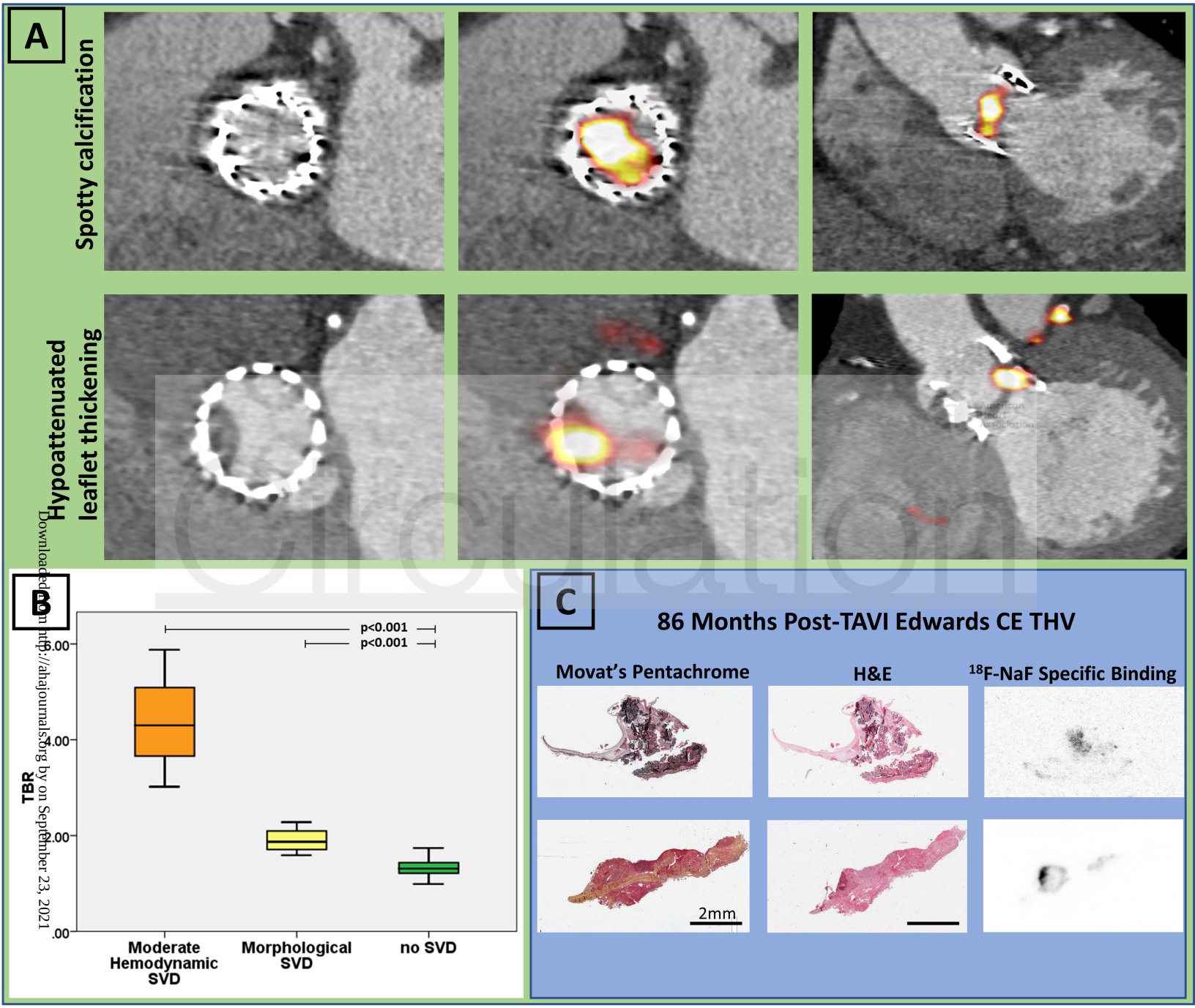
Figure 5. Comparison of imaging findings and valve deterioration in TAVI versus bioprosthetic SAVR.

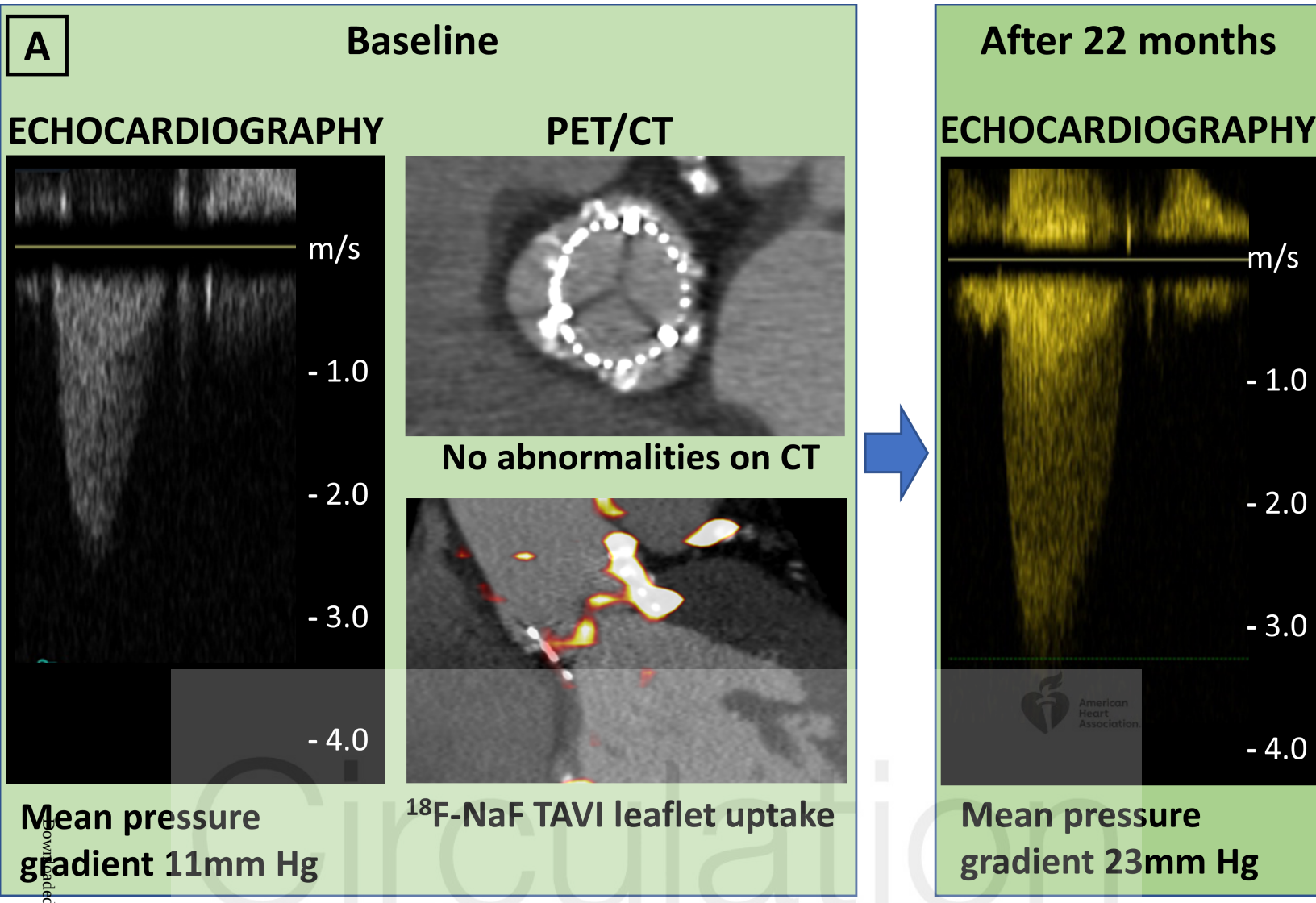
We compared echocardiographic, computed tomography (CT) and ^{18}F-sodium fluoride (^{18}F-NaF) findings in 47 patients with transcatheter aortic valve replacement (TAVI) with 51 patients with surgical aortic valve replacement (SAVR) who underwent the same research imaging protocol. We observed ^{18}F-NaF uptake on the peripheral of all TAVI valves and none of the SAVR valves. While patients with TAVI showed lower peak velocity (2.4 [2.0-2.7] vs 2.7 [2.4-3.0] m/s, p=0.03) and larger effective orifice area (1.5 [1.3-1.8] vs 1.1 [1.0-1.5] cm^2, p=0.02) than patients with SAVR, we detected baseline echocardiographic (6 vs 8% p=0.78) and CT abnormalities (15 vs 14% p=0.87) suggestive of bioprosthetic degeneration in a similar proportion of patients with either TAVI or SAVR. The overall prevalence of patients with increased leaflet ^{18}F-NaF uptake was nearly double in patients with SAVR compared to those with TAVI (29% and 15%, p=0.09). In both patients with SAVR or TAVI, baseline ^{18}F-NaF leaflet uptake was predictive of the change in the peak transvalvular velocity on echocardiography.

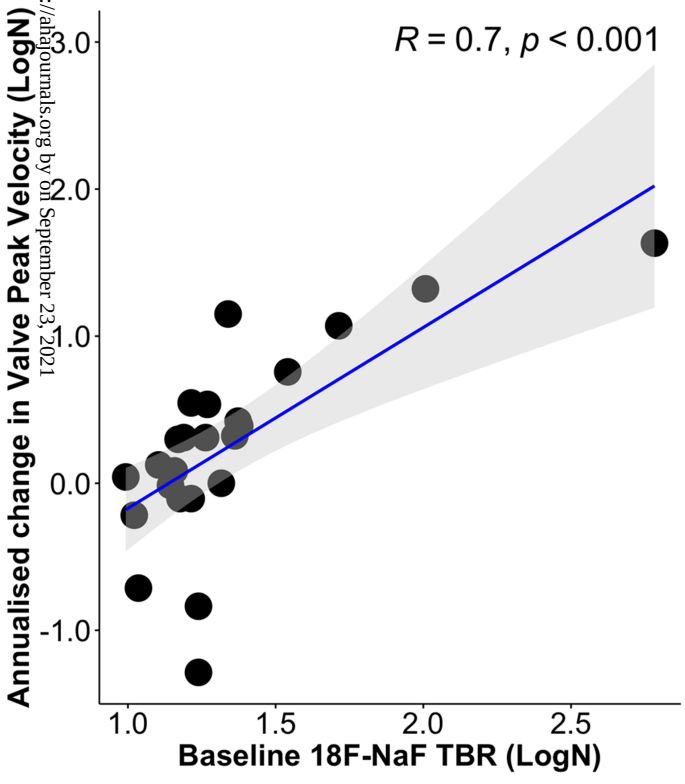
Cross-Sectional Observational Cohort Study

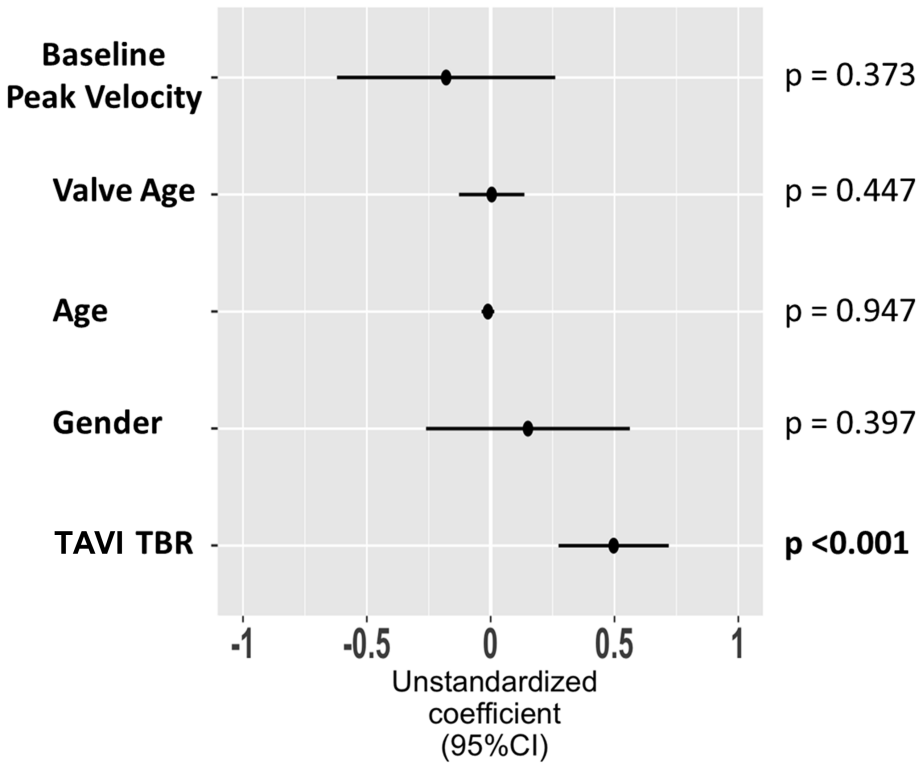




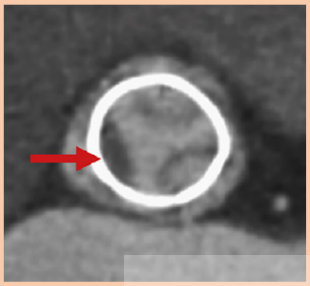
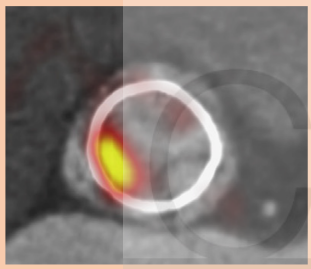
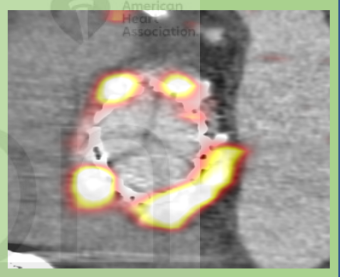
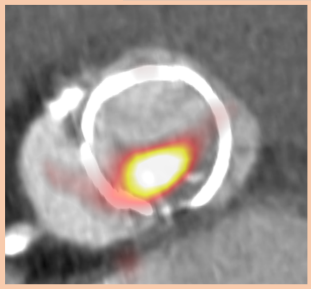
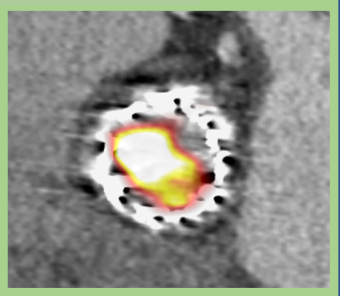
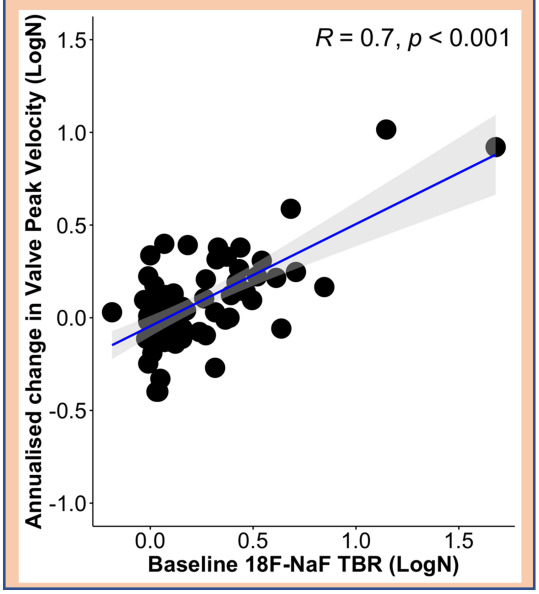








Bioprosthetic Aortic Valves

SAVR n=51		TAVI n=47
1.1 (1.0-1.5) cm^2	Effective Orifice Area	1.5 (1.3-1.8) cm^2
8%	Valve deterioration on Echocardiography	6%
 14%	Abnormalities on CT	15% 
 0%	^{18}F-NaF uptake surrounding the bioprosthesis on PET	100% 
 29%	^{18}F-NaF leaflet uptake on PET	15% 
	Prediction of deterioration with ^{18}F-NaF uptake