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Original Article

Does the transapical approach impair early recovery of systolic strain following transcatheter aortic valve replacement?

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Abstract: Background: In transcatheter aortic valve replacement (TAVR) the trans-apical approach (TA) is associated with apical myocardial injury but it is unknown if this injury impacts myocardial function. This study was performed to assess the impact of TA on apical longitudinal strain (ALS) and global longitudinal strain (GLS) after TAVR. Methods: 44 consecutive patients (age 81 ± 7 years, 48% male) underwent TAVR via trans-femoral (TF) (n=27) or TA (n=17) approach. Speckle-tracking analysis of left ventricular longitudinal strain was performed on images from peri-procedure transesophageal echocardiograms immediately before and after valve implantation. The primary endpoint was a GLS improvement of at least 25% post-TAVR. Results: GLS improved significantly above baseline after valve implantation in both TF ($p<0.001$) and TA ($p=0.027$) groups. The absolute magnitudes of ALS and GLS improvement were similar between TF and TA patients (ALS: $p=0.282$; GLS: $p=0.248$). Peak ALS and GLS achieved post-TAVR were similar between TF and TA patients (ALS: $p=0.933$; GLS: $p=0.365$). 47% of patients achieved a GLS improvement of >25%; 16 of which improved their GLS to <-15%. The severity of pre-TAVR GLS impairment was a strong independent predictor of GLS improvement (OR=1.61, $p=0.003$). A pre-TAVR GLS ≥-13.7% was 82% sensitive and 82% specific for TAVR to confer a GLS improvement >25%. Conclusion: Equal improvement in myocardial strain was observed in the TF and TA patients. Pre-TAVR GLS impairment was an independent predictor of post-TAVR GLS recovery, highlighting how it is the patient's baseline GLS dysfunction, not the method of approach, that dictates post-TAVR functional recovery.

Keywords: Transcatheter aortic valve replacement, speckle tracking analysis, strain, aortic stenosis

Introduction

TAVR has emerged as a less invasive alternative to traditional surgical aortic valve replacement (SAVR) for treating severe aortic stenosis (AS) [1, 2]. The prosthetic valve may be delivered via the trans-femoral (TF) approach, or, in patients with severe aortic calcification, peripheral artery disease, or tortuous iliac arteries, an alternate approach transapical (TA) approach may be employed. Subclinical myocardial injury is commonly observed during TAVR and appears to be more common with the TA approach [3]. Moreover, the TA approach has been shown to be an independent risk factor for death due to advanced heart failure in TAVR recipients [4]. This could be a result of the direct cannulation of the apex leading to impairment of reverse cardiac remodeling.

Two-dimensional speckle tracking echocardiography (STE) allows for the measurement of global and regional myocardial mechanical function by detecting subtle changes in myocardial strain [5-7]. By utilizing STE, systolic global longitudinal strain (GLS) impairment has emerged as an independent predictor of mortality in patients with severe AS prior to AVR [8-10]. Following AVR, GLS impairment has been shown to resolve [11-13]. However, the impact of the approach on GLS or apical longitudinal strain (ALS) recovery is unknown. Impaired GLS recovery after the TA approach could explain the poorer survival in these patients. Therefore, this study was undertaken to assess the immediate change in left ventricular (LV) strain following TAVR, determine if any difference exists based on the method of approach, and assess for predictors of immediate strain recovery.

Methods

Study design and patient population

Sixty-two consecutive patients who underwent TAVR at a single institution from 2012 to 2014 were screened retrospectively for inclusion in this study. Patient demographics, medical history, Society of Thoracic Surgeons (STS) score and echocardiographic data were obtained from the electronic medical records. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 ml/min/m^2. Access site and surgical approach were determined based on the computed tomographic angiography findings of the arterial tree. Patients with a severely torturous or calcified aorta, heavily calcified femoral artery, or an aortic diameter <6 mm, underwent TA. Patients with suboptimal TEE imaging for STE analysis, lack of same view images before and after TAVR, or patients in atrial fibrillation during the procedure were excluded from the study. This study was approved by the Institutional Review Board of Montefiore Medical Center and Albert Einstein College of Medicine.

Transcatheter aortic valve replacement

TAVR using the TF and TA approaches were performed in standard fashion under general anesthesia using the Edwards Sapien valve prosthesis or the Medtronic CoreValve [1, 2].

Pre-TAVR transthoracic echocardiography

All patients underwent transthoracic echocardiography (TTE) (Philips IE33, Philips Medical, Andover, MA) prior to undergoing TAVR. All images were acquired according to the American Society of Echocardiography guidelines [14]. Left ventricular ejection fraction (LVEF) was calculated with the biplane Simpson's method. Aortic valve area (cm^2) was calculated using the continuity equation. Mean aortic pressure gradient was calculated from the modified Bernoulli equation [15]. LV mass (gram) was calculated using the Devereux formula [16]. The degree of mitral regurgitation and aortic insufficiency was quantified based on the current practice guidelines [17].

Peri-procedure transesophageal echocardiography and strain analysis

All patients underwent peri-procedure transesophageal echocardiography (TEE) using Philips IE33 system (X7 TEE transducer, Philip Medical System, Andover, MA) during TAVR. Mid-esophageal 2 or 4-chamber views were obtained before and after deployment of the prosthetic valve at a minimum frame rate of 45fps. STE analysis of the pre- and post-TAVR TEE images was performed offline using Syngo Velocity Vector Imaging software (Ver 4.2, Siemens Healthcare, Erlangen, Germany) by two observers blinded to the clinical information. One cardiac cycle was selected based on the simultaneously recorded electrocardiogram from the onset of QRS to the onset of next QRS. The endocardium was manually traced at the end-diastolic phase and the software automatically divided the left ventricle into six segments (basal-septal, mid-septal, apical septal, apical lateral, mid lateral and basal lateral). Tracking quality was assessed visually. GLS was calculated from the mean peak longitudinal strain from all six segments, and ALS was derived from the mean peak strain of the apical septal and apical lateral segments.

The primary endpoint was an improvement in GLS of at least 25% above baseline immediately after valve deployment. The cut-off 25% was selected because it is adequately higher than intra-observer variability of strain measurements. Secondary analyses were performed comparing ALS and GLS in patients who underwent the TA versus the TF approaches and to identify predictors of GLS improvement.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD). Categorical variables are expressed in number (percentage). The D'Agostin's K test with Royston's revision was used to assess the distribution of continuous variables. Two-tailed Student t-test and Wilcoxon signed-rank test were used to com-

Table 1. Baseline patient demographics, comorbidities and transthoracic echocardiography measurements

Variables	Total N=44	TF-TAVR N=27	TA-TAVR N=17	*p*-value
Demographics				
Age, years	81 ± 7	81 ± 7	81 ± 9	0.940
Male, n (%)	21 (48%)	13 (48%)	8 (47%)	1.000
BMI (Kg/m^2)	28 ± 7	29 ± 8	27 ± 5	0.378
STS score	7.7 ± 4.4	6.2 ± 3.6	10.0 ± 4.6	0.001
Comorbidities				
Hypertension	40 (91%)	24 (89%)	16 (94%)	1.000
Hyperlipidemia	34 (77%)	20 (74%)	14 (82%)	0.716
Diabetes mellitus	15 (34%)	10 (37%)	5 (29%)	0.748
Prior CABG	15 (34%)	8 (30%)	7 (41%)	0.521
CKD	24 (55%)	13 (48%)	11 (65%)	0.359
COPD	7 (16%)	4 (15%)	3 (18%)	1.000
Echocardiography				
Indexed AVA, cm^2/m^2	0.35 ± 0.09	0.35 ± 0.10	0.35 ± 0.08	0.999
MG, mmHg	39 ± 13	40 ± 12	38 ± 14	0.654
LVEF, %	58 ± 15	57 ± 15	58 ± 15	0.839
LVDd, cm	4.9 ± 0.7	5.0 ± 0.7	4.7 ± 0.7	0.346
LVSd, cm	3.4 ± 1.0	3.5 ± 1.0	3.3 ± 0.9	0.654
LVMI, g/m^2	107 ± 37	113 ± 36	98 ± 38	0.173
Mitral insufficiency, n (%)				
None	10 (23%)	3 (11%)	7 (41%)	0.123
Mild	25 (57%)	18 (67%)	7 (41%)	
Moderate	7 (16%)	4 (15%)	3 (18%)	
Severe	1 (2%)	1 (3%)	0	
Aortic insufficiency, n (%)				
None	21 (48%)	14 (52%)	7 (41%)	0.652
Mild	22 (50 %)	13 (48%)	9 (53%)	
Moderate	1 (2%)	0	1 (6%)	
Severe	0	0	0	

AVA, aortic valve area; BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVEDD, left ventricular end diastolic diameter; LVS, left ventricular septum thickness; MG, mean trans-valvular gradient; MI, myocardial infarction; PCI, percutaneous coronary intervention; STS, society of thoracic surgeons; TF, transfemoral; TA; transapical: TAVR, transcatheter valve replacement.

pare continuous variables between TF approach and TA aoriach groups when appropriate. A two-tailed Fisher exact test was used to compare categorical variables. To compare post-TAVR strain to pre-TAVR baseline strain in each group, a paired two-tailed Student t-test or Wilcoxon signed-rank test was used as appropriate. To assess the inter-and intra-observer correlation five patients were selected at random and reanalyzed by each observer pre- and post-TAVR. A binary logistic regression analysis was performed to assess for variables associated with an immediate functional recovery in GLS of at least 25%. A two-step hierarchical method was used first assessing all variables in a univariate model, then entering all significant variables, defined as a $p<0.05$, into a multivariate model simultaneously. A receiver operating characteristic (ROC) analysis was performed to compare the ability of the three strongest predictors on univariate model to detect who will experience an immediate GLS benefit of at least 25% from TAVR. A *p*-value <0.05 were considered statistically significant. Data analy-

Table 2. Baseline longitudinal strain on transesophageal echocardiogram immediately before transcatheter aortic valve replacement

Longitudinal strain	Total N=44	TF-TAVR N=27	TA-TAVR N=17	*p*-value
Basal strain, %	-13.0 ± 7.2	-11.9 ± 6.8	-14.8 ± 7.5	0.183
Middle strain, %	-13.9 ± 7.0	-12.6 ± 6.6	-16.1 ± 7.4	0.113
Apical strain, %	-17.7 ± 7.8	-16.7 ± 7.0	-19.4 ± 8.9	0.262
Global strain, %	-14.9 ± 6.1	-13.7 ± 6.1	-16.8 ± 6.0	0.110
GLSR, $^1/s$	-1.31 ± 0.58	-1.26 ± 0.53	-1.38 ± 0.67	0.736

GLSR, global longitudinal strain rate; TF, transfemoral; TA, transapical; TAVR, transcatheter aortic valve replacement.

Table 3. Post-TAVR longitudinal strain on transesophageal echocardiogram

Longitudinal strain	Total N=44	TF-TAVR N=27	TA-TAVR N=17	*p*-value
Basal strain, %	-16.9 ± 6.9	-15.5 ± 6.7	-19.0 ± 6.9	0.107
Middle strain, %	-15.7 ± 6.1	-15.3 ± 6.2	-16.2 ± 6.1	0.637
Apical strain, %	-22.2 ± 8.5	-22.1 ± 8.3	-22.4 ± 9.1	0.933
Global strain, %	-18.3 ± 5.4	-17.7 ± 5.3	-19.2 ± 5.5	0.365
GLSR, $^1/s$	-1.66 ± 0.58	-1.55 ± 0.55	-1.83 ± 0.60	0.185

GLSR, global longitudinal strain rate; TF, transfemoral; TA, transapical; TAVR, transcatheter aortic valve replacement.

sis was performed with Stata Ver. 12 (Statacorp, College Station, TX).

Results

Of the 62 patients screening for inclusion, 18 had poor peri-procedure TEE image quality precluding STE from being performed and were removed from the study. The remaining 44 patients (mean age 81 ± 7 years, 48% male) had adequate image quality and were not in atrial fibrillation (**Table 1**). TAVR was successful in all patients, 17 underwent TA approach and 27 underwent TF approach. Forty-one patients (93%) received Edwards SAPIEN valves (Edwards Lifesciences Inc, Irvine, CA) and the remaining three patients received CoreValve valves (Medtronic, Minneapolis, MN). Patients who underwent TA approach had a higher baseline STS score compared to patients who underwent TF approach (10.0 ± 4.6 points versus 6.2 ± 3.6 points, respectively, p=0.001). The groups were otherwise similar in terms of medical co-morbidities. On pre-procedure TTE, there was no difference in aortic valve area, mean trans-valvular gradient or LVEF between TA and TF gorups.

Strain improvement based on method of approach

At baseline patients who underwent TA approach had similar strain compared to patients who underwent TF approach (**Table 2**). Immediately after valve deployment the mean GLS for the entire cohort increased from -14.9 ± 6.1% to -18.3 ± 5.4% (p<0.001). ALS also improved for the entire cohort from -17.7 ± 7.8% to 22.2 ± 8.5% (p<0.001). On subgroup analysis, patients who underwent TF approach experienced significant improvement in GLS (from -13.7 ± 6.1% to -17.7 ± 5.5%, p<0.001) and ALS (from -16.7 ± 7.0% to 22.1 ± 8.3%, p<0.001). Patients who underwent TA approach experienced significant GLS improvement (from -16.8 ± 6.0% to -19.2 ± 5.5%, p=0.027), but not ALS improvement (from -19.4 ± 8.9% to -22.4 ± 9.1%, p=0.169). There was no difference in the final GLS or ALS achieved post-TAVR between the TA and TF groups (**Table 3**). Similarly, there was no difference between patients who underwent TA approach versus TF approach in their absolute magnitude of GLS or ALS improvement.

Predictors of strain improvement

The mean absolute increase in GLS was -3.4%, 23% of the baseline mean GLS of -14.9 ± 6.1%. 22 patients achieved at least a 25% increase in their baseline GLS following TAVR, 16 of which increased their GLS to >-15%. On univariate regression analysis of predictors of a GLS improvement ≥25%, LVEF, mean trans-valvular gradient, and all strain parameters were significant (**Table 4**). On multivariate regression, the

Table 4. Binary logistic regression analysis of factors associated with GLS improvement of at least 25% immediately following TAVR

Variables	Univariate analysis		
	OR	95.0% CI	*p*-value
LVEF, per 1% increase	0.95	0.91-1.00	0.046
Mean gradient, per 1 mmHg increase	0.93	0.87-0.99	0.026
Basal strain impairment, per 1% increase	1.26	1.10-1.45	0.001
Middle strain impairment, per 1% increase	1.23	1.07-1.41	0.003
Apical strain impairment, per 1% increase	1.20	1.06-1.34	0.004
Global strain impairment, per 1% increase	1.57	1.20-2.06	0.001
GLSR, per $^1/s$ increase	22.3	3.61-138.17	0.001
	Multivariate analysis		
LVEF, per 1% increase	1.02	0.95-1.08	0.635
Mean gradient, per 1 mmHg increase	0.95	0.88-1.02	0.167
Global strain impairment, per 1% increase	1.61	1.18-2.20	0.003

LVEF, left ventricular ejection fraction.

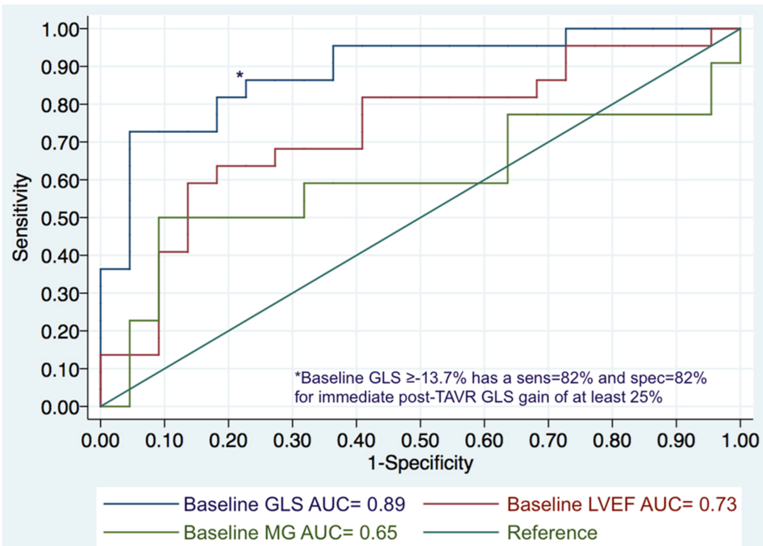

Figure 1. Receiver operating characteristic analysis comparing pre-TAVR baseline GLS, left ventricular ejection fraction and mean gradient in detecting which patients will experience at least a 25% GLS functional improvement from TAVR. GLS, global longitudinal strain; MG, mean trans-aortic gradient; LVEF, left ventricular ejection fraction.

degree of baseline GLS impairment was the only variable that remained an independent predictor of GLS improvement post-TAVR. For every 1% increase in baseline GLS impairment, the likelihood of obtaining at least a 25% improvement in GLS function with TAVR increased by a factor of 1.61 (p=0.003). When GLS was replaced with baseline ALS, BLS, MLS or GLSR impairment in the multivariate model, each strain parameter also remained independently associated with GLS functional gains post-TAVR.

On ROC analysis comparing the ability of pre-TAVR GLS, LVEF and MG to accurately identify patients who will experience a gain in GLS of at least 25% after TAVR, Pre-TAVR GLS was found to have the highest area-under-curve (AUC) of 0.89. A pre-TAVR GLS ≥-13.7% (i.e., severely impaired) was 82% sensitive and 82% specific for a GLS improvement of at least 25% above baseline with a +LR was 4.5 and -LR was 0.22 (**Figure 1**).

Interclass correlation coefficients (ICC) showed good correlation between observers and on repeated measurement of GLS and GLSR before and after TAVR (**Table 5**).

Table 5. Inter-observer and intra-observer variability analysis for all strain variables

Interclass correlation coefficients		
Variables	Pre-TAVR	Post-TAVR
Inter-observer		
Global long strain	0.89	0.90
Global long strain rate	0.67	0.91
Intra-observer		
Global long strain	0.77	0.86
Global long strain rate	0.86	0.82

Sensitivity analysis

We performed a sensitivity analysis to confirm the findings that ALS improvement was similar between TA approach and TF approach recipients using ALS matched groups. Baseline ALS in TA approach patients was -19.4 ± 8.9% which was not statistically different (p=0.110) from the baseline ALS in the TF approch patients (16.7 ± 7.0%), but all TA-TAVR strain measurements were trending lower (i.e., less

Table 6. Sensitivity analysis, comparison of strain before and after TAVR between ALS-matched groups

Variables	Pre-TAVR†	Post-TAVR	*p*-value
TF patients (N=27)			
Basal strain, %	-11.9 ± 6.8	-15.5 ± 6.7	0.018
Middle strain, %	-12.6 ± 6.6	-15.3 ± 6.2	0.025
Apical strain, %	-16.7 ± 7.0	-22.1 ± 8.3	<0.001
Global long strain, %	-13.7 ± 6.1	-17.7 ± 5.3	<0.001
TA patients (N=14)			
Basal strain, %	-15.2 ± 5.9	-17.5 ± 5.2	0.158
Middle strain, %	-14.9 ± 6.3	-15.4 ± 6.2	0.700
Apical strain, %	-16.4 ± 6.4	-20.6 ± 8.7	0.236
Global long strain, %	-15.5 ± 4.4	-17.9 ± 4.4	0.041

TF, transfemoral; TA, transapical; TAVR, transcatheter aortic valve replacement. †No significant difference was detected in strain variables between TF-TAVR and TA-TAVR patients pre-TAVR.

impairment); and based on the results of the logistic regression and ROC analysis, more impaired strain was predictive of higher strain gains. Therefore it was possible that the TA approach group did not obtain statistically significant improvement in ALS with TAVR because their baseline ALS was not sufficiently impaired. Therefore, the TA-TAVR and TF-TAVR groups were matched based on baseline ALS and their improvement in ALS was again compared.

In the ALS-matched groups, baseline ALS was -16.4 ± 6.4% in the TA approach group and 16.7 ± 7.0% in the TF approach group (p=0.791). Again, ALS improvement in the TA approach cohort after TAVR was not significantly higher than their baseline (**Table 6**).

Discussion

We made several important clinical observations in our study: first, global longitudinal strain improves immediately following TAVR irrespective of whether the valve was implanted via the TF or TA approach. Second, the absolute improvement in ALS was similar between TA and TF approach patients, a finding that suggests that the TA approach does not contribute to significant apical myocardial injury. Third, patients who underwent TA approach were sicker, with higher STS scores, and their post-TAVR apical strain was not a significantly improved over their baseline. Fourth, the severity of baseline GLS impairment is the strongest predictor of GLS recovery after TAVR and is sensitive in detecting which patients will experience this immediate global functional benefit.

Improvement in global longitudinal strain with TAVR

Impaired GLS is a well-described risk factor for future adverse events in patients with severe aortic stenosis [8-10]. It is therefore crucial for clinicians to identify which patients might gain a strain improvement with TAVR.

Of the patients who had a functional improvement of at least 25%, 73% improved their GLS above -15%, which is considered to be the lower limit of normal [18, 19]. This improvement seen on imaging could correlate to improvement in functional status for the patient. Indeed, Kempny et al. reported a significant correlation between improvement in GLS and New York Heart Association functional status after AVR [20].

In our study, the magnitude of ALS improvement in TA approach did not differ from TF approach, suggesting that direct cannulation of the LV apex does not play a significant role in remodeling. Previously reported poor outcomes in patients who underwent the TA approach could be a result of their higher burden of comorbidities [4].

Global longitudinal strain improves immediately after valve implantation in both the TF and TA approaches. This observation suggests that mechanical strain functional recovery is rapid and, based on the findings of other studies, also long-lasting [21-23]. Several mechanisms occur immediately after TAVR that support this observation. First, acute decrease in systolic load, reduction of subendocardial wall stress, and increase in LV ejection fraction occur as a result of increased aortic valve area immediately after TAVR [24]. Second, acute increase in coronary artery blood flow and myocardial perfusion occurs immediately after TAVR, driven by the decrease in LV end-diastolic pressure [25]. This off-loading of the LV and restoration of coronary perfusion allows the LV to recover its pump function rapidly. The fact that recovery of GLS is so rapid highlights the effectiveness of TAVR to improve cardiac function. This is reinforced by the observation in the present study that more strain impairment was associated with more functional recovery. Put another way, more strain impairment leaves more room for improvement. However, this observation can-not be applied to all patients. Previous studies have shown that systolic functional recovery is not seen in some patients who receive AVR and further study is required to determine why some patients do not receive a functional benefit from AVR [26].

Changes in longitudinal strain after transapical TAVR

Previous studies have shown that TA approach is associated with a higher elevation of cardiac enzymes and increased risk of death from heart failure [4, 27]. In the present study the myocardial injury, presumably caused by cannulation of the apex, does not prevent an immediate myocardial recovery. However, when analyzed based on segmental area, the apical segments did not improve significantly above their baseline. This lack of significant improvement in a segment-to-segment comparison is likely not the result of apical injury, since their post-TAVR strain function was similar to TF-TAVR patients. Other factors might be at play that prevents these patients from restoring their maximal strain function. Patients who receive TA approach TAVR typically have more atherosclerotic vascular disease and more comorbidities. Indeed in the present study, patients who underwent TA approach TAVR had significantly high STS scores.

There are a few limitations in our study that should be kept in mind. We were only able to assess the GLS with either 4 or 2 chamber view, which is an inherent weakness of TEE versus TTE. However, by using peri-procedure TEE images it allowed us to measure strain improvement in the same patient within seconds of valve replacement thus minimizing inter-reader variability within the same study. Our sample size was relatively small. Some patients were excluded owing to lack of high quality apical views. However, despite the small sample size, we were still detected significant improvement in strain after TAVR.

Transcatheter aortic valve replacement confers an immediate improvement in longitudinal systolic function irrespective of whether the valve is implanted via transfemoral or transapical approach. Despite apical cannulation with transapical approach, patients still enjoyed an improvement global in longitudinal strain equivalent to those patients undergoing transfemoral approach. The previously reported poorer outcomes in patients who underwent transapical approach is more likely due to increased comorbidity then the actual cannulation of the apex. Baseline longitudinal strain impairment is a significant predictor of the magnitude of strain improvement after TAVR. A global longitudinal strain >-13.7% (i.e., more impaired) is highly sensitive in detecting patients who experience a functional benefit from TAVR. This can be used by clinicians to predict left ventricular functional recovery. Additional study is needed to assess if these observed functional benefits seen on imaging correlate with improvement patient symptoms, functional status and outcomes.

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Disclosure of conflict of interest

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