Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study

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Summary

Background Subclinical leaflet thrombosis of bioprosthetic aortic valves after transcatheter valve replacement (TAVR) and surgical aortic valve replacement (SAVR) has been found with CT imaging. The objective of this study was to report the prevalence of subclinical leaflet thrombosis in surgical and transcatheter aortic valves and the effect of novel oral anticoagulants (NOACs) on the subclinical leaflet thrombosis and subsequent valve haemodynamics and clinical outcomes on the basis of two registries of patients who had CT imaging done after TAVR or SAVR.

Methods Patients enrolled between Dec 22, 2014, and Jan 18, 2017, in the RESOLVE registry, and between June 2, 2014, and Sept 28, 2016, in the SAVORY registry, had CT imaging done with a dedicated four-dimensional volume-rendered imaging protocol at varying intervals after TAVR and SAVR. We defined subclinical leaflet thrombosis as the presence of reduced leaflet motion, along with corresponding hypoattenuating lesions shown with CT. We collected data for baseline demographics, antithrombotic therapy, and clinical outcomes. We analysed all CT scans, echocardiograms, and neurological events in a masked fashion.

Findings Of the 931 patients who had CT imaging done (657 [71%] in the RESOLVE registry and 274 [29%] in the SAVORY registry), 890 [96%] had interpretable CT scans (626 [70%] in the RESOLVE registry and 264 [30%] in the SAVORY registry). 106 (12%) of 890 patients had subclinical leaflet thrombosis, including five (4%) of 138 with thrombosis of surgical valves versus 101 (13%) of 752 with thrombosis of transcatheter valves (p=0·001). The median time from aortic valve replacement to CT for the entire cohort was 83 days (IQR 33–281). Subclinical leaflet thrombosis was less frequent among patients receiving anticoagulants (eight [4%] of 224) than among those receiving dual antiplatelet therapy (31 [15%] of 208; p<0·0001); NOACs were equally as effective as warfarin (three [3%] of 107 *vs* five [4%] of 117; p=0·72). Subclinical leaflet thrombosis resolved in 36 (100%) of 36 patients (warfarin 24 [67%]; NOACs 12 [33%]) receiving anticoagulants, whereas it persisted in 20 (91%) of 22 patients not receiving anticoagulants (p<0·0001). A greater proportion of patients with subclinical leaflet thrombosis had aortic valve gradients of more than 20 mm Hg and increases in aortic valve gradients of more than 10 mm Hg (12 [14%] of 88) than did those with normal leaflet motion (seven [1%] of 632; p<0·0001). Although stroke rates were not different between those with (4·12 strokes per 100 person-years) or without (1·92 strokes per 100 person-years) reduced leaflet motion (p=0·10), subclinical leaflet thrombosis was associated with increased rates of transient ischaemic attacks (TIAs; 4·18 TIAs per 100 person-years *vs* 0·60 TIAs per 100 person-years; p=0·0005) and all strokes or TIAs (7·85 *vs* 2·36 per 100 person-years; p=0·001).

Interpretation Subclinical leaflet thrombosis occurred frequently in bioprosthetic aortic valves, more commonly in transcatheter than in surgical valves. Anticoagulation (both NOACs and warfarin), but not dual antiplatelet therapy, was effective in prevention or treatment of subclinical leaflet thrombosis. Subclinical leaflet thrombosis was associated with increased rates of TIAs and strokes or TIAs. Despite excellent outcomes after TAVR with the new-generation valves, prevention and treatment of subclinical leaflet thrombosis might offer a potential opportunity for further improvement in valve haemodynamics and clinical outcomes.

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See **Online** for appendix

Introduction

Transcatheter aortic valve replacement (TAVR) is the standard of care in elderly patients and an alternative to surgery in patients with severe symptomatic aortic stenosis at intermediate-to-high risk of surgery.[1–7] Reduced leaflet motion suggestive of subclinical leaflet thrombosis, as detected by high-resolution CT, has been reported with both transcatheter and surgical bioprosthetic aortic valves.[8–11] Reduced leaflet motion is present in 10–15% of patients who have TAVR, is less likely to be present in patients receiving warfarin than in those not receiving warfarin, and resolves with restoration of normal leaflet motion after initiation of anticoagulation with warfarin.[8–12]

To study reduced leaflet motion in bioprosthetic valves after TAVR or surgical aortic valve replacement (SAVR), two single-centre registries were initiated: the Assessment of Transcatheter and Surgical Aortic Bioprosthetic Valve Thrombosis and its Treatment with Anticoagulation (RESOLVE) registry and the Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed with Four-Dimensional

Research in context

Evidence before this study

We searched MEDLINE on Feb 1, 2017, for articles published in English, with the search terms "bioprosthetic valve thrombosis", "transcatheter aortic valve thrombosis", "subclinical leaflet thrombosis", "hypoattenuating leaflet thickening", and "TAVR thrombosis". Although symptomatic thrombosis represents the extreme end of the spectrum of bioprosthetic aortic valve thrombosis and is probably under-reported (prevalence of 1–2%), subclinical leaflet thrombosis with no associated symptoms is more frequent (prevalence of 10–15%) than is symptomatic bioprosthetic aortic valve thrombosis. Reduced leaflet motion detected with high-resolution CT in bioprosthetic aortic valves has been attributed to subclinical leaflet thrombosis in previously reported series. The published series have several limitations, including absence of complete clinical follow-up, no core laboratory assessment of transthoracic echocardiograms, no information about differences in the prevalence and severity of subclinical leaflet thrombosis between transcatheter and surgical valves, no adjudication of neurological events, and no information about the efficacy of novel oral anticoagulants (NOACs).

Added value of this study

We report, to our knowledge, the largest study to date of 931 patients who had CT scans done after surgical or transcatheter aortic valve replacement (TAVR) to assess reduced leaflet motion and its effect on clinical outcomes. This study is the first, to our knowledge, to report differences in subclinical leaflet thrombosis between surgical and transcatheter aortic valves. Findings from this study are also the first, to our knowledge, to show the potential efficacy of NOACs in the prevention and treatment of subclinical leaflet thrombosis in bioprosthetic aortic valves. The frequency and severity of subclinical leaflet thrombosis was lower in surgical than in transcatheter aortic valves. Patients with reduced leaflet motion had a small, but significant, increase in valve gradients. Anticoagulation was better than dual antiplatelet therapy (DAPT; standard of care for patients after TAVR) or monoantiplatelet therapy in the prevention and treatment of subclinical leaflet thrombosis; both NOACs and warfarin were effective. We also observed increased rates of neurological events, including transient ischaemic attacks and strokes or transient ischaemic attacks associated with reduced leaflet motion, although the rates of strokes were not significantly different.

Implications of all the available evidence

Our findings question the guidelines recommending DAPT after TAVR and raise the issue of whether or not warfarin or NOACs are more appropriate in certain patients than is DAPT. The risk-benefit profile of anticoagulation will be established in future clinical trials. Despite excellent outcomes after TAVR with the new-generation valves, room might exist for further improvement in outcomes through an understanding of the predictors of reduced leaflet motion and consideration of a short course of anticoagulation if findings from ongoing randomised trials substantiate these existing findings.

Computed Tomography (SAVORY) registry. On the basis of the initial cohort of 132 patients enrolled in the two registries, we previously reported our findings on reduced leaflet motion,[8] which have subsequently been corroborated by other small series.[9–13] The objective of this study was to report the prevalence of subclinical leaflet thrombosis in surgical and transcatheter aortic valves and the effect of novel oral anticoagulants (NOACs) on the subclinical leaflet thrombosis and subsequent valve haemodynamics and clinical outcomes on the basis of the two registries of patients who had CT imaging done after TAVR or SAVR.

Methods

Study design and patients

The study population included patients enrolled in the ongoing RESOLVE (NCT02318342) and SAVORY (NCT02426307) registries. RESOLVE and SAVORY are single-centre prospective registries, with RESOLVE being done at Cedars-Sinai Medical Center in Los Angeles (CA, USA) and SAVORY in Rigshospitalet in Copenhagen (Denmark); both enrolled patients with transcatheter or surgical bioprosthetic valves. The timing of CT after TAVR or SAVR was not prespecified in the registries; rather, CT scans were done at varying time intervals after TAVR or SAVR. Patients were enrolled in the RESOLVE registry between Dec 22, 2014, and Jan 18, 2017, in two ways: patients who had TAVR or SAVR were enrolled before discharge with CT scanning planned for the postdischarge follow-up visit (routinely 2 weeks for patients who had SAVR and 4 weeks for those who had TAVR) and patients with transcatheter or surgical bioprosthetic aortic valves presenting to the clinic for follow-up during the study period were offered participation in the registry (varying timepoints after TAVR or SAVR). In the SAVORY registry, patients were enrolled between June 2, 2014, and Sept 28, 2016. Patients were selected to represent the distribution of different transcatheter and surgical bioprosthetic aortic valves used at the institution (varying time intervals after TAVR or SAVR). The registries did not enrol consecutive patients who had TAVR or SAVR at the respective institutions; the registries attempted to enrol a heterogeneous patient population at different timepoints with multiple transcatheter or surgical valves. Patients with impaired renal function (estimated glomerular filtration rate of <30 mL/min) were excluded from both registries. We included in the analysis all patients who had CT imaging done with a dedicated four-dimensional volume-rendered imaging protocol after TAVR and SAVR. Both registries were approved by the institutional review board at each participating site

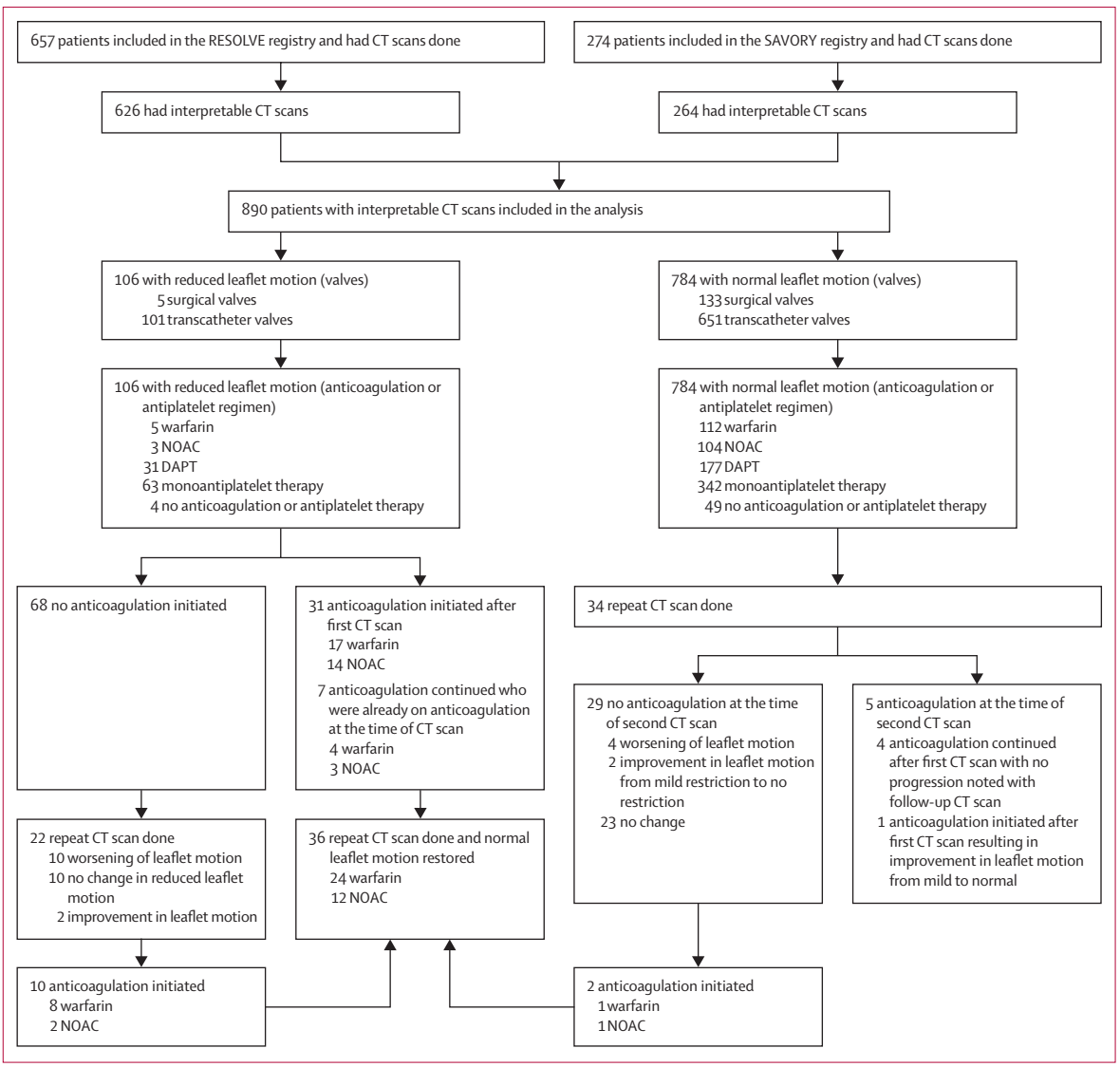

Figure 1: **Study design and effect of anticoagulation on reduced leaflet motion**
DAPT=dual antiplatelet therapy. NOAC=novel oral anticoagulant.

before study initiation. All patients provided written informed consent for participation in the registries.

Procedures

All CT scans were analysed at Cedars-Sinai Heart Institute (Los Angeles, CA, USA) in a masked fashion by a dedicated CT core laboratory. Details of the CT imaging protocol, processing, and analysis have been previously reported.[8] We assessed hypoattenuated leaflet thickening of the valve leaflets using two-dimensional (axial cross-section assessment) and three-dimensional volume-rendered imaging. We quantitatively assessed leaflet motion at maximal leaflet opening during systole using a four-dimensional volume-rendered en-face image of the prosthetic valve. We defined leaflet motion as normal, mildly reduced (<50% reduction), moderately reduced (50–70% reduction), severely reduced (>70% reduction), or immobile (absence of motion) in at least one valve leaflet (appendix). We defined reduced leaflet motion as the presence of at least moderate restriction of leaflet motion. We categorised patients with mild or no restriction of leaflet motion as having normal leaflet motion. We based quantification of reduced leaflet motion on analysis of a volume-rendered en-face image of the aortic valve prosthesis at maximal leaflet opening; we made a measurement from the inner margin of the stent frame to the margin of the affected leaflet tip and represented the distance as a percentage of the radius of the stent frame as an orthogonal line through the affected leaflet to the centre of the frame. We did clinically driven repeat CT

	Normal leaflet motion (n=784)	Reduced leaflet motion (n=106)	p value
Age (years)	78·9 (9·0)	82·0 (8·7)	0·0009
Male sex	437 (56%)	64 (60%)	0·37
Medical condition			
Chronic kidney disease	74/727 (10%)	14/98 (14%)	0·22
Haemodialysis	8/689 (1%)	1/97 (1%)	>0·99
Hypercoagulable disorder	9/642 (1%)	0/85	0·61
Hypertension	679/783 (87%)	88 (83%)	0·30
Previous stroke	63/782(8%)	9 (8%)	0·88
Previous transient ischaemic attack	36/782 (5%)	6 (6%)	0·63
Hyperlipidaemia	599/782 (77%)	78 (74%)	0·49
Diabetes	193/783(25%)	22 (21%)	0·38
PCI within 3 months before AVR	84/779 (11%)	13/104 (13%)	0·60
Congestive heart failure	588/781 (75%)	84 (79%)	0·37
Syncope	47/777 (6%)	3/105 (3%)	0·26
Atrial fibrillation	233/780 (30%)	17 (16%)	0·003
Baseline echocardiogram			
Ejection fraction (%)	57·9 (12·6)	55·5 (13·2)	0·07
Mean aortic valve gradient (mm Hg)	44·2 (13·8)	44·6 (16·1)	0·83
Peak aortic valve gradient (mm Hg)	74·2 (22·1)	73·6 (26·2)	0·79
Dimensionless index	0·23 (0·09)	0·22 (0·07)	0·27

Data are mean (SD), n (%), or n/N (%). PCI=percutaneous coronary intervention. AVR=aortic valve replacement.

Table 1: **Demographic and baseline clinical and echocardiographic characteristics**

	Frequency of reduced leaflet motion (n=106)
Transcatheter valves	101/752 (13%)
Edwards	63/453 (14%)
Edwards-Sapien	1/22 (5%)
Sapien XT	12/122 (10%)
Sapien 3	50/309 (16%)
Evolut or CoreValve	9/145 (6%)
CoreValve	3/70 (4%)
Evolut	6/75 (8%)
Lotus	12/83 (14%)
Portico	15/50 (30%)
Direct flow	0/6
Centera	1/7 (14%)
Symetis	1/8 (13%)
Surgical valves	5/138 (4%)
Epic	0/16
Freestyle	0/2
Magna	4/37 (11%)
Mitroflow	0/11
Perimount	1/39 (3%)
Trifecta	0/33

Data are n (%). The p value for transcatheter versus surgical valves is 0·001.

Table 2: **Frequency of reduced leaflet motion in different transcatheter and surgical valve types**

imaging (not prespecified in the protocol) to assess for progression or resolution of reduced leaflet motion.

Transthoracic echocardiography was done before discharge and at the time of CT scanning. All transthoracic echocardiograms (TTEs) produced in the RESOLVE registry were analysed by a dedicated echocardiographic core laboratory at Cedars-Sinai Heart Institute (by TS) in a masked fashion. All TTEs produced in the SAVORY registry were analysed in a masked fashion by two echocardiographers (ODB and KFK) at Rigshospitalet. We compared the mean aortic transvalvular gradients and velocity time integral (VTI) ratio (left ventricular outflow tract VTI to aortic valve VTI) to assess valve haemodynamics. We collected data for antiplatelet and antithrombotic therapy. We obtained clinical follow-up in all patients for death, myocardial infarction, stroke, and transient ischaemic attack (TIA). All neurological events, including strokes and TIAs, were adjudicated in a masked fashion by a stroke neurologist.[14]

Statistical analysis

We summarised continuous variables with normal distribution using means and SDs and analysed them using two-sample *t* tests. We summarised continuous variables with non-normal distributions using medians and IQRs and analysed them using Mann-Whitney U tests. We verified normality of data using Kolmogorov-Smirnov normality tests. We computed categorical variables as frequencies and percentages and compared them with χ^2 or Fisher's exact tests. After assessing baseline demographics, comorbidities, and echocardiographic and procedural variables in a univariate logistic regression model to predict reduced leaflet motion, we further assessed all variables with a p value of less than 0·20 using forward and backward model selection techniques with the Wald test as criterion and assessed the best models using Hosmer-Lemeshow goodness of fit test and other model diagnostics. We tested the assumptions of the Cox regression and noted no violations. We used Cox regression analysis to calculate hazard ratios and 95% CIs. We considered a two-sided p value of less than 0·05 to indicate significance. We did all statistical analyses using SPSS version 24.0 and Stata version 14.2.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. RRM and LS had full access to all the data in the study and were responsible for the decision to submit for publication.

Results

931 patients had CT scans done after TAVR or SAVR in the two registries (657 [71%] in the RESOLVE registry and 274 [29%] in the SAVORY registry; figure 1). Of these patients, 890 (96%) had interpretable CT scans (626 [70%] from the RESOLVE registry and 264 [30%] from the SAVORY registry) and were included in the analysis. Baseline demographic and echocardiographic characteristics are summarised in table 1.

CT scans were done in 752 (84%) patients with transcatheter valves and 138 (16%) patients with surgical valves (figure 1, table 2, appendix). Patients receiving surgical valves were younger (71·9 years [SD 8·6] *vs* 80·7 years [8·4]; p<0·0001) and had fewer comorbidities, including chronic kidney disease, hypertension, hyperlipidaemia, and congestive heart failure, than did those receiving transcatheter valves. We detected reduced leaflet motion in 106 (12%) of 890 patients. Reduced leaflet motion identified with four-dimensional, volume-rendered CT was associated with hypoattenuating opacities noted in the corresponding leaflets with two-dimensional CT in all patients (appendix). The median time from aortic valve replacement to CT scanning for the entire cohort was 83 days (IQR 33–281). The median time from SAVR to CT scanning was 163 days (79–417) and 58 days (32–236 days) from TAVR to CT scanning (p<0·0001; appendix). The prevalence of reduced leaflet motion was lower in surgical valves (five [4%] of 138) than in transcatheter valves (101 [13%] of 752; p=0·001). With multivariate analysis, transcatheter valves (compared with surgical valves), increased age, low ejection fraction, and absence of anticoagulation at the time of the index CT scan were significant predictors of reduced leaflet motion (appendix). Time from aortic valve replacement to the CT scan was not a significant predictor of reduced leaflet motion. In patients with reduced leaflet motion, the mean thickness of the affected leaflets was significantly smaller in surgical valves (1·85 mm [SD 0·77]) than in transcatheter valves (5·01 mm [1·81]; p=0·0004). The extent of leaflet motion restriction was also significantly less in surgical valves (56·9% [6·5]) than in transcatheter valves (71·0% [13·8]; p=0·004). Of the five surgical valves with reduced leaflet motion, a single leaflet was involved in four patients and two leaflets were involved in one patient. Of the 101 transcatheter valves with reduced leaflet motion, one leaflet was involved in 70 patients, two in 25, and three in six.

Data for anticoagulation at the time of index CT scanning are summarised in table 3. 224 (25%) patients were receiving anticoagulants at the time of the first CT scan after aortic valve replacement (117 [52%] warfarin; 107 [48%] NOACs; figure 1). The prevalence of reduced leaflet motion was lower among patients receiving anticoagulation (eight [4%] of 224) than among those who were on dual antiplatelet therapy (DAPT; 31 [15%] of 208; p<0·0001) or monoantiplatelet therapy (63 [16%] of 405; p<0·0001) or those who were not receiving anticoagulants (98 [15%] of 666; p<0·0001). We noted no difference in the prevalence of reduced leaflet motion between patients receiving NOACs (three [3%] of 107) or warfarin (five [4%] of 117; p=0·72), whereas both NOACs (p=0·0002) and warfarin (p=0·001) were better than no anticoagulation.

The effect of anticoagulation on reduced leaflet motion is summarised in figure 1. Among the 58 (55%) patients with reduced leaflet motion who had follow-up imaging, anticoagulation for 3 months was associated with restoration of normal leaflet motion in 36 (100%) of 36 patients (warfarin 24 [67%]; NOACs 12 [33%]), whereas reduced leaflet motion persisted or progressed in 20 (91%) of 22 patients in the absence of anticoagulation (p<0·0001; figure 2). No change in pharmacotherapy was made in the SAVORY registry after detection of reduced leaflet motion. In the RESOLVE registry, the decision to initiate anticoagulation for 3 months in patients with reduced leaflet motion and continue or discontinue anticoagulation after restoration of normal leaflet motion was based on the bleeding risk and preference of the physician and patient. After restoration of normal leaflet motion with anticoagulation, reduced leaflet motion recurred in four (50%) of eight patients in whom anticoagulation was discontinued (mean time from discontinuation of anticoagulation to recurrence of reduced leaflet motion was 164 days [SD 109]) compared with none of 15 patients who were maintained on anticoagulation (p=0·008).

Echocardiographic variables are summarised in table 4. The mean aortic valve gradient at the time of the first CT scan was significantly higher in patients with reduced leaflet motion than in those without reduced leaflet motion (appendix). Patients with reduced leaflet motion were more likely to have aortic valve gradients of more than 20 mm Hg than were those with normal leaflet motion, to have a more than 10 mm Hg increase in aortic

	Normal leaflet motion	Reduced leaflet motion	p value
Anticoagulation *vs* no anticoagulation	n=784	n=106	<0·0001
Anticoagulation	216 (28%)	8 (8%)	..
No anticoagulation	568 (72%)	98 (92%)	..
Anticoagulation *vs* DAPT	n=393	n=39	<0·0001
Anticoagulation	216 (55%)	8 (21%)	..
DAPT	177 (45%)	31 (79%)	..
Anticoagulation *vs* monoantiplatelet therapy	n=558	n=71	<0·0001
Anticoagulation	216 (39%)	8 (11%)	..
Monoantiplatelet therapy	342 (61%)	63 (89%)	..
Aspirin *vs* ADP antagonists	n=342	n=63	0·85
Aspirin	312 (91%)	57 (90%)	..
ADP antagonists	30 (9%)	6 (10%)	..
Warfarin *vs* no anticoagulation	n=680	n=103	0·001
Warfarin	112 (16%)	5 (5%)	..
No anticoagulation	568 (84%)	98 (95%)	..
NOACs *vs* no anticoagulation	n=672	n=101	0·0002
NOACs	104 (15%)	3 (3%)	..
No anticoagulation	568 (85%)	98 (97%)	..
Monoantiplatelet *vs* DAPT	n=519	n=94	0·83
Monoantiplatelet therapy	342 (66%)	63 (67%)	..
DAPT	177 (34%)	31 (33%)	..

Data are n (%). DAPT=dual antiplatelet therapy. NOAC=novel oral anticoagulant.

***Table* 3: Antiplatelet and anticoagulation therapy at the time of the CT scan**

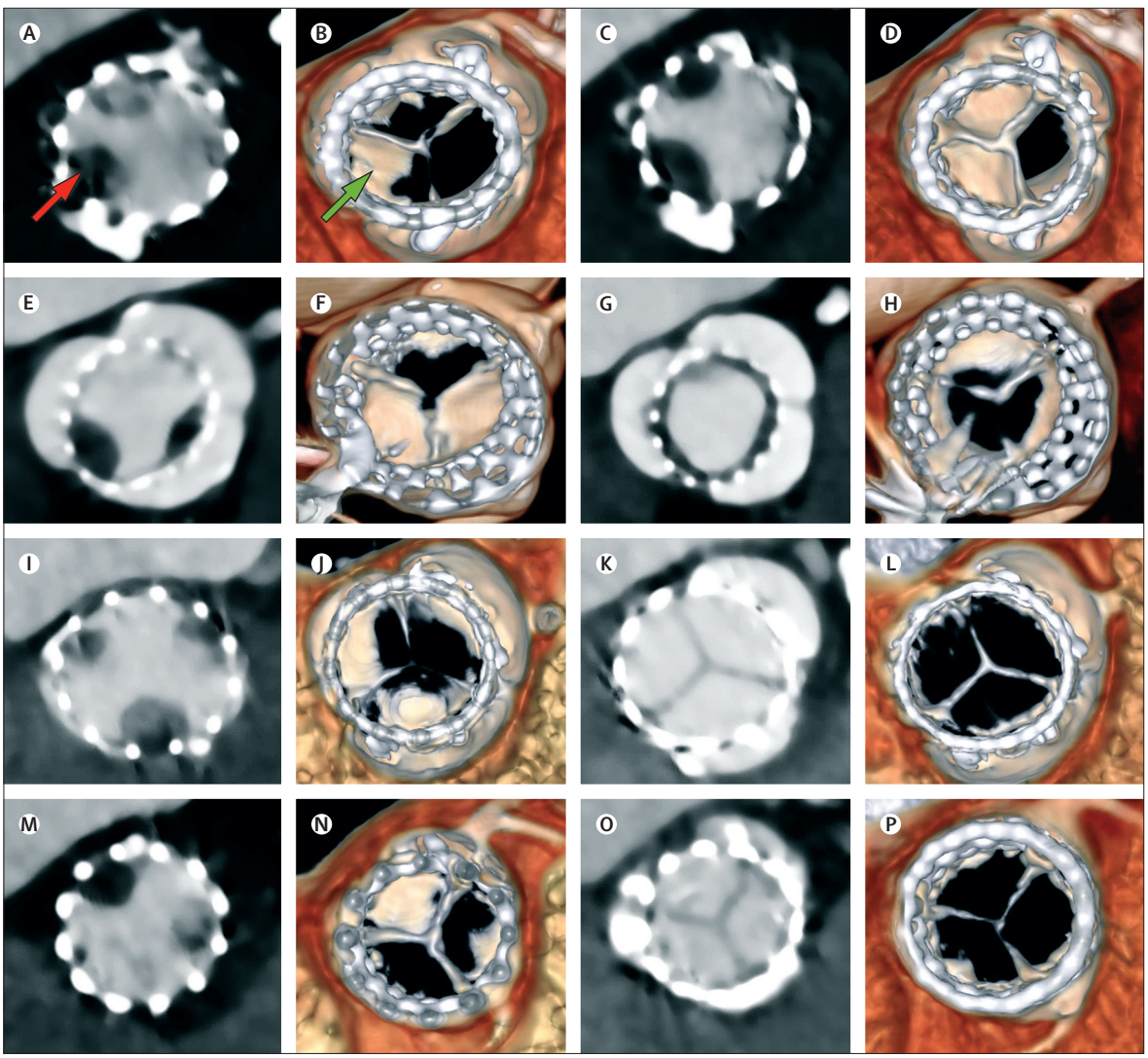

Figure 2: **Effect of dual antiplatelet therapy versus anticoagulation on hypoattenuating opacities and reduced leaflet motion**
(A–D) Reduced leaflet motion at baseline, noted to have worsening hypoattenuating opacities and reduced leaflet motion with follow-up CT in a patient receiving dual antiplatelet therapy after transcatheter aortic valve replacement. Resolution of hypoattenuating opacities and restoration of normal leaflet motion with 3 months of anticoagulation with (E–H) warfarin, (I–L) rivaroxaban, and (M–P) apixaban. The red arrow indicates hypoattenuating opacities and the green arrow represents reduced leaflet motion. Videos are provided in the supplementary material.

valve gradients at the time of the index CT scan compared with baseline, and to have an aortic valve gradient of more than 20 mm Hg and an increase in aortic valve gradient of more than 10 mm Hg. After detection of reduced leaflet motion, anticoagulation for 3 months was associated with a greater change in aortic valve mean gradients (decreased by 7·9 mm Hg [SD 13·8]) than that in patients who were not initiated on anticoagulation (increased by 0·92 mm Hg [7·94]; p=0·049).

Mean follow-up for the overall cohort was 540 days [SD 413]. Mean follow-up was similar between patients with (518 days [412]) or without (543 days [413]) reduced leaflet motion (p=0·56). Clinical outcomes are summarised in table 5. We noted no difference in the rates of death or myocardial infarction. The timing of strokes or TIAs ranged from a median of 36 days (IQR 26–236) before the CT scan to 178 days (58–416) after CT scanning. Rates of strokes were not significantly different between patients with or without reduced leaflet motion. Since neurological events in the periprocedural period are multifactorial, we compared rates of non-procedural neurological events (occurring after 72 h of the procedure) and post-CT events (after a diagnosis of reduced leaflet motion is made). Reduced leaflet motion was significantly associated with increased rates of all TIAs, non-procedural TIAs, and post-CT TIAs. The rates of all strokes or TIAs, non-procedural strokes or TIAs, and post-CT strokes or TIAs were also significantly increased in patients with reduced leaflet motion.

Discussion

Our study of 931 patients who had high-resolution CT scanning done after transcatheter or surgical aortic valve implantation is, to our knowledge, the largest dataset on this topic. We frequently detected subclinical leaflet thrombosis of bioprosthetic aortic valves presenting as reduced leaflet motion. The frequency and severity of reduced leaflet motion was lower in surgical than in transcatheter aortic valves; however, these findings need to be substantiated in the current randomised imaging substudies of trials of patients at low risk of surgery comparing TAVR and SAVR (PARTNER 3 trial [NCT02675114] and Evolut Low Risk Study [NCT02701283]). Anticoagulation with NOACs or warfarin was effective in prevention or treatment of reduced leaflet motion, but DAPT, which is the standard of care, was not. Reduced leaflet motion was likely to persist or progress in the absence of anticoagulation, whereas it resolved in all patients anticoagulated with either NOACs or warfarin. Patients with elevated gradients were more likely to have reduced leaflet motion than were those without elevated gradients; however, most patients with reduced leaflet motion detected with CT scanning had echocardiographic gradients of less than 20 mm Hg, which is considered to be within the normal range.[14] Although rates of strokes were not different, the rates of TIAs and strokes or TIAs were increased in patients with reduced leaflet motion. Despite the absence of pathological confirmation of thrombus on the bioprosthetic valve leaflets, the characteristic imaging findings coupled with the response to anticoagulation in a much larger cohort of patients than previously substantiate our previous observation that reduced leaflet motion represents subclinical leaflet thrombosis.[8]

The frequency and severity of reduced leaflet motion were lower in surgical than in transcatheter aortic valves, independent of baseline anticoagulation status. This study included patients who had TAVR or SAVR for commercially approved indications; the SAVR cohort included younger patients at low risk of surgery with fewer comorbidities than did the TAVR cohort. The time from aortic valve replacement to the CT scan was longer in the surgical cohort than in the transcatheter cohort. However, these differences are unlikely to confound our finding because in a multivariate logistic regression model, surgical bioprosthetic aortic valves were independently associated with decreased incidence of subclinical leaflet thrombosis. Additionally, reduced leaflet motion tended to persist or progress in the absence of treatment with anticoagulation, therefore the time differences are unlikely to underestimate the rates of thrombosis in surgical valves. These rates might reflect differences between TAVR and SAVR techniques and technology.

Traumatic injury to the pericardial leaflets, which at least theoretically could predispose to thrombus formation, has been reported during crimping and deployment of both balloon-expandable and self-expanding stent valves compared with non-crimped pericardial leaflets in an ex-vivo model.[15–17] Resection of the calcified native aortic valve leaflets during SAVR might alter the flow dynamics after valve replacement compared with leaving native aortic valve cusps in situ during TAVR. Incomplete expansion, or overexpansion, of the transcatheter valves compared with uniform expansion of the surgical valves might alter mechanical stress on the leaflets, predisposing them to thrombus formation. In a fatigue simulation study,[18] transcatheter valve leaflets were noted to sustain higher stresses, strains, and fatigue damage than did surgical aortic valve leaflets. Nevertheless, these findings should be interpreted in the context of findings from multiple randomised controlled trials[1–5,19–21] showing similar mortality and stroke rates, better haemodynamics, and equivalent durability of transcatheter aortic valves at 5 years compared with surgical valves. The effect of reduced leaflet motion on valve durability beyond 5 years remains to be established. Valve haemodynamics are affected by factors in addition to leaflet motion, such as prosthesis size, which is often larger with transcatheter than with surgical valves.[18] Despite excellent outcomes after TAVR, especially with Sapien 3 (Edwards LifeSciences, Irvine, CA, USA) and Evolut R (Medtronic,

	Normal leaflet motion (n=784)	Reduced leaflet motion (n=106)	p value
Post-AVR			
Ejection fraction (%)	60·4 (13·5)	58·5 (13·1)	0·14
Mean aortic valve gradient (mm Hg)	10·9 (5·7)	9·8 (4·0)	0·20
Peak aortic valve gradient (mm Hg)	20·1 (9·6)	18·6 (7·3)	0·36
VTI ratio	0·57 (0·20)	0·56 (0·21)	0·21
At the time of the CT scan			
Ejection fraction (%)	59·3 (10·8)	56·4 (11·9)	0·03
Mean aortic valve gradient (mm Hg)	10·4 (6·3)	13·8 (10·0)	0·0004
Peak aortic valve gradient (mm Hg)	19·9 (10·4)	25·3 (15·5)	0·001
VTI ratio	0·52 (0·16)	0·43 (0·17)	<0·0001
Aortic valve gradient			
>20 mm Hg	40/714 (6%)	15/96 (16%)	0·0002
>30 mm Hg	13/714 (2%)	6/96 (6%)	0·007
>40 mm Hg	5/714 (1%)	4/96 (4%)	0·02
Change in aortic valve gradient			
>10 mm Hg	9/632 (1%)	13/88 (15%)	<0·0001
>20 mm Hg	5/632 (1%)	5/88 (6%)	0·004
>30 mm Hg	2/632 (<1%)	3/88 (3%)	0·02
Aortic valve gradient >20 mm Hg and increase in gradient >10 mm Hg	7/632 (1%)	12/88 (14%)	<0·0001
Absolute change in aortic valve gradient	−0·25 (5·0)	4·3 (9·2)	<0·0001
Relative change in aortic valve gradient	0·06 (0·61)	0·50 (0·89)	<0·0001
Absolute change in VTI ratio	−0·06 (0·22)	−0·14 (0·20)	0·001
Relative change in VTI ratio	−0·04 (0·38)	−0·21 (0·26)	0·0001

Data are mean (SD) or n/N (%). AVR=aortic valve replacement. VTI=velocity time integral.

Table 4: **Echocardiographic characteristics**

	Normal leaflet motion (n=784)		Reduced leaflet motion (n=106)		Hazard ratio (95% CI)	p value
	Number of patients	Rate per 100 person-years	Number of patients	Rate per 100 person-years		
All events						
Death	34 (4%)	2·91	4 (4%)	2·66	0·96 (0·34–2·72)	0·94
Myocardial infarction	4 (1%)	0·34	1 (1%)	0·67	1·91 (0·21–17·08)	0·56
Stroke or TIA	27 (3%)	2·36	11 (10%)	7·85	3·27 (1·62–6·59)	0·001
All stroke*	22 (3%)	1·92	6 (6%)	4·12	2·13 (0·86–5·25)	0·10
Ischaemic stroke	21 (3%)	1·83	6 (6%)	4·12	2·23 (0·90–5·53)	0·08
TIA	7 (1%)	0·60	6 (6%)	4·18	7·02 (2·35–20·91)	0·0005
Non-procedural events						
Death	34 (4%)	2·91	4 (4%)	2·66	0·96 (0·34–2·72)	0·94
Myocardial infarction	4 (1%)	0·34	1 (1%)	0·67	1·91 (0·21–17·08)	0·56
Stroke or TIA	20 (3%)	1·75	8 (8%)	5·71	3·30 (1·45–7·50)	0·004
All stroke*	15 (2%)	1·31	4 (4%)	2·75	2·14 (0·71–6·44)	0·18
Ischaemic stroke	14 (2%)	1·22	4 (4%)	2·75	2·29 (0·75–6·97)	0·14
TIA	7 (1%)	0·60	5 (5%)	3·48	5·89 (1·87–18·60)	0·002
Post-CT events						
Death	34/774 (4%)	5·08	4/105 (4%)	4·61	0·92 (0·33–2·60)	0·88
Myocardial infarction	2/772 (<1%)	0·30	0/104	NA	NA	NA
Post-CT stroke or TIA	10/757 (1%)	1·53	4/98 (4%)	5·15	3·45 (1·08–11·03)	0·04
All stroke*	7/759 (1%)	1·06	2/101 (2%)	2·42	2·41 (0·50–11·61)	0·27
Ischaemic stroke	6/759 (1%)	0·91	2/101 (2%)	2·42	2·81 (0·57–13·92)	0·21
TIA*	5/772 (1%)	0·75	3/102 (3%)	3·73	5·02 (1·20–21·10)	0·03

Data are n (%) or n/N (%). TIA=transient ischaemic attack. NA=not applicable. *Includes haemorrhagic and ischaemic strokes.

Table 5: **Clinical outcomes**

Minneapolis, MN, USA) new-generation valves, room might exist for further improvement in outcomes through an understanding of the predictors of reduced leaflet motion and consideration of a short course of anticoagulation if findings from the current randomised trials (GALILEO [NCT02556203] and ATLANTIS study [NCT02664649]) substantiate these existing findings.[22]

Our study challenges the American College of Cardiology and American Heart Association[23] and European Society of Cardiology and European Association for Cardio-Thoracic Surgery[24] guidelines, which recommend DAPT after TAVR and do not recommend routine anticoagulation after TAVR. Even though DAPT is the standard of care for patients after TAVR,[1,2,4,5,19,20] we did not observe a difference in subclinical leaflet thrombosis in patients on monoantiplatelet therapy or DAPT. DAPT can thus be considered dispensable in the appropriate clinical setting. Rates of reduced leaflet motion were significantly lower in patients receiving anticoagulants; both NOACs and warfarin were better than antiplatelet therapy in prevention of reduced leaflet motion. Initiation of anticoagulation with either NOACs or warfarin resulted in resolution of hypoattenuating opacities and restoration of normal leaflet motion in all patients. To our knowledge, findings from our study show the efficacy of NOACs in the prevention and treatment of subclinical leaflet thrombosis in bioprosthetic aortic valves for the first time.

Subclinical leaflet thrombosis was predominantly haemodynamically silent and not detected by TTEs in most patients. Mean aortic valve gradients were significantly higher in patients with reduced leaflet motion than in those with normal leaflet motion, but the absolute values of mean gradients in both groups were within the normal range of gradients (<20 mm Hg)[14] and a significant elevation of gradient (mean gradient of >20 mm Hg and a rise in gradient of >10 mm Hg) was noted in only 14% of patients with reduced leaflet motion. Treatment of reduced leaflet motion resulted in a significant decrease in gradients compared with patients who were not given anticoagulants after detection of reduced leaflet motion. This finding could suggest a mechanism of possible acceleration of structural valve degeneration in bioprosthetic valves. In the clinical setting, the distinction between valve thrombosis and degeneration might often be complex and determined by response to anticoagulation.

We previously reported a preliminary association between reduced leaflet motion and TIAs on the basis of a small cohort of patients.[8] In this study, which, to our knowledge, is the largest study to date, with a mean follow-up of 540 days, with masked analysis of all CT scans and echocardiograms and masked analysis of all neurological events by a stroke neurologist, we did not observe a significant increase in strokes, but the rates of

TIAs were significantly increased in patients with reduced leaflet motion. To definitively establish an association between this imaging finding and neurological events, we further assessed neurological outcomes beyond 72 h (non-procedural) and after CT scanning (after detection of reduced leaflet motion). These results were consistent when we looked at non-procedural strokes and post-CT strokes; however, the association between reduced leaflet motion and TIAs persisted. Composite stroke or TIA rates were also significantly increased in patients with reduced leaflet motion. Investigators of previous small series[8,10,12] did not report increased rates of neurological events with reduced leaflet motion; however, all of the studies assessing reduced leaflet motion were limited by small sample size, absence of complete follow-up,[9] absence of uniform adjudication of suspected neurological events,[9–12] and surprisingly low stroke rates compared with contemporary outcomes data.[11,13] Our study findings derived from non-randomised registries do not prove causality, but only an association, and need to be substantiated in the current Food and Drug Administration-mandated imaging substudies in the randomised controlled trials.

Although leaflet thrombosis and reduced motion were frequent in this study, routine anticoagulation for all patients cannot be recommended at this time; the risk of bleeding in a predominantly elderly population with multiple comorbidities could be high.[25,26] The question of whether or not anticoagulation should be recommended is best answered by the current randomised clinical trials (GALILEO and ATLANTIS study) assessing the safety and efficacy of routine anticoagulation in patients after TAVR. Nevertheless, these findings are provocative enough to stimulate further randomised studies of the relevance of routine CT screening in all patients and early anticoagulation after TAVR, especially since the indications of TAVR are expanding into the population at low risk of surgery who might be more safely treated with anticoagulants than might the high-risk population and in whom a stroke at a younger age might be viewed as even more devastating than at an older age.

This study has certain limitations. It is observational in nature and the effect of unmeasured confounders, such as selection bias (a smaller proportion of patients who had SAVR than had TAVR had CT scans), expectation bias, the unmasked nature of the study, or more rigorous follow-up in patients with reduced leaflet motion than in those without reduced leaflet motion, on the results of the study cannot be excluded. Patients did not have a prospective neurological assessment at follow-up visits, therefore the neurological event rates in both the TAVR and surgical groups could be underestimated in this study. Consecutive CT scans were not routinely obtained at regular time intervals in all patients, thus decreasing our ability to precisely assess the time interval between occurrence of subclinical leaflet thrombosis and clinical events. Although our study reveals an association between stroke or TIA and reduced leaflet motion, the temporal separation between the clinical events and CT scans makes it difficult to state leaflet thrombosis as the definitive cause of neurological events.

Subclinical leaflet thrombosis occurred frequently in bioprosthetic aortic valves, more commonly in transcatheter than in surgical valves. Although stroke rates were not significantly different, subclinical leaflet thrombosis was associated with increased rates of TIAs and strokes or TIAs. Our study findings substantiate that anticoagulation with either NOACs or warfarin, but not antiplatelet therapy, which is the current standard of care, effectively prevents and treats subclinical leaflet thrombosis; however, whether or not this treatment results in acceptable levels of bleeding and a reduction in the rates of TIA and stroke will be established by the results of the current randomised clinical trials (GALILEO and ATLANTIS study). Our study findings can help optimise adjunctive pharmacotherapy in patients with bioprosthetic aortic valves, which might potentially result in further improvement in valve haemodynamics and clinical outcomes.

Contributors

RRM was a primary investigator for the RESOLVE registry and conceived and designed the study. RRM and TC analysed and interpreted data and wrote the manuscript. LS was a principal investigator for SAVORY, designed the study, interpreted data, and edited the manuscript. JF, DB, HJ, and TR did CT analysis and imaging interpretation. ODB collected, analysed, and interpreted data, did echocardiogram core laboratory analysis in the SAVORY registry, and edited the manuscript. KFK and TS did echocardiogram core laboratory analysis in the SAVORY registry and imaging interpretation in the RESOLVE registry. YA analysed and interpreted data and edited the manuscript. THJ, SI, MdK, and AF collected, analysed, and interpreted data. PL did neurological event adjudication in the RESOLVE registry. GF, AT, DLB, and MBL analysed and interpreted data and edited the manuscript.

Declaration of interests

DLB is a member of advisory boards for Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; is a member of the board of directors for the Boston VA Research Institute and Society of Cardiovascular Patient Care; is chair of the American Heart Association Quality Oversight Committee; is on data monitoring committees for the Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute (for his role as chair of the data and safety monitoring board of the St Jude Medical-funded PORTICO trial), Mayo Clinic, and Population Health Research Institute; has received honoraria from the American College of Cardiology (Senior Associate Editor, Clinical Trials and News, www.ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), the Duke Clinical Research Institute (clinical trial steering committees), the Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor-in-Chief, Journal of Invasive Cardiology), the Journal of the American College of Cardiology (Guest Editor; Associate Editor), the Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), the Society of Cardiovascular Patient Care (secretary and treasurer), and WebMD (Continuing Medical Education steering committees); is Deputy Editor for Clinical Cardiology; is the Chair for the NCDR-ACTION Registry Steering Committee; is the Chair for the VA CART Research and Publications Committee; has received research funding from Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest

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Bioprosthetic surgical and transcatheter heart valve thrombosis

Excellent outcomes of transcatheter aortic valve replacement (TAVR) have been experienced by patients with aortic stenosis at high and intermediate risk of surgery.[1] Findings from large randomised trials[1,2] have shown survival with TAVR that is similar to or improved compared with bioprosthetic surgical aortic valve replacement (SAVR), and very low stroke rates have been observed with new-generation devices. Investigators of echocardiographic follow-up studies[3] have consistently reported low transvalvular gradients up to 5 years after TAVR and SAVR, with slightly greater aortic valve areas after TAVR than after SAVR. Against this background, the occurrence of subclinical valve leaflet thrombosis in patients, detected with CT after TAVR or SAVR, has been described.[4]

In *The Lancet*, Tarun Chakravarty and colleagues[5] report data from two large registries (SAVORY and RESOLVE) of 890 patients undergoing TAVR or SAVR with follow-up CT (626 [70%] in the RESOLVE registry and 264 [30%] in the SAVORY registry). Masked analyses of all CT scans, echocardiograms, and neurological events were done. Subclinical leaflet thrombosis, defined as moderate or severe restriction of leaflet motion with corresponding CT-derived hypoattenuating lesions, was detected in 106 (12%) patients, including five (4%) of 138 who had SAVR and 101 (13%) of 752 who had TAVR (p=0·001). A greater proportion of patients with subclinical leaflet thrombosis had aortic valve gradients of more than 20 mm Hg and increases in aortic valve gradients of more than 10 mm Hg (12 [14%] of 88) than did those with normal leaflet motion (seven [1%] of 632; p<0·0001). Leaflet thrombosis was less frequently observed in patients using warfarin or novel oral anticoagulants (NOACs; eight [4%] of 224) than in those using dual antiplatelet or monoantiplatelet therapy (98 [15%] of 666; p<0·0001). Subclinical leaflet thrombosis was associated with development of non-procedural stroke or transient ischaemic attack during follow-up (5·71 *vs* 1·75 events per 100 person-years; p=0·004).

Several issues warrant discussion to put these results into perspective. Dynamic four-dimensional CT imaging was used for detection of subclinical thrombosis. Consensus definitions and quantification of leaflet thrombosis with CT need to be established before prospective study and clinical use. A second issue relates to the discrepancy between CT and echocardiographic findings. Investigators of previous small studies[6,7] reported a 10–15% prevalence of subclinical thrombosis with CT, whereas elevated gradients (a mean gradient of >20 mm Hg) with echocardiography were infrequent. Similar findings were present in the large RESOLVE and SAVORY registries.[5] These observations imply that CT detects early subclinical thrombosis, whereas echocardiography detects the late consequences of thrombosis—ie, valvular stenosis. These results also indicate that not all thrombosis results in valve degeneration and stenosis—ie, early thrombosis might resolve without permanent clinical sequelae. The optimal CT timing after valve implantation to detect meaningful leaflet thrombosis is thus unknown.

The timing of imaging might also affect the proportions of leaflet thrombosis with different valve types (ascertainment bias). CT scans in this study were obtained earlier after TAVR (median 58 days [IQR 32–236]) than after SAVR (163 [79–417]). Although time from implantation to CT was not an independent correlate of leaflet thrombosis, given residual confounding, this difference in timing might partly underlie the lower proportion of leaflet thrombosis detected with SAVR than with TAVR. Review of the distributions of time to CT versus leaflet thrombosis might provide additional insight. Other unmeasured confounders (eg, frailty or immunological factors) might also have predisposed the TAVR group to a higher proportion of leaflet thrombosis. However, the authors describe intrinsic structural, manufacturing, and functional differences between surgical and transcatheter valves, which might differently affect valve predisposition to thrombosis. The proportions of subclinical leaflet thrombosis varied from 0% to 30% with different transcatheter valves. Given the small sample size of each valve type studied (including surgical valves), as well as differences in patient characteristics, anticoagulation regimens, and timing of imaging, this study cannot be used to draw conclusions that different valves cause different proportions of leaflet thrombosis.

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Only randomised trials can establish whether or not a difference exists. This point is especially germane as randomised trials to date have not shown differences in clinical valve deterioration between TAVR and SAVR.[1]

Regarding the relevance of leaflet thrombosis to clinical events, a discrepancy is noted between the 10–15% prevalence of CT thrombosis in previous CT studies[6,7] and the proportion of 3–4% of patients with stroke in large clinical trials.[2] Similarly, Chakravarty and colleagues[5] report low stroke rates, which were not different between patients with (4%) and without (2%) thrombosis according to CT (p=0·18). However, the proportion of patients with transient ischaemic attacks was significantly higher in patients with thrombosis according to CT (5%) than in those without thrombosis (1%; p=0·002). In addition to subclinical leaflet thrombosis being less common in patients receiving warfarin or NOACs than in those receiving antiplatelet agents, the thrombosis resolved in all 36 patients who were given anticoagulants, but persisted in 20 (91%) of 22 patients not receiving anticoagulants (p<0·0001).

Open questions remain. Given the risks of chronic anticoagulation, should all patients be offered such therapy, or should patient selection be guided by imaging (and should this imaging be CT or echocardiography, and at what interval)? What is the optimal duration of treatment? Are NOACs preferred or as good as warfarin? Should repeat imaging be systematically done at given timepoints? And will such therapy safely enhance net clinical benefit (a greater reduction in stroke and valve deterioration than an increase in major bleeding)? Registries are able to show associations, but are unable to establish causality. As findings from this study were unable to show any permanent meaningful clinical sequelae to subclinical leaflet thrombosis, only randomised trials can address these questions. Thus, in our estimation, changes in the guidelines of the type and timing of imaging surveillance and therapy after SAVR and TAVR are premature on the basis of current knowledge. Nonetheless, this study has provided important new information to guide future investigation.

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