ORIGINAL RESEARCH ARTICLE

Impact of anticoagulation therapy on valve haemodynamic deterioration following transcatheter aortic valve replacement

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ABSTRACT

Objective To evaluate the changes in transvalvular gradients and the incidence of valve haemodynamic deterioration (VHD) following transcatheter aortic valve replacement (TAVR), according to use of anticoagulation therapy.

Methods and results This multicentre study included 2466 patients (46% men; mean age 81±7 years) who underwent TAVR with echocardiography performed at 12-month follow-up. Anticoagulation therapy was used in 707 patients (28.7%) following TAVR (AC group). A total of 663 patients received vitamin K antagonists, and 44 patients received direct oral anticoagulants. A propensity score matching analysis was performed to adjust for intergroup (AC vs non-AC post-TAVR) differences. A total of 622 patients per group were included in the propensity-matched analysis. VHD was defined as a ≥10 mm Hg increase in the mean transprosthetic gradient at follow-up (vs hospital discharge). The mean clinical follow-up was 29±18 months. The mean transvalvular gradient significantly increased at follow-up in the non-AC group within the global cohort (P=0.003), whereas it remained stable over time in the AC group (P=0.323). The incidence of VHD was significantly lower in the AC group (0.6%) compared with the non-AC group (3.7%, P<0.001), and these significant differences remained within the propensity-matched populations (0.6% vs 3.9% in the AC and non-AC groups, respectively, P<0.001). The occurrence of VHD did not associate with an increased risk of all-cause death (P=0.468), cardiovascular death (P=0.539) or stroke (P=0.170) at follow-up.

Conclusions The lack of anticoagulation therapy post-TAVR was associated with significant increments in transvalvular gradients and a greater risk of VHD. VHD was subclinical in most cases and did not associate with major adverse clinical events. Future randomised trials are needed to determine if systematic anticoagulation therapy post-TAVR would reduce the incidence of VHD.

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INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is well established for treating severe symptomatic aortic stenosis in patients who are not candidates for surgical aortic valve replacement (SAVR), and in those deemed to be at high surgical risk.[1 2] The results of large multicentre registries and prospective randomised trials[3 4] have provided evidence supporting the use of TAVR as an alternative to SAVR in intermediate-risk patients. Given this emerging trend to treat lower-risk and younger patients with transcatheter heart valve (THV) platforms, identifying factors posing an increased risk for THV deterioration is of utmost clinical relevance.

Although structural valve degeneration requiring valve replacement seldom occurs early post-TAVR, the incidence of subclinical haemodynamic valve deterioration (VHD) during the year following TAVR is around 3%–4% according to recent studies[5] (personal communication Vemulapalli *et al*, Incidence and Outcomes of Valve Hemodynamic Deterioration in Transcatheter Aortic Valve Replacement in U.S. Clinical Practice: A Report from the Society of Thoracic Surgery/American College of Cardiology Transcatheter Valve Therapy Registry ACC 2016). Also, concerns have recently emerged regarding subclinical valve thrombosis post-TAVR, with rapidly increasing transvalvular gradients likely signifying the advent of valve thrombosis despite the absence of clinical symptoms.[6–8] Moreover, several studies have suggested that the incidence of early subclinical bioprosthetic valve thrombosis leading to reduced aortic valve leaflet motion, as determined by four-dimensional CT, may be higher than expected.[9 10] In light of these findings, and given that antithrombotic regimens post-TAVR remain to be established, our aim was to determine the incidence and clinical consequences of VHD post-TAVR, according to the presence or not of anticoagulation therapy post-TAVR.

METHODS

Between May 2007 and February 2015, 3938 consecutive patients underwent TAVR across 14 participating centres in America (Canada and Colombia) and Europe (Spain, France, Italy and Belgium). Patients were considered eligible for this multicentre study if they had undergone at least two echocardiograms post-TAVR (at discharge and

at 12-month follow-up). Patients with surgical bioprosthesis dysfunction (valve-in-valve, n=66) and those with missing information about the antithrombotic treatment post-TAVR (n=196) were excluded. A total of 1210 patients failed to undergo follow-up echocardiography either because of death (n=441) or logistic reasons (n=769). A total of 2466 patients were finally included in the present analysis. Eligibility for TAVR, valve type and access route were determined at each centre by the local heart team composed of interventional cardiologists and cardiac surgeons. Clinical, procedural and echocardiographic data were prospectively gathered within a TAVR database at each participating centre. This study was not a prespecified analysis at the time of the creation of the database, data were therefore analysed retrospectively. Patients were classified into anticoagulation (AC) group and non-anticoagulation (non-AC) group according to anticoagulation treatment at hospital discharge. All participating centres were asked to report any change in anticoagulation therapy over time. Clinical follow-up was undertaken during clinical visits or through telephone contact or both at 1 and 12 months post-TAVR, and yearly thereafter in all participating centres. Clinical events were prospectively recorded and defined according to Valve Academic Research Consortium-2 (VARC-2) criteria.[11]

Echocardiographic assessment

Transthoracic echocardiography (TTE) examinations were performed at baseline, on hospital discharge and at 12 months post-TAVR. TTE examinations were conducted according to American Society of Echocardiography guidelines.[12 13] Peak transprosthetic flow velocity was determined by continuous-wave Doppler imaging. The mean transprosthetic gradient was calculated using the modified Bernoulli formula; for patients in AF, at least five consecutive beats were averaged. Absolute change in mean gradient was calculated as the gradient at follow-up minus the gradient at discharge. VHD was defined as an absolute increase in gradient of ≥10 mm Hg during follow-up[14 15] (Vemulapalli, ACC 2016).

Statistical analysis

Categorical variables are reported as n (%). Continuous variables are expressed as mean±SD or median (25th to 75th IQR) depending on variable distribution. Group comparisons were analysed using the Student's t-test or Wilcoxon rank-sum test for continuous variables, and χ^2 test for categorical variables. A propensity score matching analysis, using a one-to-one Greedy 6→1 digit-matching algorithm without replacement was performed to adjust intergroup (anticoagulation (AC group) vs no anticoagulation (non-AC group) at discharge) differences in baseline characteristics caused by the selection bias inherent to the non-randomised nature of the study. Patients were matched in 1:1 ratio. First, matches were made within a calliper width of 0.000001 ('best matches'), then calliper width increases incrementally for unmatched cases up to 0.1. Variables used in the propensity-matched algorithm were those that showed a P value <0.2 at baseline and procedural characteristics. Selected variables were age, previous coronary artery disease, chronic obstructive pulmonary disease, mean gradient (baseline), left ventricular ejection fraction (LVEF) at baseline, prosthesis size, approach and valve type, using a logistic regression analysis (online supplementary table 1). Patients with changes in anticoagulation therapy before 1-year echocardiogram were excluded from the propensity-matched analysis. Absolute standardised differences were estimated for all baseline covariates before and after matching to assess prematch and postmatch imbalances. Absolute standardised differences <10% for a given covariate indicate a relatively small imbalance. Changes in mean transvalvular gradient over time were evaluated with repeated-measures analyses of variance. Analyses were conducted on log-transformed data to adjust for its skewed distribution. Posteriori comparisons were performed using the Tukey's method. The normality assumption of variables was verified with the Shapiro-Wilk tests on the error distribution form the Cholesky factorisation of the statistical model. The analysis of variance test was used for comparing the changes in transvalvular gradient over time between groups. All analyses were performed using a hierarchical method in order to account for between-centre variability. Mortality and stroke rates were presented using Kaplan-Meier estimates and comparisons between groups were performed with the log-rank test or the Wilcoxon test for the propensity-matched cohort. All analyses were conducted using the statistical package SAS V.9.3 (SAS Institute).

RESULTS

The main baseline and procedural characteristics of the study population, according to the use of anticoagulation therapy at hospital discharge, are shown in table 1. Patients receiving anticoagulation therapy post-TAVR (n=707, 28.7%) were older (P=0.004), less likely to harbour concurrent significant coronary artery disease (P=0.002), had a lower transaortic gradient pre-TAVI (P<0.001) and tended to receive a balloon-expandable THV (P=0.108) via a transfemoral approach (P<0.001). The reasons for receiving anticoagulation therapy were atrial fibrillation in 573 patients (81%) and other causes in 135 patients (19%). A total of 663 patients received vitamin K antagonists (VKA) and 44 patients received direct oral anticoagulants (DOAC). A change in anticoagulation treatment occurred in 38 patients within the first year following TAVR (anticoagulation treatment was stopped in 18 patients, and 20 patients without anticoagulation therapy at hospital discharge received some type of anticoagulation therapy, mainly due to the occurrence of new-onset atrial fibrillation).

There was a small although significant difference between groups in mean transvalvular gradients on hospital discharge (AC group: 9.4±4.5 mm Hg, non-AC group: 9.8±4.6 mm Hg, P=0.04). At 1-year follow-up, there was a significant increase in mean gradient in the non-AC group (online supplementary figure 1), mean transprosthetic gradients were 9.1±4.2 mm Hg in the AC group (P=0.323 vs discharge) and 10.3±5.3 mm Hg in the non-AC group (P=0.003 vs discharge; P<0.02 for differences between groups). The incidence of VHD at 1-year follow-up was lower in the AC group (0.6%) compared with the non-AC group (3.7%, P<0.001 for differences between groups) (online supplementary figure 2). There were no differences in the incidence of VHD according to different generations of transcatheter valves (Cribier-Edwards/SAPIEN/SAPIEN XT vs SAPIEN 3, P=0.76; CoreValve vs Evolut R, P=0.19). Among those patients meeting the criteria for VHD, 47 patients (69%) had a mean transvalvular gradient ≥20 mm Hg at follow-up, 15 patients (19%) had gradients ≥30 mm Hg and 8 patients (7.5%) had gradients ≥40 mm Hg.

Of the 69 patients meeting criteria for VHD at 12-month follow-up, two underwent a second TAVR procedure, and five patients receiving antiplatelet therapy were treated with warfarin. Anticoagulation therapy was associated with a reduction in transvalvular gradients (to

Table 1 Baseline and procedural characteristics of the study population, according to anticoagulation therapy at hospital discharge

Variable	Anticoagulation therapy		P value
	No, n=1759	Yes, n=707	
Age (years)	80.9±7.5	81.7±6.4	0.004
Male sex	809 (46.2)	333 (47.5)	0.561
Body mass index (kg/m^2)	27.2±5.2	27.1±5.2	0.494
Diabetes mellitus	509 (29.9)	205 (29.9)	0.975
Coronary artery disease	924 (53.0)	323 (46.0)	0.002
COPD	458 (26.2)	206 (29.4)	0.119
Atrial fibrillation	191 (10.9)	573 (80.9)	<0.001
CKD (eGFR <60 mL/min)	1199 (68.2)	496 (70.2)	0.362
STS	7.2±6.5	7.9±5.9	0.074
Baseline echocardiogram			
LVEF ≥50%	1281 (72.8)	483 (68.3)	0.026
Mean gradient (mm Hg)	49.0±16.1	45.2±15.1	<0.001
Aortic regurgitation			
None/trace	1078 (67.1)	406 (63.1)	0.295
Mild	410 (25.5)	188 (29.2)	
Moderate	96 (5.9)	41 (6.4)	
Severe	23 (1.4)	8 (1.2)	
Procedural			
Approach			
Transfemoral	1390 (84.9)	513 (77.9)	<0.001
Transapical/transaortic	248 (15.2)	146 (22.2)	
Prothesis type			
Balloon expandable	797 (45.3)	346 (48.9)	0.108*
Cribier-Edwards	56 (3.2)	22 (3.1)	
SAPIEN	250 (14.2)	129 (18.3)	
SAPIEN XT	422 (23.9)	176 (24.9)	
SAPIEN 3	69 (3.9)	19 (2.7)	
Self-expandable	962 (54.7)	361 (51.1)	
CoreValve	801 (45.5)	291 (41.2)	
Evolut R	73 (4.2)	40 (5.7)	
Portico	20 (1.1)	3 (0.4)	
DirectFlow	51 (2.9)	14 (1.9)	
Lotus	15 (0.9)	11 (1.6)	0.269
Other	2 (0.1)	2 (0.3)	
Discharge echocardiogram			
LVEF ≥50%	1369 (77.8)	524 (74.1)	0.051
Mean gradient (mm Hg)	9.8±4.6	9.4±4.5	0.032
Aortic regurgitation			
None/trace	1386 (79.8)	565 (81.2)	0.597
Mild	320 (18.4)	117 (16.8)	
Moderate	30 (1.7)	13 (1.9)	
Severe	1 (0.1)	1 (0.1)	
Discharge medication			
Aspirin	1543 (90.5)	391 (56.0)	<0.001
Clopidogrel	1420 (83.2)	226 (32.4)	<0.001

Categorical variables are reported as n (%) and continuous variables as mean±SD.
*Versus self-expandable.
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; STS, Society for Thoracic Surgeons risk score.

Table 2 Incidence of clinical events in the study population, according to the occurrence of valve haemodynamic deterioration (VHD)

	VHD (%)			
	No, n=2397	Yes, n=69	HR (95% CI)	P value
Death	533 (22.2)	10 (14.5)	0.79 (0.43 to 1.48)	0.470
Cardiac death	159 (6.6)	5 (7.3)	1.32 (0.54 to 3.21)	0.542
Stroke	71 (2.9)	0	–	–

postdischarge values) in all patients. No additional measures or antithrombotic treatment changes were undertaken in 62 of the patients with VHD at 1-year follow-up. Of these, echocardiography data at 2-year follow-up was available in 19 patients. No significant progression of mean transprosthetic gradients between 1 and 2 years post-TAVR were noted in these patients (P=0.803) (online supplementary figure 3).

The Kaplan-Meier curves at 4-year follow-up according to the diagnosis of VHD are shown in online supplementary figure 4. VHD did not associate with increased death (P=0.468), cardiovascular (CV) death (P=0.539) or stroke (P=0.170) rates at follow-up (table 2). There was no association between changes in mean gradient (considered as a continuous variable) and clinical outcomes in the general cohort: all-cause mortality (HR: 0.99 for each increase of 1 mm Hg in mean gradient, 95% CI (0.97 to 1.01) P=0.305), CV death (HR: 0.99, 95% CI (0.96 to 1.02) P=0.438) or stroke (HR: 0.98, 95% CI (0.93 to 1.03) P=0.352). Similar results were observed in those patients meeting criteria of VHD: all-cause mortality (HR: 0.93 for each increase of 1 mm Hg in mean gradient, 95% CI (0.72 to 1.20) P=0.584), CV death (HR: 0.96, 95% CI (0.62 to 1.05) P=0.876) or stroke (no events).

Propensity-matched cohort

A total of 622 patients receiving anticoagulation therapy post-TAVR were matched using a propensity score matching analysis with 622 patients not receiving anticoagulation therapy. Table 3 shows the baseline and procedural characteristics of the propensity-matched population, according to anticoagulation therapy at hospital discharge. There were no significant between-group differences in baseline and procedural characteristics. The reasons for receiving anticoagulation therapy were atrial fibrillation in 497 patients (80%) and other causes in 125 patients (20%). A total of 587 patients received VKA and 35 patients received DOAC. At 1-year follow-up, there was a small but significant increase in mean transvalvular gradient in the non-AC group (figure 1). The incidence of VHD at 1-year follow-up was lower in the AC group (0.6%) compared with the non-AC group (3.9%, P<0.001 for differences between groups. There were no differences between patients with and without VHD in the rate of global death (P=0.954), CV death (P=0.383) or stroke (P=0.466) at follow-up (figure 2, table 4).

Dual antiplatelet therapy versus anticoagulation therapy subanalysis

A subanalysis comparing patients receiving dual antiplatelet therapy versus anticoagulation therapy was performed (online supplementary table 2). Patients receiving anticoagulation therapy post-TAVR were older (P=0.018), less likely to harbour concurrent significant coronary artery disease (P<0.001), had a lower transaortic gradient pre-TAVI (P<0.001) and were more likely to receive a balloon-expandable THV (P<0.001) via a transfemoral approach (P<0.001). The incidence of VHD was higher among patients treated with dual antiplatelet therapy

Table 3 Baseline and procedural characteristics of the propensity-matched population, according to anticoagulation therapy at hospital discharge

Variable	Anticoagulation therapy		P value
	No, n=622	Yes, n=622	
Age (years)	81.8±6.7	81.8±6.1	0.839
Male sex	293 (47.4)	289 (46.9)	0.864
Body mass index (kg/m^2)	27.1±5.0	27.1±5.3	0.907
Diabetes mellitus	168 (27.9)	187 (31.2)	0.207
Coronary artery disease	287 (46.1)	293 (47.1)	0.776
COPD	193 (31.0)	186 (29.9)	0.712
Atrial fibrillation	65 (10.5)	497 (79.9)	<0.001
CKD (eGFR <60 mL/min)	419 (67.4)	432 (69.5)	0.464
STS	7.8±6.6	7.7±5.7	0.846
Baseline echocardiogram			
LVEF ≥50%			
Mean gradient (mm Hg)	45.2±14.9	45.2±15.2	0.973
Aortic regurgitation			
None/trace	375 (63.9)	366 (63.4)	0.752
Mild	166 (28.3)	174 (30.2)	
Moderate	40 (6.8)	32 (5.6)	
Severe	6 (1.0)	5 (0.9)	
Procedural			
Approach			
Transfemoral	497 (79.9)	486 (78.1)	0.486
Transapical/transaortic	125 (20.1)	136 (21.9)	
Prothesis type			
Balloon-expandable	295 (47.4)	320 (51.5)	0.174*
Cribier-Edwards	22 (3.5)	22 (3.5)	
SAPIEN	104 (16.7)	117 (18.8)	
SAPIEN XT	139 (22.4)	165 (26.5)	
SAPIEN 3	30 (4.8)	16 (2.6)	
Self-expandable	327 (52.6)	302 (48.6)	
CoreValve	258 (41.5)	242 (38.9)	
Evolut R	36 (5.8)	31 (5.0)	
Portico	10 (1.6)	3 (0.5)	
DirectFlow	18 (2.9)	13 (2.1)	
Lotus	5 (0.8)	11 (1.8)	
Other	0	2 (0.3)	
Valve size			
≤23 mm	171 (27.5)	176 (28.3)	0.800
>23 mm	451 (72.5)	446 (71.7)	
Discharge echocardiogram			
LVEF ≥50%			
Mean gradient (mm Hg)	9.8±4.3	9.4±4.5	0.095
Aortic regurgitation			
None/trace	493 (80.3)	496 (81.1)	0.739
Mild	115 (18.7)	107 (17.5)	
Moderate	6 (0.9)	8 (1.3)	
Severe	0	1 (0.2)	
Discharge medication			
Aspirin	576 (92.6)	359 (57.7)	<0.001
Clopidogrel	502 (80.7)	202 (32.5)	<0.001

Categorical variables are reported as n (%); continuous variables are expressed as mean±SD.
*Versus self-expandable.
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction.

compared with those receiving anticoagulant therapy (3.4% vs 0.6%, P<0.001).

DISCUSSION

The lack of anticoagulation therapy post-TAVR influenced transcatheter valve haemodynamics, and was associated with

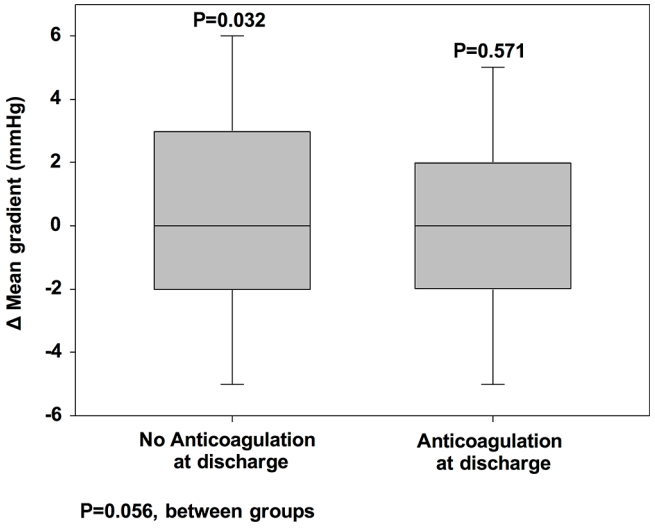

Figure 1 Absolute changes in mean transvalvular gradient between discharge and 1-year follow-up in the propensity-matched population according to the presence of anticoagulation therapy at hospital discharge (analyses conducted on log-transformed data).

increased transvalvular gradients and a higher risk of VHD at 1-year follow-up. Our data suggest that valve thrombosis is likely an important mechanism of early VHD post-TAVR. VHD was mild in the majority of cases (only 7.5% of patients diagnosed of VHD had transvalvular gradients ≥40 mm Hg) and did not associate with major adverse clinical events after a mean follow-up period of about 2 years. Also, according to the classification of bioprosthetic valve thrombosis recently proposed by Dangas *et al*,[16] among the 69 patients diagnosed with VHD, 7 and 62 patients would meet the criteria of definitive and probable valve thrombosis, respectively.

Mean transprosthetic gradients ranging from 20 to 40 mm Hg have been proposed in VARC-2 to be indicative of mild valve stenosis, whereas mean gradient >40 mm Hg is considered moderate-to-severe THV stenosis post-TAVR.[11] However, the use of a fixed cut-off point could lead to an overdiagnosis of acquired THV stenosis in patients with elevated mean transprosthetic gradients at discharge and could underestimate relevant changes in valve haemodynamics over time in those with low mean transprosthetic gradients postprocedure. In patients with established aortic stenosis, an increase in mean gradient >10 mm Hg over time is considered as a significant progression of the stenosis.[17] Also, the intraobserver and interobserver variability for the measurement of mean transaortic gradient has been established at <10 mm Hg.[18] Thus, and according to prior studies[5 14 19] (Vemulapalli, ACC 2016), the absolute increase in mean transprosthetic gradient of ≥10 mm Hg over time was established to define VHD.

Bioprosthetic valve thrombosis is an unusual but potentially life-threatening complication after SAVR. The incidence of bioprosthetic valve thrombosis requiring reoperation within the 2 years following SAVR ranges from 0.37% to 1.26%, depending on valve type.[20] However, the true incidence of bioprosthetic valve thrombosis may have been underestimated, as the occurrence of mild valve thromboses (usually not requiring reintervention) was not taken into account. Hypercoagulable states, low LVEF and factors leading to abnormal flow patterns such as small valve size, perivalvular leaks and pannus may predispose to valve thrombosis.[20] Current guidelines recommend anticoagulation therapy for 90 days after

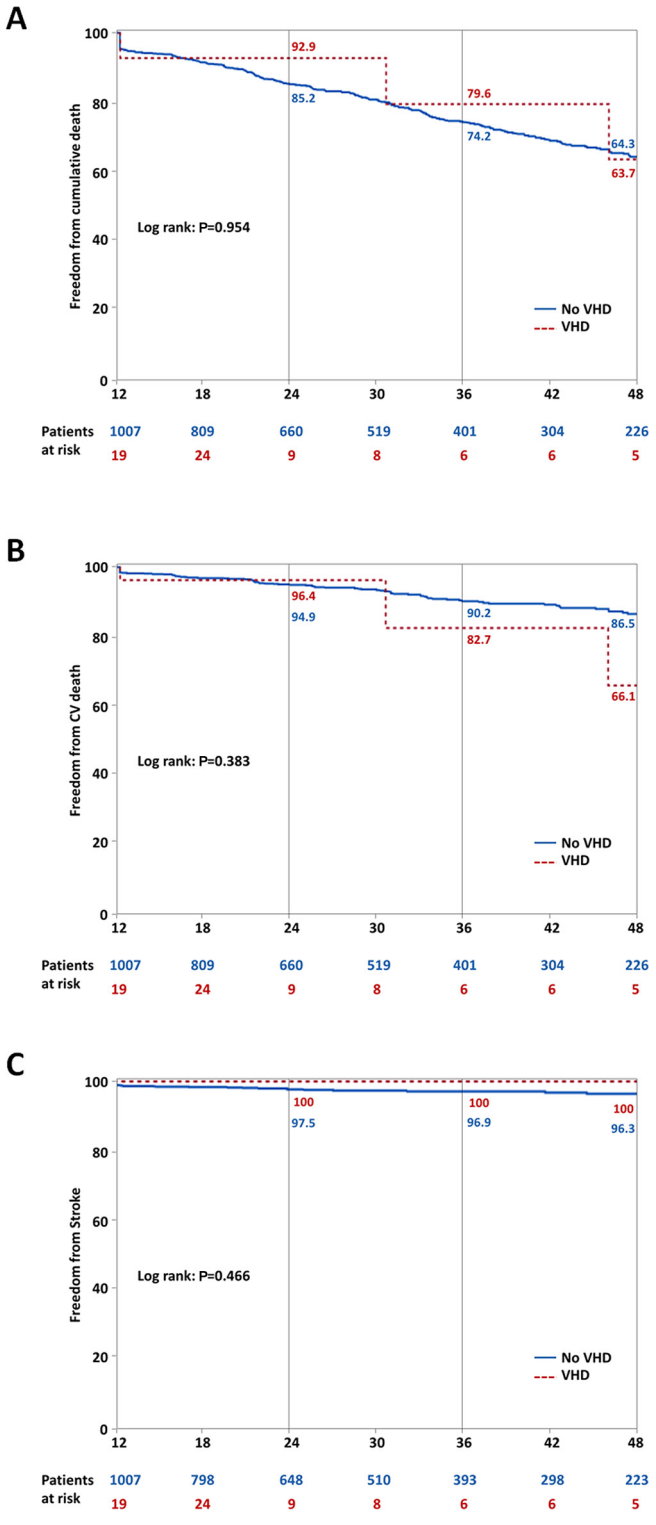

Figure 2 Kaplan-Meier survival curves following TAVR, according to VHD in the propensity-matched population. (A) Global death. (B) CV death. (C) Stroke. CV, cardiovascular; TAVR, transcatheter aortic valve replacement; VHD, valve haemodynamic deterioration.

bioprosthetic SAVR.[21 22] These recommendations were based on several observational studies that showed a reduced risk of thromboembolic complications in patients receiving warfarin. However, the risk/benefit of anticoagulation therapy after bioprosthetic SAVR remains controversial, and some studies have suggested that only high-risk patients may benefit from

Table 4 Incidence of clinical events in the matched cohort, according to the occurrence of valve haemodynamic deterioration (VHD)

	VHD (%)			
	No, n=1216	Yes, n=28	HR (95% CI)	P value
Death	307 (25.3)	4 (14.3)	0.94 (0.35 to 2.52)	0.898
Cardiac death	100 (8.2)	3 (10.7)	2.14 (0.67 to 6.77)	0.195
Stroke	31 (2.6)	0	–	–

VKA[23]. Clinically relevant bioprosthetic valve thrombosis is such an unusual event that available studies to date were underpowered to determine both the optimal type and duration of antithrombotic therapy post-SAVR.

The incidence of clinically relevant valve thrombosis post-TAVR remains uncertain. While some studies have estimated the incidence of symptomatic valve thrombosis post-TAVR at approximately 1%,[10 24] only seven patients (0.2%) meeting the criteria of VHD required a specific intervention (either anticoagulation therapy or reintervention) in our study. There is however an increasing concern about subclinical valve thrombosis post-TAVR. Leetmaa *et al*[25] reported an incidence of 4% of THV thrombosis performing multidetector CT (MDCT) within 1 and 3 months after TAVR. Interestingly, 80% of these patients were asymptomatic and had a normal transthoracic echocardiographic study. In the same direction, Pache *et al*[26] evaluated 156 patients by MDCT after a median of 5 days post-TAVR with the SAPIEN 3 THV system. Early hypoattenuated leaflet thickening (HALT) was found in about 10% of patients, and it was reversible following oral anticoagulation in all instances. Interestingly, at the time of MDCT, patients with HALT did not present with symptoms, but simply with a small, although significantly increased, mean transprosthetic gradient. Similarly, Makkar *et al*[9] found reduced leaflet motion on MDCT in up to 40% of patients treated with differing THV platforms involved in the Portico Re-sheathable Transcatheter Aortic Valve System US IDE Trial (PORTICO IDE) (mean time from TAVR to MDCT, 32 days). They also studied patients undergoing SAVR or TAVR included in the Assessment of Transcatheter and Surgical Aortic Bioprosthetic Valve Thrombosis and its Treatment with Anticoagulation (RESOLVE) and Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed with Four-Dimensional Computed Tomography (SAVORY) registries. In this cohort, a 13% incidence of reduced leaflet motion was observed at a mean follow-up of 3 months. In accordance with our results, anticoagulation with warfarin, as compared with dual antiplatelet therapy, was associated with a much lower rate of reduced leaflet motion (0% vs 55%). Among patients with reduced leaflet motion and available MDCT at follow-up, restoration of leaflet motion was noted in those treated with warfarin but only in 10% of patients who did not receive anticoagulation therapy. Hansson *et al*[10] recently reported the largest study to date evaluating the occurrence of valve thrombosis post-TAVR as assessed by MDCT and transesophageal echocardiography (TEE).[10] Among 405 patients undergoing TAVR with either the SAPIEN XT or SAPIEN 3 THVs, the incidence of valve thrombosis was 7%, and the lack of anticoagulation therapy post-TAVR was the most important factor determining a higher risk of valve thrombosis. Interestingly, THV leaflet thickening and restricted mobility (both signs suggestive of valve thrombosis) disappeared in 85% of patients treated with warfarin. This study failed to show any significant repercussion on valve haemodynamics, although some studies demonstrated a mild increase in transvalvular gradients among patients diagnosed with valve thrombosis.[26] This likely reflects

an early stage of valve thrombosis post-TAVR, prior to VHD or clinically apparent valve obstruction. In accordance with the results of our study, valve thrombosis as determined by MDCT was not associated with major adverse clinical events, including stroke or cardioembolic events. Of note, no increased risk of CV events (including stroke) was observed within the 2 years following the diagnosis of VHD in our study. Furthermore, additional echocardiographic examinations performed 1 year after the diagnosis of VHD failed to demonstrate a further deterioration in valve haemodynamics, even in the absence of anticoagulation therapy. Studies with a longer follow-up will be needed to determine whether these early subclinical changes in valve haemodynamics ultimately affect valve durability over time.

Implications and future directions

The decision of systematic anticoagulation therapy post-TAVR remains challenging. Current American Heart Association/American College of Cardiology guidelines recommend 3 months of anticoagulation following TAVR in patients at low risk of bleeding.[21] However, the 2017 ESC guidelines do not recommend anticoagulation but dual antiplatelet therapy for the first 3–6 months post-TAVR.[22] Several ongoing randomised trials will provide more evidence on the absolute benefit of anticoagulation for reducing thromboembolic events and preserving valve function after TAVR. Despite the lack of major clinical consequences, a closer clinical and echocardiographic follow-up of patients with VHD may be important due to the potential higher risk of major valve degeneration leading to structural valve failure and clinical events in such patients. Also, recent studies support that once VHD is diagnosed, anticoagulation therapy must be considered before any further intervention.[27 28]

Study limitations

Several limitations of the present study warrant further consideration including its non-randomised design with a retrospective analysis of prospectively collected data. While this was partially compensated by a strict matching process, the results of this observational study need to be confirmed by a larger, prospective randomised trial. The indication of anticoagulation was determined by each participating centre. Only patients who survived 12 months post-TAVR were included in the present analysis; hence, the real incidence of VHD may have been underestimated. Frailty assessment was not systematically performed. Also, data on bleeding events and transient ischaemic attack during follow-up, as well as heart rate and stroke volume at the time of echocardiographic examinations were not available in most patients. Transvalvular gradient assessment was made on the basis of the results of transthoracic echocardiograms analysed and reported by each centre. There was no independent echocardiographic core laboratory analysis involved in this study. TEE or MDCT studies were not systematically performed in patients meeting the criteria of VHD. Finally, following the diagnosis of VHD, the treatment was determined according to the choice of each individual centre, and no standardised protocol had been established.

CONCLUSIONS

Anticoagulation therapy following TAVR thwarted an early increase in transvalvular bioprosthetic gradients, reducing the risk of VHD within the year following the procedure. The occurrence of VHD post-TAVR did not associate with worsening clinical outcomes after a mean follow-up of about 2 years. Antithrombotic therapy post-TAVR remains an unresolved issue, and multiple ongoing randomised studies are currently evaluating the safety and efficacy of systematic anticoagulation therapy in patients undergoing TAVR. These studies represent a unique opportunity to confirm the efficacy of anticoagulation in preventing the occurrence of VHD following TAVR.

Key messages

What is already known on this subject?
The most appropriate antithrombotic regimen following transcatheter aortic valve replacement (TAVR) remains to be established, and concerns have recently emerged regarding subclinical valve thrombosis post-TAVR.

What might this study add?
The lack of anticoagulation therapy post-TAVR influenced transcatheter valve haemodynamics and was associated with a higher risk of valve haemodynamic deterioration at 1-year follow-up. Valve haemodynamic deterioration did not associate with major adverse clinical events after a mean follow-up period of 2 years.

How might this impact on clinical practice?
Prospective randomised trials are needed to quantify the impact of valve haemodynamic deterioration on long-term valve durability and to determine if a specific antithrombotic regimen post-TAVR may reduce the risk of incident valve haemodynamic deterioration.

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