EuroIntervention 2020;15:1233-1239 published online September 2019

Predictors of haemodynamic structural valve deterioration following transcatheter aortic valve implantation with latest-generation balloon-expandable valves

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00710

KEYWORDS

- aortic stenosis
- non-invasive imaging
- TAVI

Abstract

Aims: Elevated gradients have been proposed to be associated with haemodynamic structural valve deterioration (SVD) after transcatheter aortic valve implantation (TAVI); however, data regarding their characterisation remain scarce. This study sought to investigate the prevalence and predictors of moderate or greater SVD and the prevalence of valve thrombosis during follow-up after TAVI with balloon-expandable valves.

Methods and results: A total of 691 patients undergoing transfemoral TAVI were enrolled. The primary endpoint was moderate or severe haemodynamic SVD during 12-month follow-up after TAVI, defined as (I) mean transvalvular gradient ≥20 mmHg or (II) mean transvalvular gradient increase ≥10 mmHg. The primary endpoint was observed in 10.3% after TAVI. Use of a 20 mm valve, valve-in-valve procedure and absence of oral anticoagulation (OAC) were independently associated with haemodynamic SVD, whereas valve-in-valve procedure and absence of OAC were the only significant variables after accounting for death as a competing event. Absence of OAC was significantly associated with haemodynamic SVD (RR 8.65; p=0.004) and death (RR 3.57; p=0.06), whereas valve-in-valve procedure was only associated with haemodynamic SVD (RR 52.76; p<0.001). Valve thrombosis was present in 0.87% (6/691) of the patients.

Conclusions: The prevalence of moderate or greater haemodynamic SVD during the first 12 months after TAVI is 10.3%. Procedural factors and pharmacotherapy seem to play a key role during manifestation. Future studies should focus on the underlying mechanisms.

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SUBMITTED ON 03/08/2019 - REVISION RECEIVED ON N/A - ACCEPTED ON 03/09/2019

DOI: 10.4244/EIJ-D-19-00710

Abbreviations

CIF	cumulative incidence function
CRR	competing risk regression
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
OAC	oral anticoagulation
SVD	structural valve deterioration
TAVI	transcatheter aortic valve implantation
THV	transcatheter heart valves
VARC	Valve Academic Research Consortium

Introduction

Transcatheter aortic valve implantation (TAVI) has been performed increasingly over the last decade and is currently recommended for patients with severe aortic stenosis who are considered at high or intermediate risk for conventional aortic valve replacement[1]. Results from contemporary randomised trials in low-risk TAVI patients will probably broaden the indication of use with this disruptive technology[2,3].

Although the efficacy and safety of TAVI have been demonstrated in large, randomised trials[4,5], data regarding long-term valve function are limited[6-8]. Standardised definitions of bioprosthetic structural valve deterioration (SVD) after TAVI have been published recently to enable objective evaluation of transcatheter heart valves (THV). Elevated gradients have been proposed to be associated with haemodynamic SVD[9].

The objective of this study was to investigate the prevalence and predictors of moderate or greater haemodynamic SVD during follow-up in the first 12 months after TAVI with balloon-expandable valves in a large contemporary patient cohort and further assess the prevalence of valve thrombosis.

Methods

STUDY POPULATION AND PROCEDURES

Between January 2014 and April 2018, 872 consecutive patients with severe aortic stenosis or degenerated bioprosthetic aortic valves underwent transfemoral TAVI with balloon-expandable valves (SAPIEN 3; Edwards Lifesciences, Irvine, CA, USA) at the Department of Cardiovascular Diseases, German Heart Centre Munich, Germany. Patients with device failure according to the updated Valve Academic Research Consortium (VARC)-2 criteria were excluded from final analyses (n=78)[10]. Furthermore, patients with missing echocardiographic data during follow-up were excluded from final analyses (n=103). Finally, a total of 691 patients satisfied these criteria and were included in the final analysis. All patients were discussed by a multidisciplinary Heart Team and found eligible for transfemoral TAVI. All patients provided written informed consent. Post-procedural pharmacotherapy consisted of dual antiplatelet treatment with aspirin and clopidogrel for at least three months in patients without an indication for oral anticoagulation (OAC) or prior coronary intervention; when patients had an indication for OAC, single-therapy OAC was prescribed unless the patient also had an indication for antiplatelet treatment. Triple therapy was only prescribed in case of recent coronary intervention entailing reduced dose OAC.

DEFINITION OF ENDPOINTS AND FOLLOW-UP

The primary endpoint of this study was moderate or greater haemodynamic SVD during follow-up in the first 12 months after TAVI, defined as (I) mean transvalvular gradient ≥20 mmHg or (II) mean transvalvular gradient increase ≥10 mmHg compared with previous measurements after TAVI. Moreover, crude rates of both moderate and severe haemodynamic SVD as well as bioprosthetic valve failure (BVF) were reported individually. Additionally, elevated transvalvular gradients were investigated by transoesophageal echocardiography and/or multislice computed tomography (CT) at the discretion of the treating physician to rule out valve thrombosis.

Data collection involved demographic information, procedural data, as well as clinical and echocardiographic assessment. Adverse events were recorded throughout the follow-up period. All clinical endpoints, procedural data and in-hospital complications were categorised according to the updated VARC-2 criteria. Transthoracic echocardiography was performed at baseline, at discharge, at least once during 12-month follow-up after TAVI and yearly thereafter (up to four years).

STATISTICAL ANALYSIS

Categorical variables are expressed as frequencies and proportions and were compared using the chi-square or Fisher's exact test, as appropriate. Continuous variables are presented as mean with standard deviation (SD) or median with interquartile range (IQR) and compared using the Student's t-test or Mann-Whitney U test, respectively.

For dichotomous analysis, patients were divided into strata with and without haemodynamic SVD. Cox proportional hazards analysis was performed to determine factors associated with the primary endpoint. Possible covariables were selected by clinical relevance and were as follows: female gender, New York Heart Association (NYHA) Class III/IV, previous myocardial infarction, previous stroke, previous malignancy, previous pacemaker implantation, peripheral artery disease, anaemia, left ventricular ejection fraction (LVEF) <35%, mitral regurgitation grade III/IV, valve-in-valve procedure, use of a 20 mm valve, predilatation, post-dilatation and OAC at discharge. Corresponding hazard ratios (HR) were computed.

Additionally, multivariable competing risk regression (CRR) was performed using the R package "cmprsk" (R Foundation for Statistical Computing, Vienna, Austria). Similar to conventional multivariable regression analysis, this method aims to find predictors of the primary endpoint while adjusting for statistically relevant cofactors and accounting for death as a competing event. Due to the limited number of events (haemodynamic SVD and/or death), risk regression models were constrained to the following predictor variables to avoid model overfitting: age, use of a 20 mm valve, previous malignancy, valve-in-valve procedure and OAC. Additionally, cumulative incidence function (CIF) estimates from competing risk data were calculated for valve-in-valve procedures and OAC.

A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using JMP, Version 13 (SAS Institute Inc., Cary, NC, USA), R Version 3.3.2 (R Foundation for Statistical Computing) and IBM SPSS Statistics, Version 24.0 for Macintosh (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics of the entire population are shown in **Table 1**. A total of 691 patients were included in this analysis (mean age 80.0±6.2 years, 42% female). The population was a contemporary and unselected cohort of patients with a median logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) I of 13.0% [7.9-21.4]. Procedural data and in-hospital outcomes are provided in **Table 2**.

HAEMODYNAMIC SVD AFTER TAVI

The prevalence of moderate or greater haemodynamic SVD during the first 12 months after TAVI was 10.3% (71/691). There was incremental prevalence observed over time during the first 12 months after TAVI: 1.9% (13/691) at 30-day and 10.3% (71/691) at 12-month follow-up. Moderate haemodynamic SVD was observed in 9.4% (65/691), whereas severe haemodynamic SVD was observed in only 0.9% (6/691). Moreover, BVF was observed in 1.88% (13/691).

Baseline characteristics according to the primary endpoint are shown in **Table 1**. Patients with haemodynamic SVD (n=71) had a lower rate of atrial fibrillation (p=0.003) and previous strokes (p=0.03) and were less likely to be treated with oral anticoagulants (p=0.007). Regarding procedural data, valve-in-valve procedures (p<0.001) were more frequently performed, whereas predilatation (p=0.023) was less frequently performed in patients with elevated gradients **(Table 2)**.

Cox proportional hazards analysis revealed that use of a 20 mm valve (hazard ratio [HR] 9.43; p<0.001) and valve-in-valve procedure (HR 9.92; p<0.001) were independent predictors of haemodynamic SVD during follow-up after TAVI, whereas OAC (HR 0.46;

Table 1. Baseline characteristics.

		Haemodynamic SVD			
		All patients (n=691)	No (n=620)	Yes (n=71)	*p*-value
Age (years)		80.0±6.2	80.0±6.1	79.9±6.4	0.877
Female gender		291 (42.1%)	258 (41.6%)	33 (46.5%)	0.432
BMI (kg/m^2)		27.0±4.7	27.0±4.7	26.9±4.5	0.918
Log. EuroSCORE I (%)		13.0 [7.9-21.4]	13.0 [7.9-21.1]	14.8 [7.0-23.3]	0.523
NYHA Class III/IV		451 (65.3%)	409 (66.0%)	42 (59.2%)	0.253
Arterial hypertension		623 (90.2%)	561 (90.5%)	62 (87.3%)	0.397
Hypercholesterolaemia		519 (75.1%)	471 (76.0%)	48 (67.6%)	0.123
Diabetes mellitus		206 (29.8%)	192 (31.0%)	14 (19.7%)	0.050
Coronary artery disease		501 (72.5%)	452 (72.9%)	49 (69.0%)	0.487
Previous myocardial infarction		77 (11.1%)	69 (11.1%)	8 (11.3%)	0.972
Previous PCI		292 (42.3%)	266 (42.9%)	26 (36.6%)	0.310
Previous CABG		59 (8.5%)	52 (8.4%)	7 (9.9%)	0.674
Previous stroke		73 (10.6%)	71 (11.5%)	2 (2.8%)	0.025
Previous malignancy		137 (19.8%)	124 (20.0%)	13 (18.3%)	0.735
Previous pacemaker		82 (11.9%)	78 (12.6%)	4 (5.6%)	0.086
Peripheral artery disease		96 (13.9%)	88 (14.2%)	8 (11.3%)	0.500
COPD		97 (14.0%)	87 (14.0%)	10 (14.1%)	0.990
Atrial fibrillation		291 (42.1%)	273 (44.0%)	18 (25.4%)	0.003
Anaemia		304 (44.0%)	278 (44.8%)	26 (36.6%)	0.186
LVEF ≤35%		80 (11.6%)	73 (11.8%)	7 (9.9%)	0.633
Mitral regurgitation grade III/IV		29 (4.2%)	27 (4.4%)	2 (2.8%)	0.540
PAP >60 mmHg		76 (11.3%)	69 (11.4%)	7 (10.3%)	0.784
Mean gradient (mmHg)		43 [34-51]	42 [34-50]	46 [37-53]	0.067
Aortic valve area (cm^2)		0.72 [0.59-0.88]	0.72 [0.59-0.88]	0.73 [0.59-0.84]	0.665
Creatinine clearance (ml/min)		56±21	56±21	54±18	0.392
Medication at discharge	Dual antiplatelet therapy*	379 (54.8%)	330 (53.2%)	49 (69.0%)	0.011
	Oral anticoagulation	308 (44.6%)	287 (46.3%)	21 (29.6%)	0.007

* Aspirin plus second antithrombotic agent. BMI: body mass index; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; EuroSCORE: European System for Cardiac Operative Risk Evaluation; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PAP: pulmonary artery pressure; PCI: percutaneous coronary intervention

Table 2. Procedural data and in-hospital outcome.

	Haemodynamic SVD			
	All patients (n=691)	No (n=620)	Yes (n=71)	*p*-value
Valve-in-valve procedure	16 (2.3%)	6 (1.0%)	10 (14.1%)	<0.001
Predilatation	640 (92.6%)	579 (93.4%)	61 (85.9%)	0.023
Post-dilatation	201 (29.1%)	184 (29.7%)	17 (23.9%)	0.314
Procedural time, min	49.0 [41.0-60.0]	49.0 [41.0-60.0]	52.0 [39.0-60.0]	0.490
Fluoroscopy time, min	11.1 [8.3-14.5]	11.0 [8.3-14.3]	12.3 [7.5-15.8]	0.164
Contrast, ml	100 [85-130]	102 [90-130]	100 [80-130]	0.209
Major vascular complication	46 (6.7%)	41 (6.6%)	5 (7.0%)	0.891
Life-threatening bleeding	18 (2.6%)	15 (2.4%)	3 (4.2%)	0.365
Major stroke	4 (0.6%)	4 (0.6%)	0 (0%)	0.999
Renal failure (incl. dialysis)	8 (1.2%)	7 (1.1%)	1 (1.4%)	0.582
New pacemaker implantation	51 (7.4%)	47 (7.6%)	4 (5.6%)	0.552
Days in hospital	5.0 [4.0-6.0]	5.0 [4.0-6.0]	5.0 [3.0-6.0]	0.595
Days on intensive care unit	1.0 [1.0-1.0]	1.0 [1.0-2.0]	1.0 [1.0-1.0]	0.036

p=0.003) was a protective factor of haemodynamic SVD. Based on these observations, crude rates of haemodynamic SVD were further analysed in patients with and without OAC **(Figure 1)**.

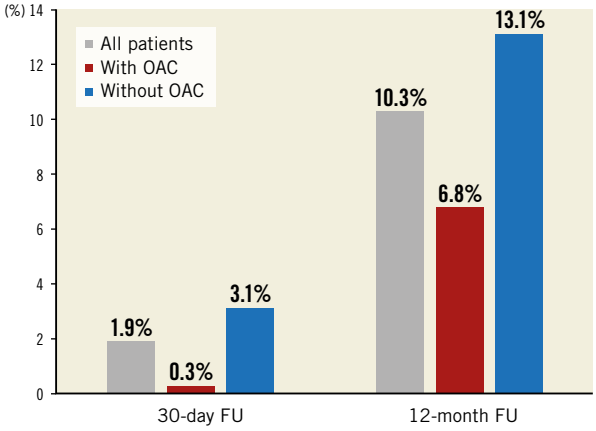

Figure 1. *Crude rates of haemodynamic structural valve deterioration during follow-up after TAVI in patients with and without oral anticoagulation.*

The crude mortality rate 12 months after TAVI was 4.3% (30/691). After CRR accounting for death as a competing event, valve-in-valve procedure (relative risk [RR] 13.01; p<0.001) and OAC (RR 0.39; p<0.001) were the only significant predictor and protective factor of haemodynamic SVD, respectively. According to CIF estimates, absence of OAC was significantly associated with both haemodynamic SVD (RR 8.65; p=0.004) and death (RR 3.57; p=0.06), whereas valve-in-valve procedure was only significantly associated with haemodynamic SVD (RR 52.76; p<0.001) but not with death (RR 0.89; p=0.35) **(Figure 2)**.

Long-term echocardiographic follow-up was available in a subgroup of patients, namely 107 patients at two-year follow-up and

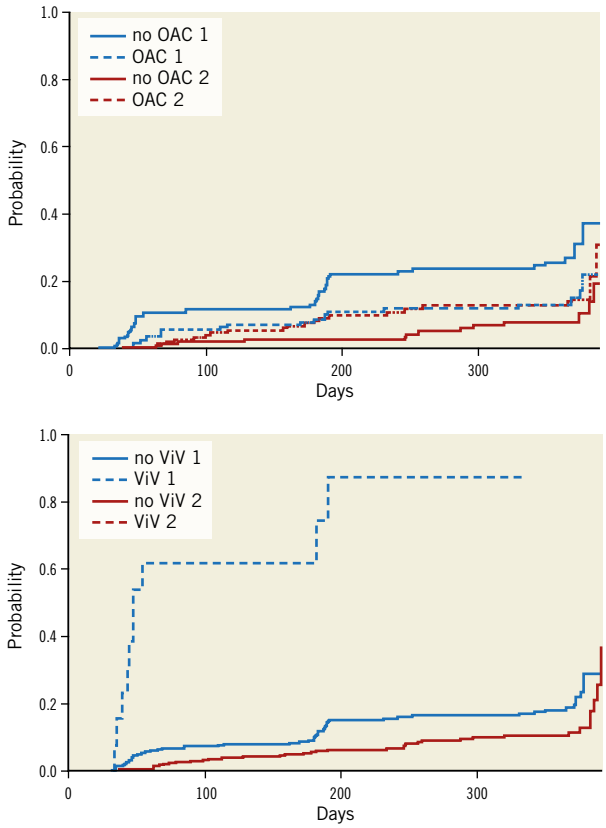

Figure 2. *Cumulative incidence function estimates from competing risk data for oral anticoagulation and valve-in-valve (ViV) procedures. 1: haemodynamic SVD, 2: death. Note that CIF for death in cases with and without ViV are superimposed.*

48 and 31 patients at three- and four-year follow-up, respectively. Haemodynamic SVD was observed in 9.3% (10/107) at two years, 10.4% (5/48) at three years and 6.5% (2/31) at four-year follow-up.

BIOPROSTHETIC VALVE THROMBOSIS

Bioprosthetic valve thrombosis was present in 0.87% (6/691) of the entire cohort and 8.5% (6/71) of patients with haemodynamic SVD during follow-up after TAVI **(Figure 3, Moving image 1, Moving image 2)**. The clinical characteristics of patients with valve thrombosis are shown in detail in **Supplementary Table 1**. At detection time, median transvalvular gradient was 28 mmHg (IQR 25-47). All patients were on single or dual antiplatelet therapy. OAC with either phenprocoumon (international normalised ratio [INR] target range 2.0-3.0) or apixaban (5 mg twice daily) was initiated in all cases after valve thrombosis was diagnosed; valve thrombosis was successfully resolved in all cases **(Figure 4)**.

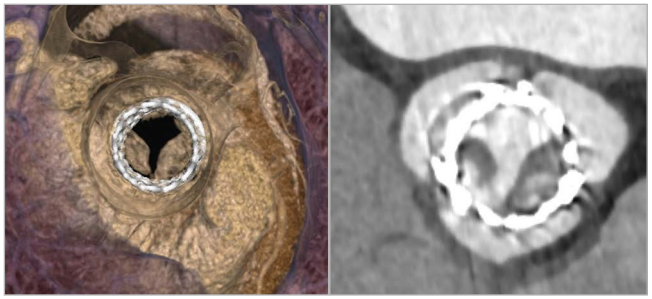

Figure 3. *Computed tomography images showing a case of valve thrombosis after valve-in-valve TAVI.*

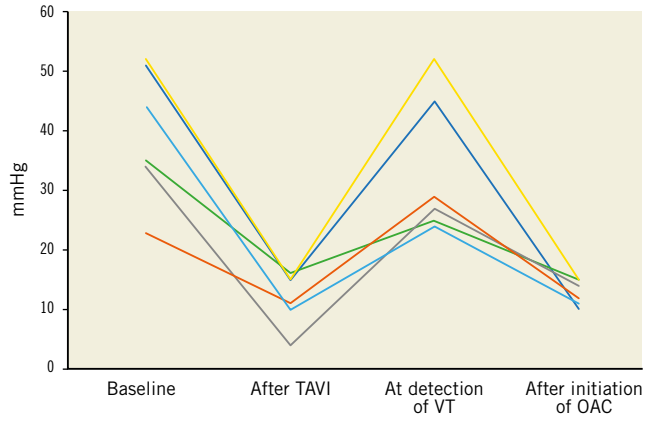

Figure 4. *Mean transvalvular gradients of patients with valve thrombosis at baseline, after TAVI and during follow-up after TAVI.*

Discussion

The present study investigated the prevalence of moderate or greater haemodynamic SVD during follow-up after TAVI and also assessed the prevalence of valve thrombosis. To our knowledge, this is the first study using CRR to account for the probability of death as a competing event. The results can be summarised as follows. The prevalence of moderate or greater haemodynamic SVD was 10.3% during 12-month follow-up after TAVI. Cox proportional hazards analysis revealed that haemodynamic SVD after TAVI was more frequent using a 20 mm valve or in case of valve-in-valve procedures and less frequent in case of OAC. Valve thrombosis was present in 0.87% of the entire cohort during follow-up after TAVI.

BIOPROSTHETIC STRUCTURAL VALVE DETERIORATION

Bioprostheses are prone to SVD. Experience from surgically implanted bioprostheses indicates onset of SVD six to eight years after implantation[11]. Heterogeneous definitions have been a major limitation in the past[12]. In these studies, diagnosis of SVD often involved the need for re-operation or clinically apparent symptoms, hence the prevalence of SVD has probably been underestimated.

Despite the widespread use of TAVI since its inception in 2007, long-term data beyond five years are still limited[6-8]. As we proceed into the period in which SVD has been observed with surgical bioprostheses, standardised definitions have now been proposed[9]. Haemodynamic SVD, which can be assessed by means of echocardiography, requires special attention. According to updated VARC-2 and European Association of Percutaneous Cardiovascular Interventions (EAPCI) criteria, we investigated moderate or greater haemodynamic SVD during the first 12 months after TAVI[9,10].

PREVALENCE AND PREDICTORS OF HAEMODYNAMIC SVD

In this study, moderate or greater haemodynamic SVD was present in 10.3% of all patients treated with balloon-expandable valves. To date, available studies regarding haemodynamic SVD after TAVI are scarce with conflicting results. Early randomised TAVI studies and large registries have reported unchanged valve function up to five years after TAVI, although these data are generally limited by high mortality rates in this cohort of inoperable/high-risk patients[6,7,13]. In contrast, other authors have reported low rates of haemodynamic SVD in up to 5% of patients undergoing TAVI as well as a mild, but significant increase of gradients over time after TAVI[14,15].

The clinical relevance of haemodynamic SVD after TAVI is unknown. An association with an increased risk of adverse cardiovascular events has not been reported to date[16]. Nevertheless, given the current trend to treat younger, lower-risk patients, identifying predictors associated with an increased risk for haemodynamic SVD is of utmost relevance; further research is needed to assess the clinical impact of haemodynamic SVD. Apparently, short-term follow-up after TAVI is warranted since most patients with haemodynamic SVD presented within the first year after TAVI[14].

In the present Cox proportional hazards analysis, haemodynamic SVD was less frequently observed in case of treatment with oral anticoagulants after TAVI and more frequent using a 20 mm valve or in case of valve-in-valve TAVI procedures. The observed association of OAC and haemodynamic SVD is in line with previous studies that have already reported OAC providing protection from haemodynamic SVD[14,15]. This particular finding is of tremendous interest given the current uncertainty and low evidence level with regard to the optimal pharmacotherapy after TAVI.

Just recently, the authors of the FRANCE TAVI registry have shown for the first time that OAC at discharge is a significant and independent predictor of increased long-term mortality after TAVI[17]. As a higher operative risk might partly account for this observation, CRR with death as a competing event seems appropriate in these patients. Our analysis revealed that OAC is a significant protective factor of haemodynamic SVD after TAVI, whereas it is a predictor of death after TAVI.

The observational character of our and other available studies and the given collinearity of several variables further support the urgent need for data from ongoing randomised trials evaluating the optimal pharmacotherapy after TAVI. For the time being, pharmacotherapy after TAVI should be applied according to current guidelines[1].

MECHANISMS OF STRUCTURAL VALVE DETERIORATION

Currently, mechanisms leading to (haemodynamic) SVD are incompletely understood. Various reasons might account for elevated transvalvular gradients following procedural success. In the present analysis, patients with device failure according to VARC-2 criteria were excluded from further analyses to focus on actual valve deterioration during follow-up.

Recently, bioprosthesis thrombosis after TAVI has become a major concern[18]. The incidence of valve thrombosis after TAVI ranges from 0.6-2.8% in the literature[19-21], whereas subclinical leaflet thrombosis has been observed in 6-40%[18,22]. In our current analysis, valve thrombosis was present in 0.87% of the entire cohort and 8.5% of patients with haemodynamic SVD. Interestingly, it was observed in patients with moderate (mean transvalvular gradients ≥20 mmHg and <40 mmHg) and those with severe (mean transvalvular gradients ≥40 mmHg) haemodynamic SVD.

So far, the clinical relevance of bioprosthesis thrombosis has not been fully understood[18]. Data regarding subclinical leaflet thrombosis are mostly derived from routine CT scans after TAVI. Midterm follow-up suggested no impact on mortality or stroke rates in these patients[22]. However, thorough validation of elevated transvalvular gradients to predict (subclinical) leaflet thrombosis remains an important unmet need.

In contrast to the uncertainty regarding optimal pharmacotherapy after TAVI until ongoing randomised trials have bridged the gap of evidence, OAC seems effective in treating actual bioprosthesis thrombosis after TAVI[15,20,21]. In our cohort, all cases of valve thrombosis were on antiplatelet therapy at the time point of detection, and thrombosis resolved after initiation of OAC with either phenprocoumon or apixaban, with a reduction of mean transvalvular gradients to <20 mmHg. The duration of required OAC has yet to be established.

Trials comparing different valve designs will also provide further information on the potential role of valve design on transvalvular gradients. Presumably there will be predominance of elevated gradients in balloon-expandable valves, which is most likely due to their deployment in an intra-annular position introducing bias towards higher transvalvular gradients, when compared to self-expanding valves placed in a supra-annular position.

Future research should focus on dissecting the mechanisms of haemodynamic SVD, to enable differentiation of isolated elevated gradients, subclinical leaflet thrombosis and symptomatic valve thrombosis and their clinical impact.

Limitations

This is a single-centre observational study. Only patients with device success and available echocardiographic examinations during follow-up were included. Consequently, the major findings of the current analysis cannot be extrapolated to patients surviving in the absence of echocardiographic follow-up.

Conclusions

During the first 12 months after TAVI, 10.3% of the entire cohort had moderate or greater haemodynamic SVD and valve thrombosis was observed in 0.87% of all patients. Pharmacotherapy and procedural factors seem to play a key role during manifestation. Future histopathological and imaging studies should focus on dissecting the mechanisms of haemodynamic SVD, subclinical leaflet thrombosis and manifest transcatheter heart valve thrombosis, while prospective randomised trials are required to investigate the optimal pharmacotherapy after TAVI.

Impact on daily practice

So far, data regarding the prevalence and predictors of haemodynamic SVD remain scarce. This study provides evidence that 10.3% of all patients treated with latest-generation balloon-expandable valves developed moderate or greater haemodynamic SVD during the first 12 months after TAVI. Valve thrombosis was present in 0.87% of the entire cohort. Procedural factors and pharmacotherapy seem to play a key role during manifestation. After accounting for death as a competing event, oral anticoagulation and valve-in-valve procedures were significantly associated with haemodynamic SVD.

Conflict of interest statement

M. Joner received lecture fees and a research grant from Edwards Lifesciences and Boston Scientific. The other authors have no conflicts of interest relevant to this work to disclose.

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Supplementary data

Supplementary Table 1. Characteristics of patients with diagnosed valve thrombosis during follow-up after TAVI.

Moving image 1. Case of valve thrombosis after valve-in-valve TAVI, assessed using 4D-CT.

Moving image 2. Case of valve thrombosis after valve-in-valve TAVI, assessed using 4D-CT.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00710

Supplementary data

Supplementary Table 1. Characteristics of patients with diagnosed valve thrombosis during follow-up after TAVI (n=6).

No.	Age	Gender	Valve size	Time to valve thrombosis (days)	NYHA	Pharmacotherapy		Therapy of valve thrombosis*	Mean gradient at detection	Mean gradient after initiation of OAC	Resolution of valve thrombosis
						At discharge after TAVI	At detection				
1	73	male	29 mm	370	NYHA I-II	ASS+clopidogrel	ASS	Phenprocoumon	45 mmHg	10 mmHg	yes
2	77	female	23 mm	54	NYHA II-III	ASS+clopidogrel	ASS+clopidogrel	Phenprocoumon	29 mmHg	12 mmHg	yes
3	81	male	23 mm	74	NYHA II	ASS+clopidogrel	ASS+clopidogrel	Apixaban	27 mmHg	14 mmHg	yes
4	77	female	23 mm	48	Asymptomatic	ASS+clopidogrel	ASS+clopidogrel	Phenprocoumon	52 mmHg	15 mmHg	yes
5	80	male	29 mm	320	Asymptomatic	ASS+clopidogrel	ASS	Apixaban	24 mmHg	11 mmHg	yes
6	61	male	26 mm	40	NYHA I-II	ASS+clopidogrel	ASS+clopidogrel	Phenprocoumon	25 mmHg	15 mmHg	yes

* either apixaban 5 mg twice daily or phenprocoumon (INR target range 2.0-3.0).
ASS: aspirin; NYHA: New York Heart Association; OAC: oral anticoagulation