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ORIGINAL PAPER

Haemodynamic prosthetic valve performance in patients with early leaflet thrombosis after transcatheter aortic valve implantation

Manuel Hein[1] · Jan Minners[1] · Nikolaus Jander[1] · Philipp Breitbart[1] · Christian Stratz[1] · Gregor Pache[2] · Franz-Josef Neumann[1] · Philipp Ruile[1]

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Abstract

Aims We sought to evaluate haemodynamic prosthetic valve performance in patients with early leaflet thrombosis (LT) after transcatheter aortic valve implantation (TAVI).

Method and Results In this retrospective observational study, 59 patients with LT underwent clinical and echocardiographic follow-up. During a median follow-up of 383 days 41 patients received antiplatelet therapy (APT-group) and 18 patients oral anticoagulation due to atrial fibrillation (AC-group). The mean pressure gradient (MPG) at baseline did not differ between groups ($P=0.875$). During follow-up, MPG increased from 11.0 (9.0; 14.5) to 13.0 mmHg (10.0; 18.0)_ in the APT-group ($P=0.010$) but remained unchanged in the AC-group ($P=0.297$) resulting in a significantly higher MPG in patients on antiplatelet therapy ($P=0.024$). Similarly, change of MPG per year was significantly higher in the APT-group [1.4 (− 0.9; 7.0) vs. − 0.6 (− 2.5; 1.1), $P=0.014$]. Seven (17.1%) patients in the APT-group and two(11.1%) patients in the AC-group developed MPGs of at least 20 mmHg ($P=0.558$). Three patients (7.3%) in the APT- and none in the AC-group developed symptoms of obstructive thrombosis ($P=0.239$). In our adjusted analysis, only lack of anticoagulation was significantly associated with change in gradients during follow-up ($P=0.012$).

Conclusions In patients with LT, antiplatelet-, but not anticoagulant therapy, was associated with significant increases in MPG, which may lead to symptomatic obstructive valve thrombosis.

Keywords Transcatheter aortic valve implantation (TAVI) · Aortic stenosis · Leaflet thrombosis · Hypo-attenuated leaflet thickening · Echocardiography

Introduction

Asymptomatic early leaflet thrombosis (LT), as diagnosed on computed tomography angiography (CTA) after transcatheter aortic valve implantation (TAVI), was initially described in 2013 and has subsequently been confirmed in a number of reports [1–7]. Clinical outcomes are generally considered benign without increased rates of stroke or mortality [2, 4, 5, 8]. On the other hand, published data on haemodynamic prosthetic valve performance and the incidence of clinically relevant obstructive thrombosis in patients with LT are conflicting. While some studies showed no increase in mean pressure gradient over time, others report an influence of LT-extent on echocardiographic parameters [1–5, 8–10]. Recently, we demonstrated a significant negative correlation between thrombotic burden as assessed by serial CTA and oral anticoagulation therapy [3]. Previous studies on this topic are, however, limited by short-term follow-up periods and small numbers of patients included. We, therefore, set out to investigate the impact of LT on haemodynamic prosthetic valve performance and clinical outcomes in patients on antiplatelet therapy as compared with patients on oral anticoagulation. The current paper reports on a subpopulation from a previous publication [11]. To assess potential hemodynamic consequences of LT and to compare the course of LT depending on concomitant antithrombotic

✉ Manuel Hein
manuel.hein@universitaets-herzzentrum.de

[1] Department of Cardiology and Angiology II, University Heart Center Freiburg-Bad Krozingen, Suedring 15, 79189 Bad Krozingen, Germany

[2] Section of Cardiovascular Radiology, Department of Radiology, University of Freiburg, Hugstetter Straße 55, 79106 Freiburg im Breisgau, Germany

therapy, only LT patients with a FU of > 200 days were included in the current analysis.

Methods

Patients and valve types

In our institution, we perform routine post-TAVI CTA for clinical indication to assess the correct position, expansion and sizing of the THV and to exclude aortic injury. Our cohort comprised patients with LT diagnosed by routine post-TAVI-CTAs prior to discharge of the hospital stay for valve implantation and available FU data at least 200 days after the procedure. Leaflet thrombosis (LT) was defined as subclinical leaflet thrombosis without haemodynamic consequences according to the EAPCI consensus statement [12]. For the purpose of our study, LT had to be detectable in at least two different projections and two different time reconstruction intervals on CTA. Valve thrombosis at follow-up, on the other hand, was defined by an increase to a mean gradient of at least 20 mmHg or an increase of at least 10 mmHg irrespectively of clinical symptoms [12, 13].

Exclusion criteria were: death before follow-up data acquisition, refusing of participation in the study and intermittent oral anticoagulation. Implanted valve types were the following commercially available transcatheter heart valves (THV): SAPIEN XT, SAPIEN 3 (both Edwards Lifesciences, Irvine, California, USA), CoreValve, Evolut R (both Medtronic, Minneapolis, USA), Lotus valve (Boston Scientific, Natick, Massachusetts, USA), Portico valve (St. Jude Medical, Minneapolis, Minnesota, USA).

All baseline and FU data were obtained from our institutional database. This observational cohort study was approved by the local institutional review board and complies with the Declaration of Helsinki.

Study flow

During the time period from May 2012 to December 2016, 1112 patients were treated with TAVI, thereof 629 patients were examined with routine CTA. We identified 88 consecutive patients with LT [diagnosed by CTA after a median of 5 (IQR 4; 6) days post procedure] (Figs. 1, 2). 29 patients were excluded from our analysis due to various reasons (Fig. 1). Of those, 11 patients were excluded because of intermittent anticoagulation for 3–6 months because of initial thrombus finding due to initial clinical concerns of the treating physicians. Complete FU information with mean pressure gradient (MPG) and clinical data were available in 59 patients, including 41 on antiplatelet therapy (APT-group) and 18 on anticoagulation (AC-group). The anticoagulation group consisted of 10 patients on phenprocoumon and 8 patients on novel oral anticoagulants (Apixaban, Rivaroxaban, Dabigatran) in combination with clopidogrel for 6 months. In 2 cases patients did not receive additional Clopidogrel because of bleeding concerns.

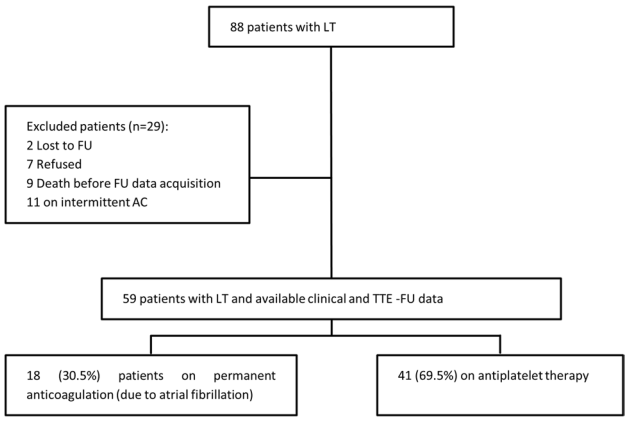

Fig. 1 Study profile. *TAVR* transcatheter aortic valve replacement, *CTA* computed tomography angiography, *FU* follow-up, *LT* Early asymptomatic leaflet thrombosis, *TTE* transthoracic echocardiography, *AC* anticoagulation

Echocardiographic assessment

Patients were either examined in our outpatient clinic, as inpatients or locally by experienced cardiologists. At the time of the examination, the examiner was blinded for the previous pressure gradients. The simplified Bernoulli formula was used to calculate the mean pressure gradient (MPG).

Haemodynamic valve obstruction was defined as an increase in MPG to an absolute value of at least 20 mmHg or at least 10 mmHg increase in mean gradient [12]. Prosthesis valve area was calculated using the continuity equation and indexed to body surface area calculated by the Mosteller formula (AVA_{index}). Paravalvular leakage (PVL) was classified as follows: 0 = none, 1 = trace, 2 = mild, 3 = moderate and 4 = severe PVL according to the recommendations of the Valve Academic Research Consortium (VARC) [13].

Antithrombotic therapy

At our institution, all patients were pre-loaded with either 400 mg effervescent acetylsalicylic acid or a combination of 400 mg effervescent acetylsalicylic acid and 600 mg clopidogrel. Peri-interventional heparin, in general, 5000 IU with adjustments for high or low body weight, was administered. After implantation, the patients received dual antiplatelet

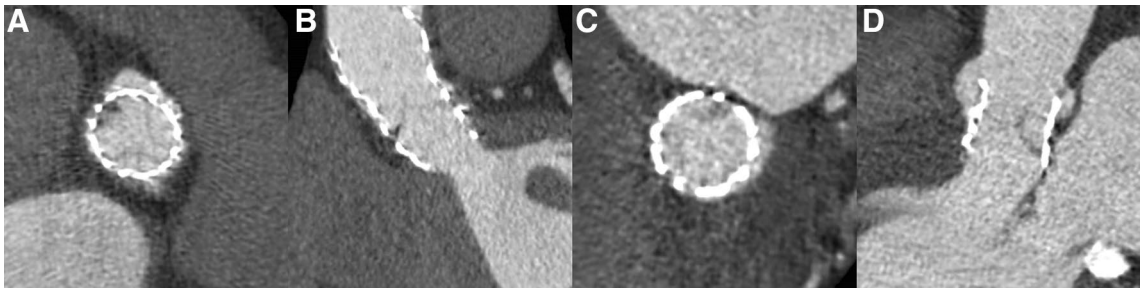

Fig. 2 CTA at baseline. Axial and oblique reconstructions showing leaflet thrombosis of an Evolut R prosthesis (**a, b**) and a SAPIEN 3 prosthesis (**c, d**)

therapy with acetylsalicylic acid (100 mg daily) and clopidogrel (75 mg daily) for 6 months, thereafter 100 mg acetylsalicylic acid daily. In case of established indication for oral anticoagulation, therapy consisted of a combination of clopidogrel (75 mg daily) and anticoagulation therapy for 6 months. The anticoagulation group consisted of 10 patients on phenprocoumon and 8 patients on different kinds of novel oral anticoagulants (Apixaban, Rivaroxaban, Dabigatran). All but two additionally received Clopidogrel 75 mg per day for 6 months. Two did not receive additional Clopidogrel because of bleeding concerns.

Statistical analysis

All statistical analyses were performed with SPSS-software (SPSS-version 23.0, Chicago, Illinois). Categorical data are reported as frequencies and percentages. Differences between groups for categorical variables were tested with the χ^2 test (or Fisher's exact test when expected cell sizes were <5). Kolmogorov–Smirnov-Test was used to test continuous variables for normal distribution. Non-normally distributed data are reported as median and interquartile range and were compared using Mann–Whitney *U* test. Normally distributed data are reported as mean and standard deviation and were compared using Student's *t* test. Wilcoxon test for paired samples was used to evaluate changes in mean pressure gradient of each group. The association of the difference in MPG between follow-up and baseline normalized to 1 year and patient or procedural characteristics was examined by univariate one-factor and multi-factorial ANOVA/ANCOVA. As independent variables, we entered all variables with a difference at baseline between the APT- and the AC-group at $P<0.1$.

Results

Patient characteristics

Patient characteristics of the whole study population and stratified to antithrombotic therapy (AC- and APT-group) are presented in Table 1. Patients on anticoagulation tended to be more often female ($P=0.059$) and had a lower BMI (24.9 ± 2.2 vs. 27.6 ± 3.7, $P=0.006$). The indication for anticoagulation was atrial fibrillation in all patients of the AC-group. Logistic Euroscore 1, as well as other clinical characteristics, did not differ significantly between groups. Among the procedural characteristics, there were no significant differences between groups (e.g. valve type, $P=0.326$; valve size, $P=0.217$). Patients were comparable with respect to calculated AVA_{index} and MPG at discharge ($P=0.780$ and 0.875, respectively; Table 1).

Valve performance during follow-up

The FU time of both groups was comparable with 368 (289; 520) days in the APT-group and 456 (342; 624) days in the AC-group, $P=0.292$. In our entire cohort, we found stable gradients [ΔMPG/Year 0.0 (− 1.2; 4.8) mmHg/year]. Stratifying our cohort to the antithrombotic regimen revealed significant differences in the course of MPG between the APT-group and the AC-group (Fig. 3). Patients on antiplatelet therapy exhibited a significant increase in MPG [11.0 (9.0; 14.5) mmHg at baseline to 13 (10.0; 18.0) at FU, $P=0.010$], whereas MPG of the AC-group did not change significantly [11.0 (9.0; 16.0) mmHg at baseline to 9.5 (8.0; 14.0) mmHg at follow-up, $P=0.297$, Fig. 3a]. The resulting change of MPG per year was 1.4 (− 0.9; 4.8) mmHg/year in the APT-group compared to − 0.6 (− 2.5; 1.1) mmHg in patients on anticoagulation (Fig. 3b). These changes in MPG/year were significantly different between both groups ($P=0.014$) and MPG at the time of FU was significantly higher in the APT-group compared to the AC-group $P=0.024$, Fig. 3a).

Table 1 Baseline characteristics

	All patients ($n=59$)	APT-group ($n=41$)	AC-group ($n=18$)	P value
FU (days)	383 (306; 569)	368 (289; 520)	456 (342; 624)	0.292
Age	83.6 ± 5.5	83.4 ± 5.50	84.2 ± 5.5	0.581
Female	32 (54.2)	19 (46.3)	13 (72.2)	0.059
BMI (kg/m^2)	26.8 ± 3.6	27.6 ± 3.7	24.9 ± 2.2	0.006
History of stroke	9 (15.2)	5 (12.1)	4 (22.2)	0.324
Diabetes	14 (23.7)	10 (24.4)	4 (22.2)	0.857
Hypertonus	58 (98.3)	40 (97.6)	18 (100.0)	0.504
History of smoking	14 (23.7)	7 (17.1)	7 (38.9)	0.070
Atrial fibrillation	18 (30.5)	0	18 (100.0%)	na
Coronary artery disease	45 (76.3)	32 (78.0)	13 (72.2)	0.628
History of myocardial infarction	6 (10.2)	5 (12.2)	1 (5.6)	0.437
Log Euroscore 1 (%)	14.1 ± 10.1	14.0 ± 10.9	14.5 ± 8.4	0.650
LV-EF (%)	48.3 ± 9.8	48.3 ± 8.9	48.2 ± 11.8	0.735
Previous heart surgery	7 (11.9)	6 (14.6)	1 (5.6)	0.307
Access route				
Transfemoral	58 (98.3)	40 (97.6)	18 (100)	0.504
Transapical	1 (1.7)	1 (2.4)	0 (0)	
Valve type				0.326
Ballon-expandable (Sapien 3/Sapien XT)	41 (79.7)	31 (82.9)	13 (72.2)	
Self-expandable (CoreValve/Evolut R)	7 (12.1)	5(12.1)	2 (11.1)	
Mixed group (Lotus, Portico)	5 (8.5)	2 (4.9)	3 (16.7)	
Prosthesis size				0.217
Small (23 mm)	14 (23.7)	8 (19.5)	6 (33.3)	
Medium (24–27 mm)	33 (55.9)	26 (63.4)	7 (38.9)	
Large (29–31 mm)	12 (20.3)	7 (17.1)	5 (27.8)	
AVA_{index} at discharge	0.90 ± 0.20	0.89 ± 0.19	0.92 ± 0.21	0.780
PPM				
Insignificant (> 0.85 cm^2/m^2)	37 (62.7)	25 (61.0)	12 (66.7)	0.737
Moderate (0.85–0.65 cm^2/m^2)	16 (27.1)	11 (26.8)	5 (27.8)	
Severe (< 0.65 cm^2/m^2)	6 (10.2)	5 (12.5)	1 (5.6)	
Postdilatation	5 (8.5)	4 (9.8)	1 (5.6)	0.594
PVL at time of CTA				0.940
None/trace	43 (73.2)	30 (72.2)	13 (72.2)	
Mild	16 (27.1)	11 (26.8)	5 (27.8)	
MPG after implantation (mmHg)	11.0 (9.0; 16.0)	11.0 (9.0; 14.5)	11.0 (8.8; 16.0)	0.875

P value for two-sided test

APT antiplatelet therapy, *AC* anticoagulation therapy, *FU* follow-up, BMI body mass index, *LV-EF* left ventricular ejection fraction, *PVL* paravalvular leakage, *MPG* mean pressure gradient, *AVA index* prosthetic valve area per body surface area, *CTA* computed tomography angiography, *PPM* patient-prosthesis mismatch

Values are mean ± SD, *n* (%) or median (interquartile range)

Table 2 illustrates the occurrence of haemodynamic valve obstruction with respect to antithrombotic therapy. Nine patients of the entire cohort (15.3%) showed mean pressure gradients of at least 20 mmHg at the time follow-up, two (11.1%) on anticoagulation and seven (17.1%) on APT ($P=0.558$). Four (9.8%) patients in the APT-group and no patient in the AC-group revealed an increase of at least 10 mmHg ($P=0.172$). Additional clinical information of those patients is given in Table 3.

Clinical follow-up

Three patients (7.3% of the ATP-group) developed dyspnoea during follow-up and were diagnosed with clinically

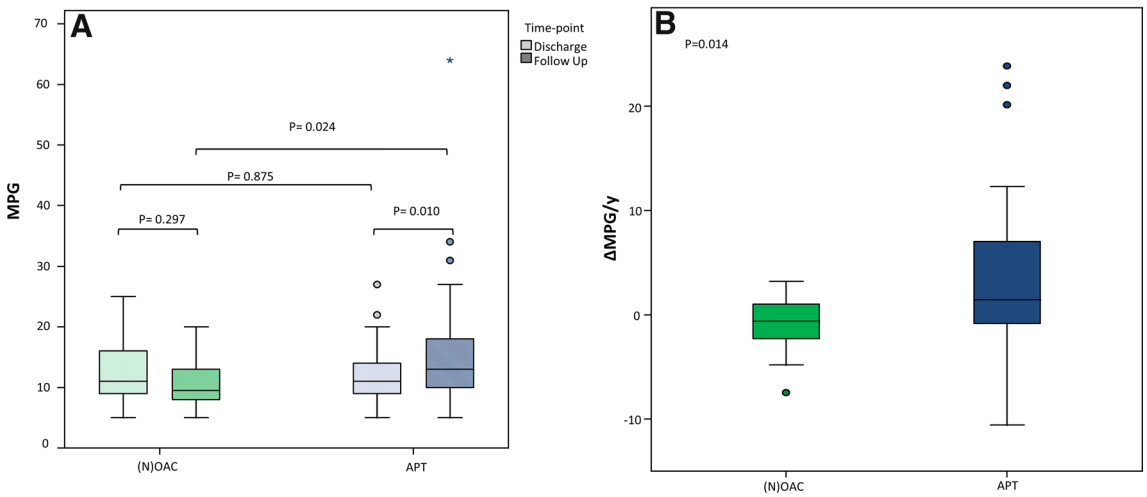

Fig. 3 Boxblots. Mean pressure gradient (MPG) in mmHg of both groups at baseline and follow up (**a**). Comparison of ΔMPG/year of both groups (**b**). Shown are medians with interquartile range

Table 2 Comparison of occurrence of haemodynamic valve obstruction with respect to antithrombotic therapy

	All patients, *n* (%)	AC-group, *n* (%)	APT-group, *n* (%)	*P* value
≥ 20 mmHg at FU	9 (15.3, [CI 6.8–25.4])	2 (11.1, [CI 0.0-25.7])	7 (17.1, [CI 5.7.0–28.6])	0.558
ΔMPG ≥ 10 mmHg	4 (6.8, [CI 1.7–13.6])	0	4 (9.8, [CI 0.7–18.8])	0.172
Symptoms	3 (5.1%, [CI 0.0–11.9])	0	3 (7.3, [CI 0.0–15.3])	0.239

ΔMPG delta mean pressure gradient from baseline to follow-up, *FU* follow-up

Table 3 Clinical characteristics of all patients with valve thrombosis at follow-up

	Valve type	Valve size	MPG baseline	MPG FU	ΔMPG	FU days	Symptoms	Therapy baseline	Therapy at FU
1	S3	23	19	20	1	257	None	Rivaroxaban15mg + Clopidogrel 6mo	Rivaroxaban 15 mg
2	S3	23	18	24	6	461	None	DAPT 6 mo	ASS 100 mg
3	S3	26	9	20	11	356	None	DAPT 6 mo	ASS 100 mg
4	S3	26	12	64	52	942	Dyspnoea	DAPT 6 mo	ASS 100 mg
5	S3	26	12	34	22	368	Dyspnoea	DAPT 6 mo	ASS 100 mg
6	Lotus	25	6	23	17	260	Dyspnoea	DAPT 6 mo	ASS 100 mg
7	Lotus	23	16	20	4	454	None	Phenprocoumon	Phenprocoumon
8	S3	23	27[a]	31	4	292	None	DAPT 6 mo	ASS 100 mg
9	S3	23	18	27	9	469	None	DAPT 6 mo	ASS 100 mg

MPG mean pressure gradient in mmHg, *mo* months, *FU* follow-up, *(N)OAC* (novel) oral anticoagulation therapy, *DAPT* = dual antiplatelet therapy

[a]No relevant leaflet restriction detectable at baseline in CTA

overt haemodynamic valve obstruction as defined by an increase in MPG of at least 20 mmHg and symptoms. Oral anticoagulation was initiated in two cases. The MPG of the first patient decreased from 64 to 42 mmHg after a short period of 4 weeks on phenprocoumon (a further FU examination was refused by the patient), the MPG of the second patient from 34 to 11 mmHg after 3 months on Rivaroxaban. Both patients stated to be free from symptoms on anticoagulation. A third patient in the ATP-group revealed an increase in MPG to 23 mmHg, but was

Table 4 AN(C)OVA Association between clinical factors and Δ mean pressure gradient/Year. AC = anticoagulation

	Unadjusted analysis		Adjusted analysis	
	Contrast estimate (mmHg)	*P* value	Contrast estimate (mmHg)	*P* value
Female sex		0.365		0.471
BMI		0.776		0.349
History of smoking		0.666		0.444
AC	− 4.373	0.016	− 6.377	0.013

subsequently diagnosed with prosthetic valve endocarditis and underwent surgery. None of the patients developed relevant valve regurgitation during follow-up. Regarding TIA, ischemic or haemorrhagic stroke, only one patient of the APT-group suffered an ischemic stroke.

Predictors of change in valve gradient

In the univariate analysis, lack of anticoagulation was significantly associated with ΔMPG/Year ($P = 0.016$, Table 4). After adjustment for BMI, history of smoking, and sex, lack of anticoagulation remained an independent predictor of an increase in ΔMPG/Year ($P = 0.013$).

Discussion

To the best of our knowledge, this is the largest study to date systematically investigating haemodynamic prosthetic valve performance in patients with LT after TAVI. The main findings of our study are: First, haemodynamic prosthetic valve performance is acceptable in the majority of patients with LT over a median follow-up of 383 (306; 569) days. Second, patients on antiplatelet therapy demonstrate a small but significant increase in mean pressure gradient not seen in patients on anticoagulation. Third, clinically relevant valve obstruction (obstructive thrombosis) was rare and developed in patients on antiplatelet therapy only.

Haemodynamic prosthetic valve performance

Prior studies reported a favourable long term haemodynamic performance of THV with either no significant change or minor increases in MPG with follow-up of up to 5 years [14–16]. However, data on haemodynamic valve performance in patients diagnosed with LT is inconsistent [1–4, 8, 17]. On the one hand, a number of reports demonstrate stable MPGs including the study by Sondergaard et al., who observed stable MPGs during a mean follow-up of 298 ± 141 days in 16 patients, even when signs of LT progression on CTA were present [5, 8–10]. On the other hand, Vollema et al. reported an increase in MPG after 6 months in their cohort of 16 patients with LT compared to the 112 patients without LT [10]. Our study covering a median follow-up of 383 (306; 569) days demonstrates a benign course in the majority of patients with LT, but also relevant increases in MPG in a few on APT.

Antiplatelet therapy versus anticoagulation

The data presented here suggest that the haemodynamic consequences of LT differ between patients on antiplatelet therapy compared to patients on anticoagulation. Whereas LT is associated with an increase in MPG in patients on standard antiplatelet therapy, no significant changes were observed on anticoagulation. These findings might correspond to progression of LT in patients with APT and less progression or resolution of LT on anticoagulation as demonstrated on serial CTA [3, 4, 8]. Supporting this notion, lack of anticoagulation has been associated with an increase in MPG in a large registry of patients undergoing TAVI, potentially caused by undiagnosed LTs [16]. Our data showed increasing gradients in LT patients on APT. However, we have no data on the point in time when gradients start to diverge from patients on anticoagulation therapy, as we did not perform sequential prospective examinations. Furthermore, it is unclear if anticoagulation for the first 6 months post TAVI is sufficient to avoid an increase in gradient beyond 6 months, as our anticoagulated group was on permanent therapy because of atrial fibrillation.

Obstructive thrombosis

The incidence of LT is reported in 4–40% of all TAVI patients, but clinically relevant valve obstruction is rare [1, 3–5, 8]. Similarly, in the present study 3 patients (7.3%) of the antiplatelet group (representing 5.1% of the overall cohort) developed symptomatic valve obstruction and 2 were treated with oral anticoagulants with subsequent regression of gradients, suggesting prosthetic valve thrombosis rather than structural valve deterioration as the underlying pathology. In line with others, we observed no relevant transvalvular aortic regurgitation, supporting the notion that LT is usually not associated with the development of clinically relevant THV regurgitation [1–4, 8, 17].

Limitations

Although the largest study so far on this topic, the number of patients in our study is still limited. Echocardiographic follow-up was performed by different examiners using

various ultrasound systems. This might hamper the precision of the results. An influence by differences in baseline- and procedural characteristics cannot be excluded due to the non-randomized nature of our study. Specifically, BMI was higher in the APT-group and atrial fibrillation was present in all anticoagulated patients. However, AN(C)OVA showed no influence of BMI on changes in MPG over time. Furthermore, patients on intermittent anticoagulation were excluded, as a meaningful comparison of this third, very small group, was not possible.

Conclusion

Patients with LT after TAVI on chronic anticoagulation demonstrate favourable medium-term haemodynamic prosthetic valve performance compared to patients on antiplatelet therapy. Clinically relevant obstructive thrombosis was diagnosed in patients on antiplatelet therapy only. Randomized trials are needed to assess the role of anticoagulation in patients with LT.

Compliance with ethical standards

Conflict of interest Dr. Pache: consultant for Edwards Lifesciences Inc. The other authors have no conflicts of interest to declare.

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