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CLINICAL RESEARCH

Could anticoagulation avoid bioprosthesis subclinical thrombosis in patients undergoing transcatheter aortic valve replacement?

Le traitement anticoagulant permettrait-il d'éviter la thrombose infra-clinique des bioprothèses aortiques implantées par voie percutanée ?

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KEYWORDS
Transcatheter aortic valve implantation;
Aortic stenosis;
Antithrombotic agents;
Thrombosis;
Bleeding

Summary
Background. — Despite a lack of clear evidence, current European guidelines recommend antiplatelet therapy after transcatheter aortic valve replacement (TAVR). Recent investigations suggest that bioprosthesis thrombosis after TAVR is not uncommon and may be prevented by anticoagulation, but not by antiplatelet therapy.
Aims. — The study objective was to assess the impact of the antithrombotic regimen on post-TAVR early haemodynamics.
Methods. — Patients eligible for TAVR with an Edwards SAPIEN 3 valve were included in this prospective observational study. Patients undergoing long-term anticoagulation before

Abbreviations: AF, atrial fibrillation; DAPT, dual antiplatelet therapy; LVEF, left ventricular ejection fraction; NOAC, non-vitamin K oral anticoagulant; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TAVR, trancatheter aortic valve replacement; VARC, Valve Academic Research Consortium; VKA, vitamin K antagonist.

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TAVR continued their treatment, whereas previously non-anticoagulated patients received antiplatelet therapy. The primary endpoint was the mean transaortic gradient assessed by transthoracic echocardiography at the first post-TAVR follow-up. Safety was assessed by two composite endpoints: bleeding/vascular complications and major adverse postoperative events.
Results. — Among 135 included patients, 78 were discharged on antiplatelet therapy and 57 on anticoagulation. Both groups had similar baseline characteristics, except for supraventricular arrhythmia (7.7% on antiplatelets vs. 89.5% on anticoagulation; $P < 0.001$). At 1—2 months after TAVR, the mean transaortic gradient was significantly higher in the antiplatelet therapy group versus the anticoagulation group (13.0 ± 4.0 vs. 9.0 ± 2.8 mmHg; $P < 0.001$, independently of prosthesis size). Safety analyses showed no significant differences of the composite endpoints.
Conclusion. — Prolonged anticoagulation after TAVR was associated with lower early transaortic gradients than antiplatelet therapy. Anticoagulation treatment may limit clinical and subclinical thrombosis without increasing early postoperative complications.

MOTS CLÉS
TAVI ;
Rétrécissement aortique ;
Traitements antithrombotiques ;
Thrombose ;
Saignement

Résumé
Contexte. — Malgré le manque de preuves, un traitement antiagrégant plaquettaire est actuellement recommandé après remplacement valvulaire aortique percutané (TAVI). Plusieurs publications suggèrent une incidence élevée de thromboses de prothèses TAVI, qui pourraient régresser sous anticoagulation.
Objectifs. — Étudier l'impact du traitement antithrombotique sur l'évolution de l'hémodynamique valvulaire.
Méthodes. — Les patients recevant un TAVI par prothèse Edwards SAPIEN 3 étaient inclus prospectivement dans cette étude monocentrique observationnelle. Ceux recevant une anticoagulation au long cours avant le TAVI poursuivaient leur traitement, alors que les patients non anticoagulés recevaient une bi-anti-agrégation plaquettaire à la sortie de l'hôpital. Le critère de jugement principal était le gradient transaortique moyen déterminé par échocardiographie transthoracique au trentième jour postopératoire. La sécurité de chaque thérapie était évaluée par deux critères composites : complications hémorragiques ; évènements postopératoires majeurs.
Résultats. — Parmi les 135 patients inclus, 78 recevaient une anti-agrégation plaquettaire et 57 une anticoagulation. Les groupes étaient similaires en termes de caractéristiques préopératoires hormis l'antécédent d'arythmie supraventriculaire. Au trentième jour, le gradient transaortique moyen avait significativement augmenté chez les patients sous antiagrégants alors qu'il restait stable chez les patients anticoagulés (13 ± 4 vs 9 ± 3 mmHg ; $p < 0{,}001$, indépendamment de la taille de la prothèse). Les analyses de sécurité ne montraient pas de différence sur les critères composites.
Conclusions. — Dans les suites d'une intervention de TAVI, les gradients transvalvulaires étaient moins élevés chez les patients sous anticoagulants que chez ceux sous antiagrégants plaquettaires. L'anticoagulation pourrait limiter la survenue de thromboses, cliniques ou infracliniques, sans augmenter les complications postopératoires précoces.

Background

Transcatheter aortic valve replacement (TAVR) is growing in popularity worldwide as an efficient and safe procedure for the treatment of severe aortic valve stenosis. European guidelines [1] support its use in severe symptomatic patients who are considered unsuitable for surgery. However, postoperative severe bleeding has been described as a major determinant of mortality in TAVR patients [2], and cerebrovascular thrombotic events were more frequent than with standard therapy in a randomized study [3]. The rationale for antiplatelet therapy after the procedure was initially due to a balance between cerebrovascular ischaemic event prevention and bleeding avoidance. However, after almost 10 years of practice and more than 300,000 procedures worldwide, no clear data are available on the ideal antithrombotic regimen after TAVR. Several studies have investigated the role of antiplatelet therapy,

as reviewed by Aryal et al. [4], without confirming a clear benefit. Despite the lack of evidence, American guidelines recommend dual antiplatelet therapy (DAPT) for the first 3—6 months after the procedure in antithrombotic-naïve patients, followed by aspirin or a thienopyridine alone [5]. In patients already receiving anticoagulation, treatment should be prolonged either alone or with additional low-dose aspirin [6].

A recent review on antiplatelet administration following TAVR did not demonstrate any significant difference between single antiplatelet therapy and DAPT regarding adverse clinical and cerebral events at 1 month [7]. However, this review suggested a potential benefit of single antiplatelet therapy because of a trend towards less life-threatening and major bleeds. In parallel, a case report has described bioprosthesis thrombosis after TAVR despite antiplatelet treatment [8], and a recent study demonstrated possible subclinical leaflet thrombosis in bioprosthetic aortic valves that could be prevented by anticoagulation but not by antiplatelet therapy [9]. These findings are supported by several subsequent studies, as discussed by Stewart [10]. Along with the lack of benefit associated with antiplatelet therapy, these findings suggest that an antithrombotic regimen based on anticoagulation rather than antiplatelet therapy might be a better strategy in TAVR patients.

The objective of this study was to assess the impact of the antithrombotic regimen (anticoagulation versus antiplatelet therapy) on valvular haemodynamics assessed at the first follow-up echocardiography after TAVR.

Methods

Study design and patient population

Eligible patients were those scheduled to undergo transfemoral TAVR using the balloon-expandable Edwards SAPIEN 3 valve (Edwards Lifesciences Inc., Irvine, California) at the University Hospital of Nantes, France. All consecutive eligible patients identified between September 2014 and October 2015 were prospectively included in the study. Data were collected in our local database and exported to the FRANCE-TAVI Register (run by the French Society of Cardiology). All patients gave consent for the use of their data.

Inclusion criteria were:

- severe aortic stenosis as defined by European guideline criteria [1];
- severe symptoms (New York Heart Association [NYHA] class II or higher);
- functional improvement expected after TAVR.

Exclusion criteria were:

- anatomic reason making it impossible to perform TAVR;
- life expectancy < 12 months due to comorbid conditions;
- patient refusal to undergo the procedure;
- indication for a valve-in-valve or CoreValve (Medtronic, Minneapolis, Minnesota) procedure.

In previously anticoagulated patients, vitamin K antagonist (VKA) or non-vitamin K oral anticoagulant (NOAC) treatment was suspended 2 days before TAVR to obtain an international normalized ratio < 2 at the beginning of the procedure. Treatment was reintroduced a few hours after the procedure, with a bridge of intravenous unfractionated heparin (monitored anti-Xa activity [0.2—0.3 IU/mL]) until target international normalized ratio achievement. No antiplatelet treatment was added at hospital discharge to limit haemorrhagic risk. Non-anticoagulated patients received lifelong aspirin and a P2Y12 inhibitor (mostly clopidogrel, or ticagrelor when the patient was previously following this treatment) for at least 1 month. Single antiplatelet therapy was prescribed in patients at very high bleeding risk or with a previous haemorrhagic complication.

Endpoints

The primary clinical endpoint was the mean transaortic gradient estimated by transthoracic echocardiography at the first follow-up echocardiography. Secondary endpoints were: major vascular complications and major/life-threatening bleeding, analysed as composite and separate endpoints; and major adverse postoperative events (stroke or myocardial infarction, early rehospitalization for heart failure, pacemaker requirement, tamponade, and stage 2 or 3 acute kidney injury), analysed as composite and separate endpoints. All major adverse events were defined according to Valve Academic Research Consortium (VARC)-2 criteria [11].

Procedure and techniques

The results of an exhaustive preoperative appraisal were discussed by the Heart Team (including an interventional cardiologist, a non-interventional cardiologist, a cardiac surgeon, an anaesthesiologist and a geriatrician) and all patients underwent the percutaneous procedure according to European guidelines [1]. Transfemoral procedures were undertaken as previously described [12]. Implantation of the SAPIEN 3 valve was preceded by balloon dilatation of the native aortic valve, but no post-dilatation was undertaken. A single dose of heparin (0.5 mg/kg) was injected into all patients immediately after positioning the major transarterial access without activated clotting time control.

All patients underwent echocardiography before the procedure and before hospital discharge. Follow-up echography was planned 1 month after TAVR, but could be completed up to 8 weeks after the procedure. Standard echocardiographic data were collected by two independent observers who were blinded to treatment.

Statistical analysis

The sample size was derived from the results of a previous series of 95 patients implanted with the SAPIEN 3 valve in our centre. Continuous variables are reported as means ± standard deviations and compared using the Student's *t*-test. We used the Chi^2 test or Fisher's exact test to compare categorical variables. A two-sided *P*-value of < 0.05 was considered to indicate statistical significance. The impact of prosthesis size on mean transaortic gradient was investigated in multivariable analysis. Statistical analyses were performed with the Statistical Package for Social Science 20.0® software (IBM Corp., Armonk, New York).

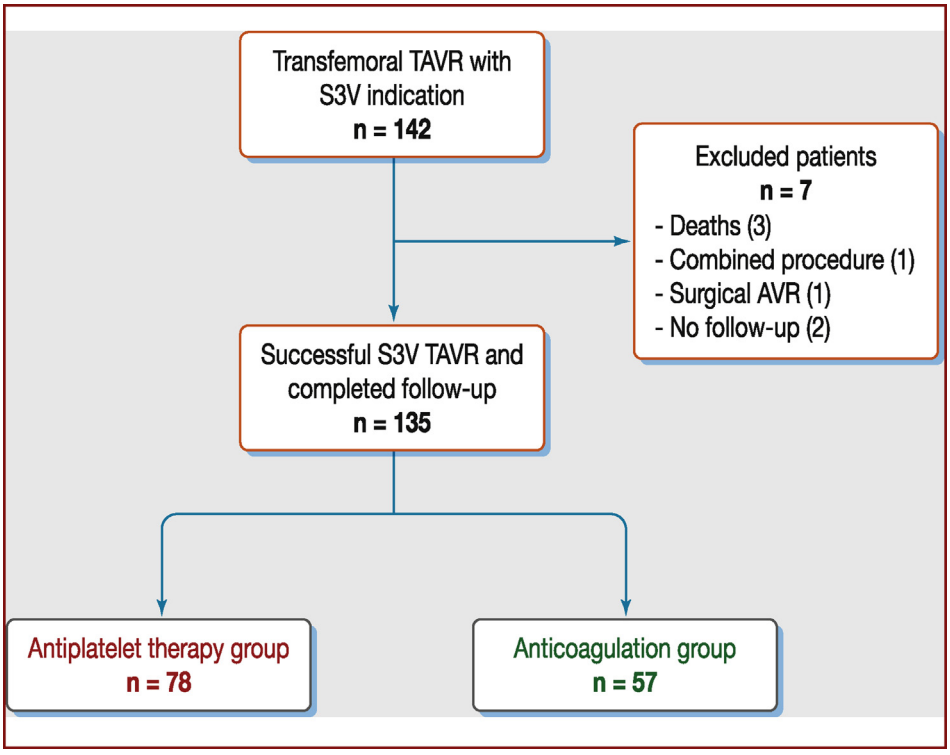

Figure 1. Study flow chart.

Results

Study population

Between September 2014 and October 2015, 142 patients were recommended to undergo transfemoral TAVR with the SAPIEN 3 valve by the Heart Team (Fig. 1). Seven patients were not included in the analysis: three died within 30 days of TAVR (one annulus rupture during TAVR and two non-cardiac deaths after hospital discharge), one underwent a procedure that combined TAVR and mitral valve repair with MitraClip (Abbott Medical, Santa Clara, California), one required surgical aortic valve replacement for annulus rupture during TAVR, and two did not complete follow-up (one due to cirrhotic complications and one refusal). Overall, 135 patients were included in the analysis: 78 patients received antiplatelet therapy and 57 patients who were already taking anticoagulants for different underlying conditions continued their treatment after the procedure (54 on VKAs and three on NOACs). The indication for previous anticoagulation was supraventricular arrhythmia in 54 patients; two patients presented repeated venous thromboembolic events and one had a mitral mechanical prosthesis. In the antiplatelet therapy group, 12 patients received single antiplatelet therapy (because of very high bleeding risk or previous haemorrhagic complication) and 66 received DAPT.

Preoperative characteristics

Preoperative characteristics were largely similar in both groups (Table 1). Statistical analysis showed no significant differences regarding demographic data, clinical status, cardiovascular risk factors and non-cardiac comorbidities. Data from the preoperative check-up were also similar regarding coexistence of significant coronary artery disease, indication for percutaneous coronary intervention (PCI), operative risk scores, preoperative echocardiography, and urgency of the procedure. The only significant difference between the groups was observed for supraventricular arrhythmias, which were more frequent in the anticoagulation group (89.5% vs. 7.7%; $P < 0.001$).

Primary clinical endpoint

Echocardiographic data at first follow-up were available for all included patients and no discontinuation of antithrombotic treatment was observed. The mean transaortic gradient at first follow-up was significantly lower in the anticoagulation group than in the antiplatelet group (9.0 ± 2.8 vs. 13.0 ± 4.0 mmHg; $P < 0.001$; Fig. 2). For patients receiving antiplatelet therapy, there was no significant difference in mean transaortic gradient according to receipt of single antiplatelet therapy or DAPT (13.6 ± 5.2 vs. 12.9 ± 3.8 mmHg, respectively; $P = 0.83$).

Mean transaortic gradient was negatively correlated with the size of the prosthesis, leading to significantly higher gradients with the 23-mm prosthesis ($P < 0.001$; Fig. 3). Multivariable analysis confirmed the absence of a significant interaction between prosthesis size and antithrombotic regimen ($P = 0.31$). After adjustment for prosthesis size, mean transaortic gradient was still significantly lower in the anticoagulation group than in the antiplatelet group ($P < 0.001$).

No thrombosis was detected during subsequent follow-up in anticoagulated patients, but three cases were reported among patients on DAPT (one for each prosthesis size) 4—7 months after the procedure. In these patients, mean

Table 1 Preoperative characteristics.

	Antiplatelet therapy group ($n=78$)	Anticoagulation group ($n=57$)	P
Age (years)	81.6 ± 7.5	83.0 ± 5.6	0.22
Men	39 (50.0)	32 (56.1)	0.48
Clinical history			
NYHA class			0.28
I or II	42 (53.8)	36 (63.2)	
III or IV	36 (46.2)	21 (36.8)	
Angina CCS ≥ 2	16 (2.05)	8 (14.0)	0.33
Body mass index (kg/m^2)	26.9 ± 4.5	27.3 ± 4.3	0.63
Previous CABG	3 (3.8)	6 (10.5)	0.17
Previous cardiac surgery	2 (2.6)	1 (1.8)	0.62
Previous PCI	10 (12.8)	13 (22.8)	0.13
Peripheral vascular disease	20 (25.6)	12 (21.1)	0.54
Chronic pulmonary disease	19 (24.4)	16 (28.1)	0.63
Permanent pacemaker	5 (6.4)	8 (14.0)	0.14
Creatinine clearance (mL/min)	62.6 ± 22.2	65.3 ± 32.6	0.58
Supraventricular arrhythmia	6 (7.7)	51 (89.5)	< 0.001
EuroSCORE II (%)	4.4 ± 2.8	4.7 ± 5.6	0.68
Coronary stenosis ≥ 50%	37 (47.4)	21 (36.8)	0.22
PCI before TAVR	12 (15.4)	4 (7.0)	0.14
Preoperative echocardiography			
LVEF (%)	55.6 ± 13.5	55.2 ± 12.4	0.85
Mean aortic gradient (mmHg)	53.4 ± 22.1	48.8 ± 18.7	0.20
Aortic valve area (cm^2)	0.66 ± 0.15	0.67 ± 0.15	0.61
Severe aortic regurgitation	1 (1.3)	0	0.58
Severe mitral regurgitation	3 (3.8)	1 (1.8)	0.64
Operation status			0.34
Elective	66 (84.6)	51 (89.5)	
Urgent	11 (14.1)	4 (7.0)	
Emergency	1 (1.3)	2 (3.5)	

Data are expressed as mean ± standard deviation or number (%). CABG: coronary artery bypass grafting; CCS: Canadian Cardiovascular Society; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; TAVR: transcatheter aortic valve replacement.

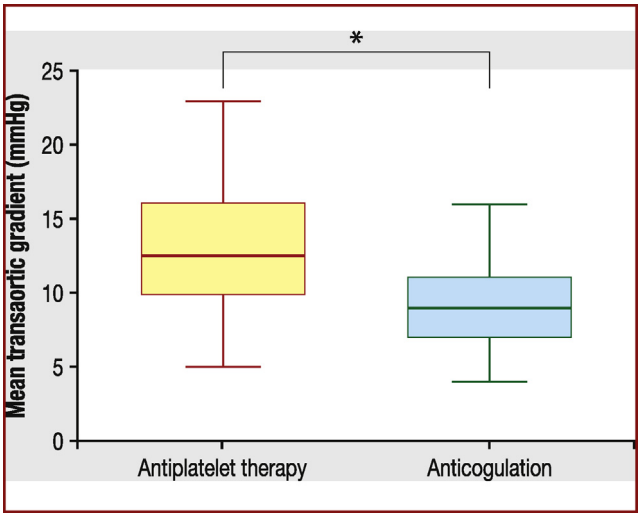

Figure 2. Primary clinical endpoint: mean transaortic gradient for each treatment group. *$P < 0.001$.

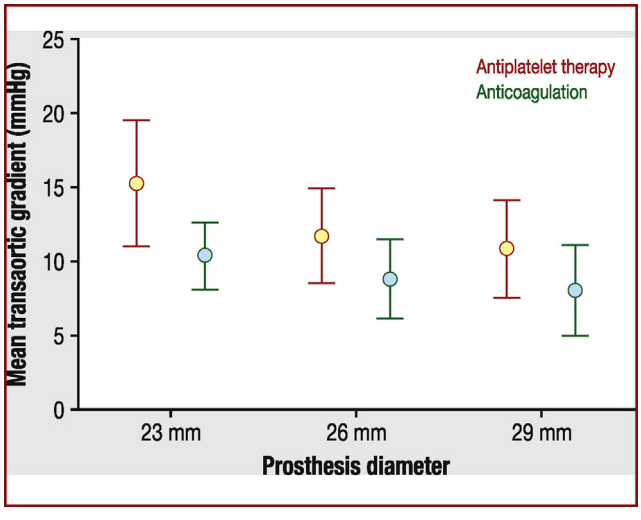

Figure 3. Subgroup analysis: impact of prosthesis diameter on mean transaortic gradient for each treatment group (antiplatelet therapy and anticoagulation).

transaortic gradients were quite elevated (but not pathological) at hospital discharge (14.8 mmHg) and at first follow-up (18.2 mmHg). Thrombosis was suspected on further echocardiography, and was confirmed in two patients by transoesophageal echocardiography and computed tomography scanning. The three cases were clinically relevant, with high levels of dyspnoea (NYHA II or III). The gradients returned to normal after anticoagulation in all three patients.

Secondary clinical endpoints

The safety analysis did not demonstrate any significant difference between the antiplatelet and anticoagulation groups in terms of haemorrhagic complications (12.8% vs. 7.0%; $P = 0.28$) or major adverse postoperative events (26.9% vs. 33.3%; $P = 0.28$) (Table 2).

Echocardiographic data at first follow-up were similar in both groups apart from a significantly lower transaortic peak velocity in anticoagulated patients (2.0 ± 0.4 vs. 2.3 ± 0.4 m/s; $P < 0.001$; Table 2). In the antiplatelet group, small but significant increases were observed between hospital discharge and first follow-up echocardiography in mean transaortic gradient (11.2 ± 4.5 and 13.0 ± 4.0 mmHg, respectively; $P = 0.01$) and transaortic peak velocity (2.1 ± 0.5 and 2.3 ± 0.4 m/s, respectively; $P = 0.006$). No such increases were observed in anticoagulated patients, who had stable mean transaortic gradient (9.8 ± 3.4 and 9.0 ± 2.8 mmHg, respectively; $P = 0.17$) and peak velocity (2.0 ± 0.4 and 2.0 ± 0.4 m/s, respectively; $P = 0.87$).

Perioperative data — success of the intervention, use of local anaesthesia (almost 90%), duration of the procedure, radiation dose and duration of hospital stay — were similar in both groups.

Discussion

To the best of our knowledge, this is the first study to focus on the assessment of transaortic gradient post-TAVR to evaluate the impact of the antithrombotic regimen on valvular haemodynamics. At first echocardiographic follow-up, performed 1—2 months after TAVR, the mean transaortic gradient had increased significantly in the antiplatelet therapy group while it remained stable in the anticoagulation group, suggesting that anticoagulation may limit clinical and subclinical early thrombosis.

Our population's preoperative clinical and echocardiographic characteristics were very similar to those reported in another study [13] and registry [14]. Included patients were carefully selected according to European guidelines [1] to derive maximum benefit from TAVR, and no deaths from cardiac causes were reported in the first weeks after the procedure.

The balloon-expandable SAPIEN 3 valve is the latest generation of transcatheter aortic valves. An observational study reported a reduction in moderate-to-severe aortic regurgitations and major vascular complications compared with previous generations of bioprostheses [15]. The safety of the SAPIEN 3 valve was confirmed in our study population: the procedural success was high (133/135 [98.5%]), we observed few moderate aortic regurgitations (4/135 [3.0%]) and no severe aortic regurgitations, and there was a low incidence of postoperative major complications (29.6%).

Table 2 Clinical endpoints at first follow-up (1—2 months after TAVR).

	Antiplatelet therapy group ($n = 78$)	Anticoagulation group ($n = 57$)	P
Bleeding/vascular complications (composite endpoint)	10 (12.8)	4 (7.0)	0.28
Major bleeding	7 (9.0)	4 (7.0)	0.76
Major vascular complications	5 (6.4)	4 (7.0)	0.58
Major adverse postoperative events (composite endpoint)	21 (26.9)	19 (33.3)	0.42
Stroke or myocardial infarction	2 (2.6)	0	0.51
Early rehospitalization for heart failure	2 (2.6)	0	0.51
Pacemaker requirement	14 (17.9)	14 (24.6)	0.39
Tamponade	1 (1.3)	1 (1.8)	0.67
Stage 2 or 3 acute kidney injury	5 (6.4)	6 (10.5)	0.53
Echocardiographic results			
LVEF (%)	57.6 ± 9.4	56.5 ± 10.8	0.52
Aortic valve area (cm^2)	1.7 ± 0.4	1.8 ± 0.4	0.24
Transaortic peak velocity (m/s)	2.3 ± 0.4	2.0 ± 0.4	< 0.001
Moderate-to-severe aortic regurgitation	1 (1.3)	3 (5.3)	0.31
Severe mitral regurgitation	1 (1.3)	0	0.58

Data are expressed as mean ± standard deviation or number (%). LVEF: left ventricular ejection fraction; TAVR: transcatheter aortic valve replacement.

Most studies that have investigated the role of the antithrombotic regimen following TAVR have focused on antiplatelet therapy, and no comparison has been made with anticoagulation. Bioprosthetic thrombosis used to be considered a rare event following TAVR, with an incidence estimated at 1% per year [11]. Only recently has a potential role for thrombosis been suggested in early prosthetic failure [16] and new evidence indicates that this phenomenon may be underestimated [10] or subclinical [9]. The diagnosis of our three cases of thrombosis, in patients on DAPT, seems to strengthen this hypothesis. Contrary to Pache et al. [17], who did not observe any association between antithrombotic regimen and hypo-attenuated leaflet thickening, we demonstrated — using reproducible echocardiographic criteria — a significant relationship between lower transaortic gradient and anticoagulation treatment. Our hypothesis is that an early and partial thrombosis of the bioprosthesis may be preventable by anticoagulation, but not by antiplatelet therapy.

The use of an antithrombotic regimen after aortic valve replacement with a bioprosthesis has been more thoroughly documented for surgical than for transcatheter procedures, and extrapolation may be possible. An antithrombotic regimen used to be indicated for at least 3 months after surgical replacement with an aortic bioprosthesis [18], as it was shown that most thromboembolic events happened during this period [19]. However, a lack of supportive evidence [20] led the latest European guidelines [1] to recommend a single antiplatelet regimen — aspirin, whereas the American guidelines still recommended a VKA for 3—6 months after surgery [5]. A recent study [21] has shown potential benefits for prolonged anticoagulation, with lower mortality rates being reported in long-term anticoagulated patients. However, these controversial results cannot be extrapolated to high-risk TAVR patients.

The rationale for antiplatelet therapy after TAVR is based on the prevention of cerebrovascular events, while limiting perioperative and late bleedings, which have been recognized as major risk factors for mortality [22]. However, the ischaemic benefit of aspirin is often offset by an increase in bleeding events, which has been observed in patients with atrial fibrillation (AF) [23] as well as in subjects without cardiovascular disease [24]. In AF patients, the addition of clopidogrel to aspirin was not considered suitable because of an increased risk of major haemorrhage, despite a reduction in major vascular events, especially stroke [25]. In our study, we did not observe any significant difference in serious early haemorrhagic complications between patients receiving anticoagulation or antiplatelet treatment, but the study had limited power to detect such difference. Haemorrhagic complications were non-significantly more frequently observed in the antiplatelet therapy group, and none occurred in patients previously denied anticoagulation because of a history of serious bleeding. The results obtained with this cohort, in line with findings from recent studies [26,27], suggest an underestimated potential for anticoagulation following TAVR, although long-term bleeding (not evaluated in this study) remains an important concern. In 'real-world' observational studies, AF patients treated with anticoagulants have similar rates of major haemorrhagic complications as patients receiving antiplatelet therapy or no antithrombotic therapy, but they have lower rates of ischaemic stroke [28]. The net benefit associated with anticoagulation is consistently observed [29], an interesting point supporting its use in aged TAVR patients.

Our study has several limitations. Although it is a single-centre study, this limitation is compensated by a high patient volume and the use of standard patient recruitment. We chose an observational design to compare patients under long-term anticoagulation and patients receiving antiplatelet therapy because of the absence of guidelines supporting the safety of anticoagulation after TAVR. Randomized and long-term studies will be necessary to confirm the safety of anticoagulation after TAVR. If our findings are confirmed, patients with a high risk of bleeding and borderline operative risk scores may be seriously considered for conventional surgery, as patients implanted with bioprostheses surgically are no longer recommended to receive anticoagulation.

Conclusions

This study is the first to demonstrate significantly lower transaortic gradients 1—2 months after TAVR in patients receiving anticoagulation versus antiplatelet therapy, with no significant difference in major haemorrhagic or life-threatening complications. These findings were maintained regardless of prosthesis size, and heighten the current scientific and medical concern about the ideal antithrombotic regimen after TAVR. Further clinical studies are required to confirm our observational data in order to define the best treatment strategy in our patients.

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None.

Disclosure of interest

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