Case Report

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Lessons to Learn from Two Cases of TVAR Thrombosis: A Case Series and Literature Overview

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Abstract

We report two consecutive cases in a month of transcatheter aortic valve thrombosis, one involving the new Sapien 3 Ultra valve (Edwards Lifesciences, Irvine, CA) treated surgically. These cases highlight the importance of standardization of periprocedural and post procedural anticoagulation protocols to avoid this serious complication.

Keywords: Anticoagulation; Antiplatelet therapy; Edwards Sapien 3 Ultra; TAVR thrombosis

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Abbreviations

ACT: Activating Clotting Time

DAPT: Dual Antiplatelet Therapy

MG: Mean Gradient

NOAC: Non-Vitamin K Oral Anticoagulants

PVL: Paravalvular Leak

SAPT: Single Antiplatelet Therapy

TAVR: Transcatheter Aortic Valve Implantation

THV: Transcatheter Heart Valve

TTE: Transthoracic Echocardiography

VKA: Vitamin K Antagonists

Introduction

The 2-year results of PARTNER 3 demonstrated an increased risk (2.6%) of valve thrombosis in low surgical risk patients who underwent TAVR [1]. Moreover, subclinical thromboses were as high as 13% at 30-day in the TAVR arm of the computed tomography substudy [2]. These data shed light on an unmet need of optimal periprocedural and post procedural anticoagulation regimen in the growing TAVR population.

In this case series, we report two consecutive cases of early thrombosis of THV, one involving the new Sapien 3 Ultra valve (Edwards Lifesciences, Irvine, CA).

Case 1

A 78-year-old man was referred for symptomatic severe aortic stenosis. TTE and baseline and procedural characteristics are summarized in (Table 1). He underwent elective transfemoral implantation of a 26-mm Sapien 3 Ultra valve (Edwards Lifesciences, Irvine, CA). Antiplatelet treatment with aspirin was continued peri-procedurally without any interruption. Immediate hemodynamics were favorable with trace paravalvular leak and a MG of 5 mmHg. After a pacemaker implantation for a complete atrioventricular block, a pre-discharge TTE performed on day 7 revealed an asymptomatic increase in aortic valve MG to 54 mmHg. Computed tomography imaging showed a restricted leaflet opening and a 1.5 x 1.1cm mass suspicious for thrombus (Figure 1). A surgical treatment was decided after initiation of intravenous anticoagulation therapy. Aortic valve replacement was successfully performed at day 8 with TAVR explant and implantation of a 23-mm InspirisResilia valve (Edwards Lifesciences, Irvine, CA). Post-operative period was uneventful, and patient was asymptomatic at one-month follow up.

	Case #1	Case #2
Baseline		
Age, Sex	78 years, Male	78 years, Female
EuroScore II / STS (%)	4.2 / 4.88	7 / 3.6
Comorbidities	Diabetes, hyperlipidemia, hypertension	Hypertension, peripheral vasculopathy
Risks factors for thrombosis	Unknown	Unknown
Pre doppler mean gradient / EF	65 mm Hg / 70 %	36 mm Hg / 55 %
Annular valve area / perimeter	440 mm² / 75 mm	441 mm2 / 76 mm
Periprocedural data		
Sapien valve	26-mm S3 Ultra	26 mm S3
Pre doppler mean gradient	65 mm Hg	36 mm Hg
Pre-TAVR antithrombotic regimen	Aspirin 80 mg/day	Aspirin 325 mg
Procedural ACT (pre / deployment/ final)	No P2Y12-inhibitor	+ clopidogrel 300 mg
IV Heparin	147 / 234 / 208 s	147 / 234 / 241 s
Protamine administration	6000 IU (90 IU/kg)	9000 IU (80 IU/kg)
Procedure time	No	No
Peri-procedural complications	38 min	48 min
Post-TAVR antithrombotic regimen	Permanent pacemaker implantation, pneumonia	Permanent pacemaker implantation
	Aspirin 80 mg/day	Aspirin 80 mg/day

Thrombosis presentation		
Symptoms	No (in hospital)	Left-sided HF (NYHA 4/4)
Time since implantation	7 days	21 days
Doppler mean gradient	54 mmHg	62 mmHg
MDCT attenuated mass	Yes	No
Thrombosis management and early outcome		
IV heparin / duration	Yes / 1 day	Yes / 1 week
MG decreased under heparin?	No	No
Surgery	Yes (23-mm Inspiris)	Yes (23-mm Inspiris)
Recommended treatment	Aspirin + VKA (3 months)	Aspirin + VKA (3 months)
One month follow-up	Asymptomatic	Asymptomatic

Table 1: Patient characteristics, procedural data and thrombosis management.

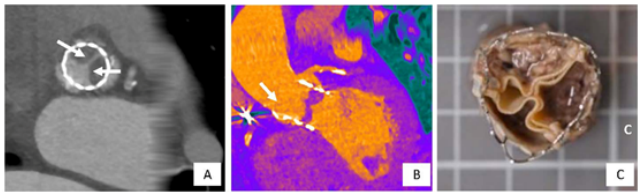

Figure 1: Computed tomography imaging and macroscopic appareances of Edwards Sapien Ultra thrombosed leaflets: Panel A: Multidetector computed tomography in transversal axis shows hypoattenuated mass near the stent frame (arrows) that extend to the cusp with decreased leaflet movement, confirmed in long axis by Panel B. Panel C: Explanted transcatheter heart valve demonstrating thrombosis.

Case 2

An intermediate risk (STS Score: 3.6%) 78 years old female underwent a transfemoral TAVR with an Edwards S3 26 mm (Edwards Lifesciences, Irvine, CA) with good immediate hemodynamic results (MG of 4 mmHg and mild PVL) followed by a pacemaker implantation due to a left bundle branch block. TTE and baseline procedural characteristics are summarized in (Table 1). Antiplatelet treatment with aspirin was continued peri-procedurally without any interruption. Three weeks later, she was re-hospitalized for acute left heart failure secondary to a severe THV thrombosis (MG: 62 mmHg), treated surgically with THV explantation and an aortic valve replacement with Inspiris 23mm (Edwards Life sciences, Irvine, CA) bioprosthesisvalve (Figure 2). Patient was discharged day 7 and was asymptomatic at one-month follow-up with no PVL and a MG of 4 mmHg on TTE.

Discussion

To our best knowledge, this is the first reported case of SAPIEN 3 Ultra thrombosis. The SAPIEN 3 Ultra is the latest iteration of balloon-expandable valve by Edwards Life sciences (Irvine, CA, USA) with an improved sealing skirt and a modified delivery system.

Clinical thrombosis is defined as a combination of the THV dysfunction (increased MG $\geq$ 20 mmHg or at least moderate regurgitation) and an imaging evidence of leaflet thrombosis. Common presentation includes isolated elevated gradients, dyspnea and thromboembolic events [3]. Many factors such obesity, reduced ejection fraction, stent frame under-expansion, patient prothesis mismatch and use of balloon-expandable valve may predispose to THV thrombosis.

Optimal procedural ACT during TAVR and the heparin reversal at the end of the procedure remain controversial. In our routine practice, we target an ACT close to 250 seconds and avoid systematic use of protamin. Al-Kassou et al. recently showed a significantly lower rates of life-threatening and major bleeding complications with protamin administration compared with patients without heparin reversal, without any increasing of clinical thromboembolic event [4].

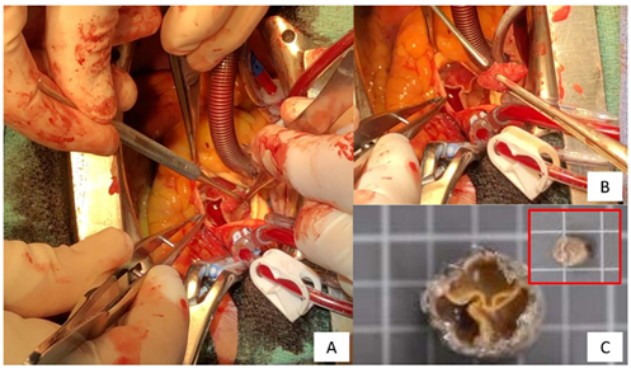

Figure 2: Peroperative and macroscopic appareances of Edwards Sapien S3 thrombosed leaflets: Panel A demonstrates the severely thrombosed three leaflets of the Sapien S3, and a really tickened thrombus with a gelatinous appareance, as shown by the Panel B. Panel C describes the Edwards Sapien S3 piece of resection and a typical thombus without any endocarditis diagnosis.

In the current cases, less than 100 UI/Kg of heparin was administrated, and the ACT was under 250 seconds. This may have favored the THV thrombosis, as both patients had no identified risk factors for device thrombosis except the use of balloon expandable valve.

A literature review of optimal anticoagulation strategy after TAVR over the last five years was performed and summarized in (Table 2). The ARTE trial compared SAPT (aspirin alone) to DAPT (aspirin + clopidogrel) and was prematurely stopped. The composite of death, MI, stroke or transient ischemic attack, or major or life-threatening bleeding tended to occur more frequently in the DAPT group (15.3% vs. 7.2%, p = 0.065). Any difference in valve hemodynamic status at discharge between the 2 groups was observed but 4-D CT data wasn't available [5]. These results were also confirmed by the POPULAR-TAVI trial [6]. NOAC was also tried as a potential alternative strategy in the GALILEO trial which compared a therapy including rivaroxaban 10mg daily (+ aspirin for 3 months) versus a DAPT therapy. Main results demonstrated a higher rate of major or life-threatening bleeding, death and thromboembolic complications in rivaroxaban group as compared to DAPT strategy [7]. Nonetheless, the GALILEO-4D substudy analyzed 4-D computed tomography imaging at 90 days after randomization and showed a lower rate of subclinical aortic leaflet-motion abnormalities in the NOAC arm [8]. The ATLANTIS trial (NCT 02664649) studied the anticoagulation after TAVR, irrespective of the need of NOAC (using only apixaban) at a dose-regimen labeled for non-valvular atrial fibrillation and tested versus VKA or aspirin. One of the primary endpoints is symptomatic valve thrombosis. Results were recently presented at the ACC.21 congress and demonstrated the non-superiority of apixaban compared to the standard of care despite a numerical reduction of valve leaflet thrombosis when compared with SAPT. Considering these data, our routine practice is tailored based on the 2019 Canadian cardiovascular society who recommends aspirin alone after TAVR if there is no indication of DAPT or anticoagulation [9].

Finally, our two cases were treated surgically. The indication was a large size thrombus and high embolic risk in the first case and a failure

Trial	N	Design	Inclusion Criteria	Primary Outcome and main findings	Publication date
ARTE					
(Aspirin Versus Aspirin Plus Clopidogrel as Antithrombotic Treatment Following Transcatheter Aortic Valve Replacement with a Balloon-Expandable Valve) NCT02436655	222	Randomized and multicenter trial, compared SAPT (N = 111) vs. DAPT (N = 111) in patients undergoing TAVR with a balloon-expandable valve	Patients with clinical in- dications for TAVR with a balloon-expandable Edwards SAPIEN XT or SAPIEN 3 valve	Rate of death, myocardial infarction, ischemic stroke or TIA, or major or life-threatening bleeding. [Time Frame: 3 monthsfollow-up] Primary outcome tended to occur more frequently in DAPT group (15.3% vs. 7.2%, P = 0,065). No differences in valve hemodynamic status	April 2017
POPULAR-TAVI					
(Aspirin with or without Clopidogrel after Transcatheter Aortic Valve Implantation) NCT02247128	665	Randomized and multicenter trial, compared SAPT with aspirin alone (N = 331) vs. DAPT (N = 334) with aspirin + clopidogrel for 3 months in patients undergoing TAVR	All patients scheduled to undergo TAVR, without indication for long-term oral anticoagulation	All bleeding (including minor, major, and life-threatening or disabling bleeding) And non–procedure-related bleeding over a period of 12 months Bleeding event occurred more frequently in DAPT group than in SAPT group (26.6% vs. 15.1%; P = 0.001), while non-procedure related bleeding occurred respectively in 24.9% in DAPT vs. 15.1% in SAPT group (P = 0.005)	October 2020
GALILEO					
(A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement) NCT02556203	1644	Randomized and multicenter trial comparison of Rivaroxaban 10mg die (+ aspirin for 3 months; N = 826) vs. DAPT (long-term aspirin + clopidogrel for 3 months; N = 818) after successful TAVR in patients without an established indication of oral anti-coagulation	Adult patient, aged more than 18 years-old Successful TAVR without peri-procedural complication	Combination of death from any cause or thromboembolic events (including any stroke, myocardial infarction, symptomatic valve thrombosis, systemic embolism, deep-vein thrombosis, or pulmonary embolism) [Time Frame: 17 months follow-up] Primary safety outcome: composite of life-threatening, disabling, or major bleeding. Rivaroxaban group was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than DAPT group	January 2020
ATLANTIS					
(Oral anti-Xa anticoagulation after trans-aortic valve implantation for aortic stenosis: The randomized ATLANTIS trial) NCT 02664649	1510	Prospective, multicenter, phase IIIb, open-label, randomized trial. Parallel assignment Stratification according to the need for a long-term anticoagulation for another reason than the TAVR procedure Patients willberandomized1:1 Experimental arm: Apixaban 5mg bid or a 2.5 mg bid if indicated is combined with anti-platelet therapy. Control arm: VKA therapy if indication for oral anticoagulation or antiplatelet therapy alone (single or dual) or the combination of both if needed.	Adult patient, aged more than 18 years-old Clinically successful TAVR irrespective of prior antithrombotic treatment.	Combination of all-cause death, TIA/stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep venous thrombosis, systemic embolism, life-threatening, disabling or major bleeding.	Always ongoing (soon expected). First results presented a ACC/AHA.21 Congress

Table 2: Last main and ongoing trials for anticoagulation strategy after TAVR.

of first line anticoagulation therapy in the second one. This is supported by the ESC/EACTS guidelines in operable patients although anticoagulation is recommended as first-line therapy (class IC) [10].

Conclusion

In conclusion, these 2 cases of consecutive THV thrombosis highlight the importance of an optimal peri and post-procedural anticoagulation/anti-platelet therapies especially for newer valves with higher sealing fabric feature. ATLANTIS and GALILEO trialsbring a similar information to this anticoagulation dilemma and confirm our routine practice.

Disclosures

WBA has received research grants from Medtronic and Edwards Lifesciences. The other authors have nothing to disclose in relation with this manuscript.

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