JACC: CASE REPORTS VOL. 3, NO. 10, 2021

CASE REPORT

INTERMEDIATE

CLINICAL CASE

Late Clinical Valve Thrombosis After Transcatheter Aortic Valve Replacement Despite Non-Vitamin K Anticoagulant

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ABSTRACT

This study presents the case of a late clinical leaflet thrombosis 1.5 years after percutaneous aortic valve replacement, despite adequate non-vitamin K anticoagulant therapy. Optimal antithrombotic therapy after transcatheter aortic valve replacement remains undetermined. After switching to vitamin K antagonist therapy, complete resolution occurred at 3 months follow-up. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2021;3:1275–1280) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 90-year-old female who had undergone percutaneous aortic valve replacement in September 2018, presented in May 2020 to the emergency department with worsening dyspnea and exercise intolerance. Her blood pressure was 110/68 mm Hg with bilateral lung crackles and peripheral edema, suggestive of congestive heart failure. Transthoracic echocardiography (TTE) showed severely elevated gradients across the bioprosthesis (**Figures 1 and 2,** Videos 1 and 2). N-terminal pro-B-type natriuretic peptide concentration was elevated at 6,289 pg/ml. She was admitted for further work-up.

LEARNING OBJECTIVES

- To identify clinical valve thrombosis through its symptoms and multimodality imaging.
- To understand treatment options for clinical valve thrombosis.
- To check for therapeutic compliance and drug-drug/drug-supplement interaction when assessing clinical valve thrombosis under DOAC.

MEDICAL HISTORY

The patient was a 90-year-old female with permanent atrial fibrillation (AF) on long-term full-dose edoxaban (60 mg daily). Uncomplicated percutaneous aortic valve replacement with a 27-mm self-expandable Portico bioprosthesis (St Jude Medical, St Paul, Minnesota) had been performed 1.5 years earlier due to symptomatic severe aortic valve stenosis. Post-procedural echocardiography at the time was within normal limits, with a mean transvalvular gradient of 12 mm Hg and minimal paravalvular leakage. Antithrombotic regimen consisted of 6 months of clopidogrel in combination with a reduced dose of edoxaban (30 mg daily), after which monotherapy with full-dose edoxaban was restarted.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received January 5, 2021; revised manuscript received May 28, 2021, accepted June 1, 2021.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2021.06.012

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

DOAC = direct oral anticoagulants

INR = international normalized ratio

LVEF = left ventricular ejection faction

MDCT = multidetector computed tomography

OAC = oral anticoagulation

TAVR = transcatheter aortic valve replacement

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

VKA = vitamin K antagonist

DIFFERENTIAL DIAGNOSIS

Congestive heart failure symptoms and high transvalvular gradients may indicate degeneration of the aortic valve prosthesis due to pannus, deformation of the stent frame, or valve thrombosis.

INVESTIGATIONS

Transesophageal echocardiography (TEE) showed turbulent flow across the aortic valve prosthesis and reduced leaflet mobility, with visualization of valve thrombosis (**Figure 3,** Videos 3, 4, and 5). Left ventricular ejection fraction (LVEF) was moderately reduced (40%). Multidetector computed tomography (MDCT) showed hypoattenuation of the bioprosthetic leaflets, confirming clinical valve thrombosis (**Figure 4**).

Because clinical valve thrombosis developed under anticoagulation, extensive evaluation for therapeutic compliance or drug-drug/drug-supplement interaction was carried out, although the latter could not be found (**Table 1**). Therapeutic compliance was (hetero-) anamnestically adequate.

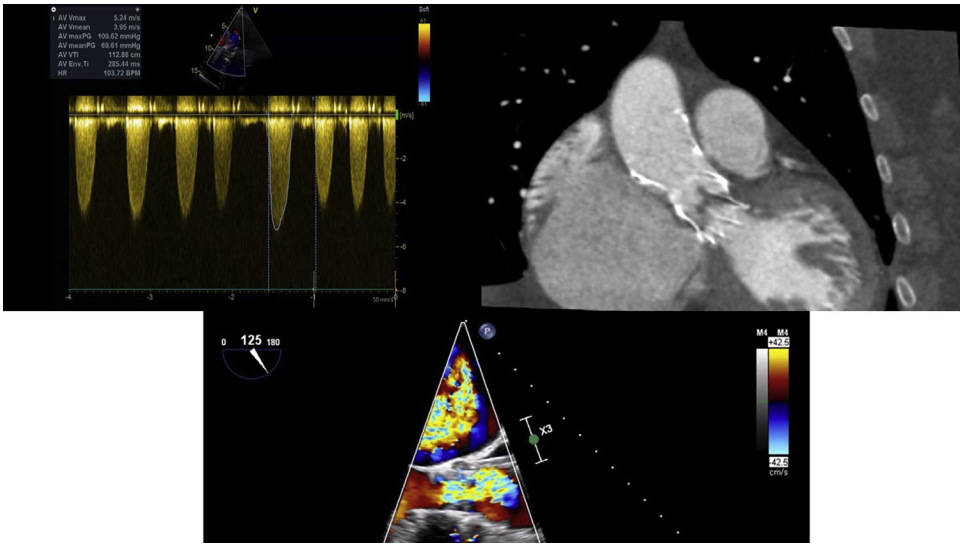
MANAGEMENT

Because of hemodynamic stability at presentation, vitamin K antagonist (VKA) was started with heparin bridging until target international normalized ratio (INR) was reached. Despite transvalvular gradients remaining high, reduction of dyspnea occurred within a couple of days. Clinical follow-up at 3 months showed normalization of transvalvular gradients and LVEF (**Figure 5**) with improvement of exercise capacity and absence of dyspnea.

DISCUSSION

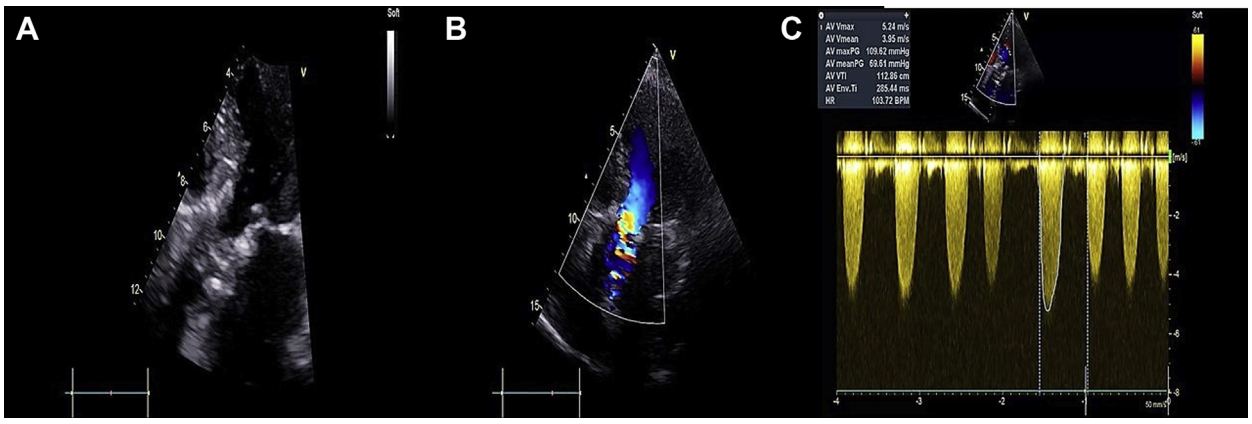
It has recently become apparent that subclinical leaflet thrombosis is not rare and is frequently diagnosed as an incidental finding on routine imaging after transcatheter aortic valve replacement (TAVR). At 1-year follow-up, subclinical leaflet thrombosis can be found in up to 24% of patients (1). As most of these leaflet thromboses are subclinical and asymptomatic, the natural history of this phenomenon and its clinical relevance remains a matter of debate. On the other hand, clinical valve thrombosis seems to be rare and occurs in 0.61% to 2.8% of cases (2). The definition of clinical valve thrombosis is quite heteroge-

FIGURE 1 Visual Abstract



From **left to right**: transthoracic echocardiography continuous-wave Doppler across the aortic valve shows severely elevated gradients. Coronal computed tomography view shows hypoattenuation of the leaflets, suggestive of thrombosis. Transesophageal echocardiography 3-chamber view with color Doppler across the aortic valve bioprosthesis with "color paucity sign."

FIGURE 2 **Transthoracic Echocardiography at Presentation**

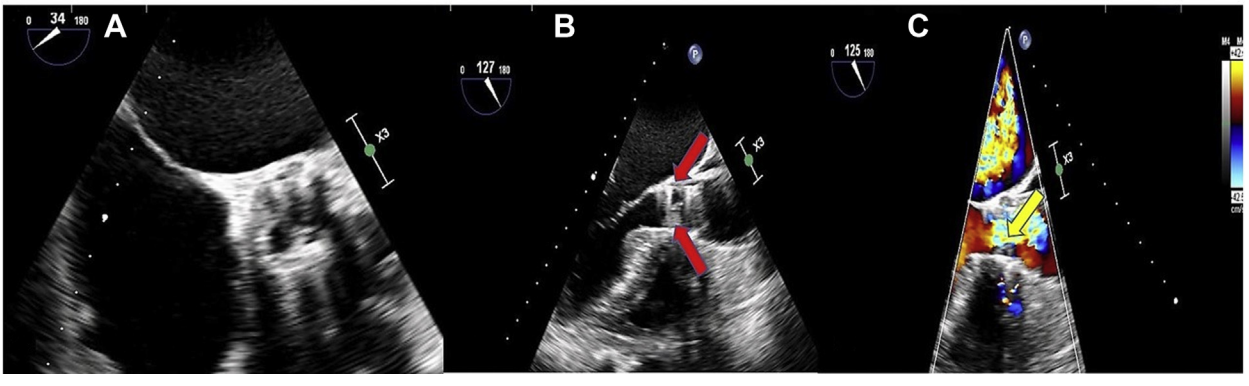


(A) Apical 5-chamber view showing hazy aspect of the bioprosthesis. **(B)** Apical 5-chamber view showing turbulent flow on color Doppler. **(C)** High transvalvular gradients across aortic valve bioprosthesis on continuous wave Doppler. Maximal pressure gradient: 109 mm Hg; mean pressure gradient: 69 mm Hg. Patient in atrial fibrillation with beat-to-beat variation in stroke volume and thus pressure gradients.

neous among different studies, but generally progressive heart failure symptoms in the setting of increasing transvalvular gradients and evidence of hypoattenuation on computed tomography (CT) or restrictive leaflet mobility on CT or TEE are needed. Most of these clinical valve thromboses can be adequately treated with anticoagulation if the patient is hemodynamically stable at presentation. If not, bailout surgical aortic valve replacement or valve-in-valve TAVR should be considered on an individual basis. Duration of anticoagulation is another issue of debate. Treatment should at least continue until complete resolution of valve thrombosis.

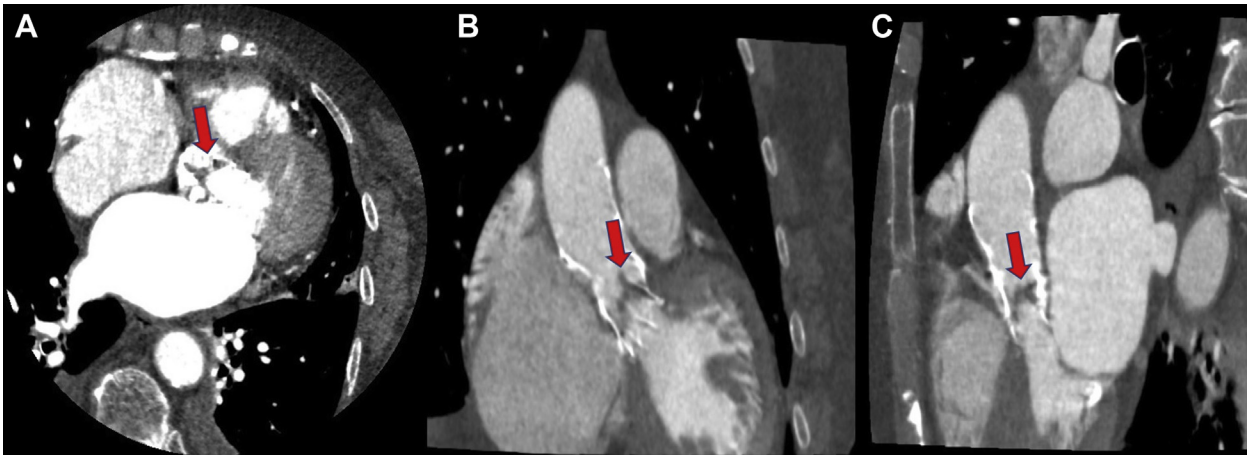
The authors describe a case of clinical valve thrombosis in a patient, despite adequate anticoagulation with edoxaban, which seems to be very rare. Therapeutic compliance was adequate (hetero) anamnestically, although anti-Xa activity or edoxaban concentration was not tested at the time of admission, making incompliance still a possibility. Although drug-drug interactions are of lesser concern with direct oral anticoagulants (DOAC) than VKA, it is

FIGURE 3 **Transesophageal Echocardiography**



(A) Short-axis view. **(B)** Long-axis view with visualization of thrombus at the base of the prosthesis leaflets **(red arrows)**. **(C)** Color Doppler shows turbulent flow across prosthesis with "color paucity sign" **(yellow arrow)**.

FIGURE 4 Computed Tomography Graphic Evaluation at Presentation



(A) Axial view. **(B)** Coronal view. **(C)** Sagittal view. **Red arrows** indicate hypoattenuation of the prothesis leaflets, conforming valve thrombosis.

still important to recognize possible interactions with other drugs that lead to increased or decreased biological activity (Table 1). After thorough evaluation, a significant drug-drug or drug-supplement interaction could not be found. Underexpansion of the bioprosthesis could have been another contributing factor to thrombosis. However, preoperative CT estimated annular size at 23.7 mm with an estimated perimeter of 76.8 mm, which is suitable for a Portico 27-mm prosthesis and making underexpansion unlikely (Figure 6).

Determining optimal antithrombotic regimen in patients undergoing TAVR and concomitant indication for oral anticoagulation (OAC) remains challenging. Although anticoagulation alone after TAVR may be safe, with less bleeding events as opposed to anticoagulation plus antiplatelet therapy, conflicting evidence exists among specific anticoagulation strategy (DOAC vs. VKA) in patients with indication of OAC (3). European guidelines mention VKA is preferred in the first 3 months after TAVR, after which DOAC can be considered (4). American guidelines, on the other hand, discourage use of DOAC after bioprosthetic valve implementation (both surgical or transcatheter) (5). As the use of DOAC in mechanical heart valves is associated with increased risk of thromboembolic and bleeding complications (6), several observational studies also observe a trend to increased ischemic events with DOAC after TAVR (7). Other observational studies, however, do not (8). Large randomized controlled trials are ongoing to further evaluate whether DOAC effectively presents

TABLE 1 Overview of Significant Drug-Drug Interactions Leading to a Decreased Plasma Concentration of Edoxaban

Drug	Effect on P-gp and CYP	Effect on Edoxaban Concentration	Possible Effect	Recommendation
Carbamazepine	Strong induction	Decrease	Possible decrease	Use with caution
Levetiracetam	P-gp induction	Decrease	Significant decrease	Should not be used
Phenobarbital	Strong CYP3A4 and P-gp induction	Decrease	Significant decrease	Use with caution
Phenytoin	Strong CYP3A4 and P-gp induction	Decrease	Decrease	Use with caution

CYP = cytochrome P450; P-gp = P-glycoprotein.

FIGURE 5 **Transthoracic Echocardiography After 3 Months of Anticoagulation With Vitamin K Antagonist Shows Complete Normalization of Transvalvular Gradients**

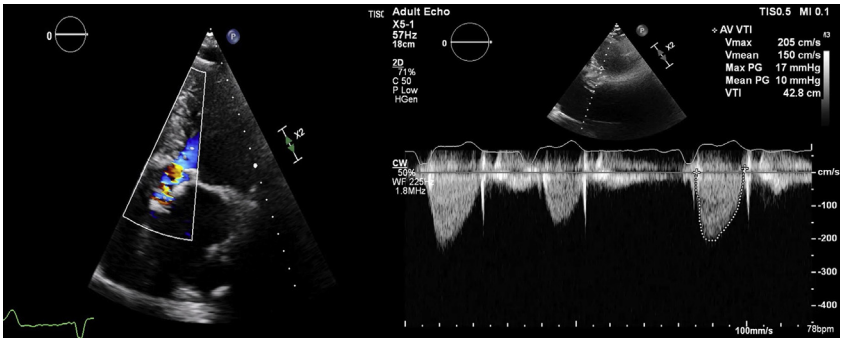
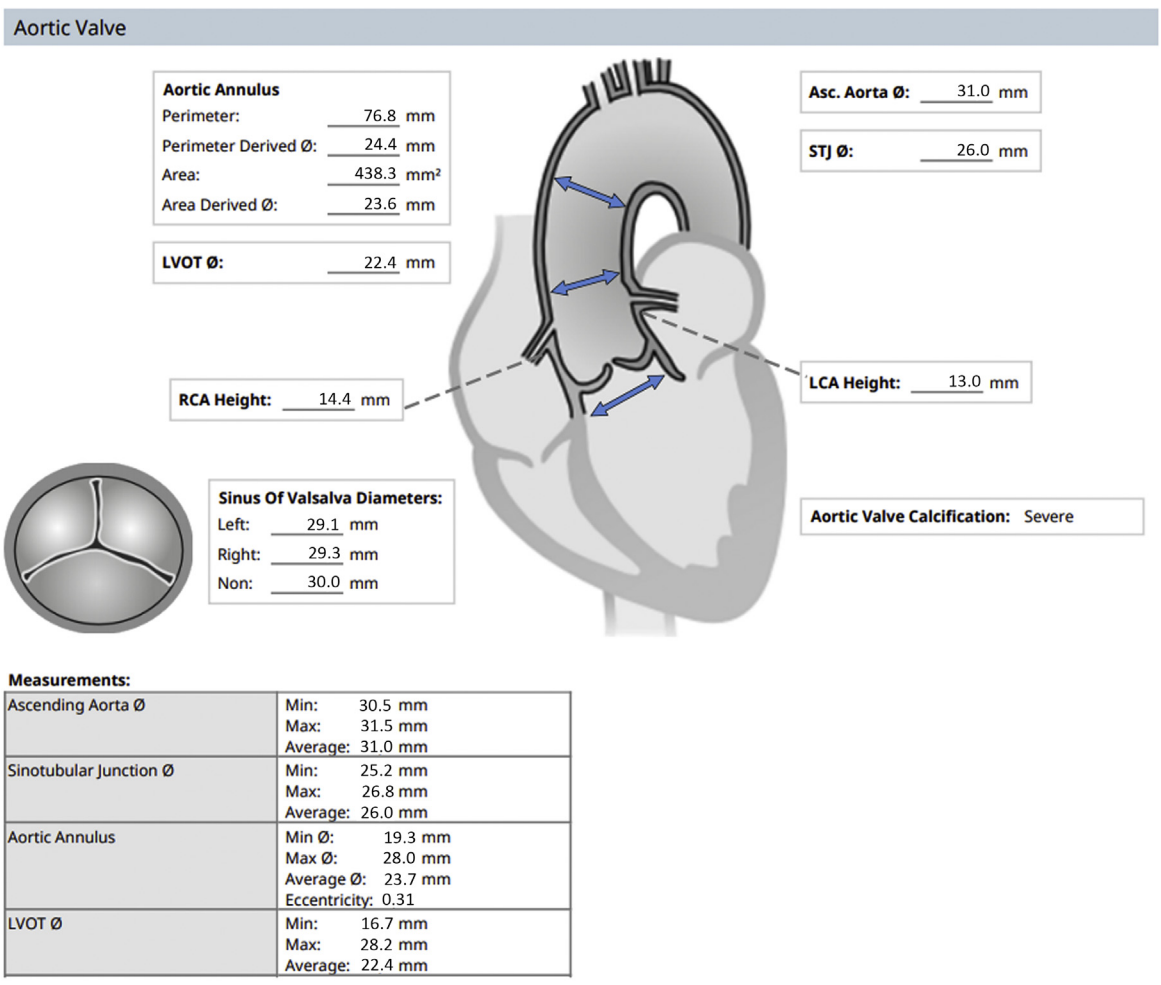


FIGURE 6 **Preoperative Computed Tomography Estimating Optimal Size of Aortic Prosthesis**



Aortic annulus calculated at 23.7 mm, with estimated perimeter of 76.8 mm. Optimal size was estimated at Portico 27-mm prosthesis. Asc. = ascending; LCA = left coronary artery; LVOT = left ventricular outflow tract; RCA = right coronary artery; STJ = sinotubular junction.

an increased risk of thromboembolic events in patients undergoing TAVR with concomitant OAC indication (9,10).

FOLLOW-UP

The patient remained asymptomatic with normal transvalvular gradients. Lifelong VKA will be prescribed.

CONCLUSIONS

Subclinical leaflet thrombosis after transcatheter aortic valve implementation is a frequent finding in routine follow-up, and its natural evolution and, thus, clinical relevance remain to be determined. Clinical valve thrombosis is estimated to be a rare finding and in most cases is adequately treated with anticoagulation. Whether DOAC or VKA is preferable in this setting is unclear, with observational data suggesting an increased thromboembolic risk with DOAC as compared to VKA, although quality of evidence is poor. The authors' case strengthens this concern with the development of clinical valve thrombosis under DOAC with full resolution after 3 months of VKA therapy. Large randomized controlled trials are ongoing, hopefully closing this debate in the near future.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS anticoagulation, case report, heart failure, thrombosis, transcatheter aortic valve replacement

APPENDIX For supplemental Videos, please see the online version of this paper.