Leaflet thrombosis after valve-in-valve transcatheter aortic valve implantation: a case series

Dincer Aktuerk 1*, Saeed Mirsadraee 2, Cesare Quarto 1, Simon Davies 3, and Alison Duncan 3

1Department of Cardiothoracic Surgery, Royal Brompton Hospital, Sydney Street, Chelsea, London SW3 6NP, UK; 2Department of Radiology, Royal Brompton Hospital, Sydney Street, Chelsea, London SW3 6NP, UK; and 3Department of Cardiology, Royal Brompton Hospital, Sydney Street, Chelsea, London SW3 6NP, UK

Received 15 January 2020; first decision 14 February 2020; accepted 19 June 2020; online publish-ahead-of-print 20 July 2020

Background
Valve-in-valve transcatheter aortic valve implantation (ViV-TAVI) in degenerated surgical aortic valve replacement (SAVR) is an alternative to redo-SAVR. However, reports on leaflet thrombosis following ViV-TAVI are emerging and subclinical thrombosis has gained recent attention. Although the incidence of transcatheter heart valve (THV) thrombosis after TAVI for native aortic valve disease is low, current imaging studies suggest the incidence of subclinical THV thrombosis may be significantly higher. While anticoagulation strategies for THV patients for native aortic stenosis presenting with symptomatic obstructive thrombosis has been described, the optimal management and anticoagulation therapy of patients with THV thrombosis following ViV-TAVI are less evident.

Case summary
We report a case series of three patients presenting with early and late THV thrombosis after ViV-TAVI. Two patients presented clinically on single antiplatelet therapy and one patient presented with subclinical valve thrombosis whilst taking a non-vitamin K oral anticoagulation agent.

Discussion
Leaflet thrombosis after ViV-TAVI is an important cause of THV degeneration and may present subclinically. Imaging modalities such as serial transthoracic echocardiograms and multidetector computerized tomography aid diagnosis and guide management. Patient-individualized risk- vs. -benefit prophylactic post-procedural oral anticoagulation may be indicated.

Keywords
Transcatheter aortic valve implantation • Valve-in-valve • Thrombosis • Case series

Learning points
• Multimodality imaging is pivotal for both diagnosis and assessment of treatment success in patients with transcatheter heart valve (THV) thrombosis following valve-in-valve transcatheter aortic valve implantation (ViV-TAVI).
• Optimal anticoagulation for THV thrombosis following ViV-TAVI is not defined, but appears less likely among patients on oral anticoagulation compared to patients on single antiplatelet therapy.
• Patient-individualized, risk-vs.-benefit, prophylactic oral anticoagulation may be indicated in patients undergoing ViV-TAVI for a failing surgical aortic bioprosthesis.
Introduction

Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic valve stenosis is an alternative to conventional surgical aortic valve replacement (SAVR). However, reports of transcatheter heart valve (THV) leaflet thrombosis following TAVI are emerging. Although clinically evident obstructive THV thrombosis after TAVI for native aortic valve disease is rare (<1%), the incidence of subclinical THV thrombosis is 5–23%. Clinical THV thrombosis after valve-in-valve transcatheter aortic valve implantation (ViV-TAVI) is reported in 7.6% of cases. Although anticoagulation strategies for patients with native aortic valve disease undergoing TAVI who present with symptomatic obstructive THV thrombosis have been described, the optimal management and anticoagulation therapy of patients with THV thrombosis following ViV-TAVI are less clear. In our case series, we report the diagnosis and management of three patients presenting with THV thrombosis after ViV-TAVI. All patients gave their informed consent to undergo ViV-TAVI procedure and for their clinical data to be used for scientific purposes.

Timeline

| Patient | Surgical aortic valve replacement | Valve-in-valve transcatheter aortic valve implantation (TAVI) | Onset of symptoms | Multislice CT confirming leaflet thrombosis | Most recent follow-up |
|---------|------------------------------------|-------------------------------------------------------------|------------------|------------------------------------------|----------------------|
| Patient 1 | September 1990 | March 2011 | Asymptomatic | March 2018 | October 2019 |
| Patient 2 | July 2009 | December 2012 | April 2018 | May 2018 | NA |
| Patient 3 | Jan 2008 | May 2018 | August 2018 | August 2018 | November 2019 |

Case presentations

Patient 1

A 72-year-old man with long-standing atrial fibrillation (AF) on long-term Apixaban and Parkinson’s disease underwent SAVR with a 27 mm [true internal diameter (ID) 22 mm] Aspire device (Vascutek, Inchinnan, UK) in 1990. He re-presented in 2011 (on Apixaban 2.5 mg twice daily) with symptoms of heart failure secondary to structural degeneration of his SAVR [severe transvalvular aortic regurgitation (AR)] and underwent a ViV-TAVI with a 26-mm self-expanding CoreValve (Medtronic, Minneapolis, MN, USA). Post-procedural transthoracic echocardiography (TTE) reported a well-seated THV device with no paravalvular leak (PVL), peak/mean THV gradients of 15/8 mmHg, respectively, Doppler velocity index (DVI) of 0.40, and aortic valve area (AVA) of 1.87 cm². He was initiated on single antiplatelet therapy and re-commenced on Apixaban for AF. He remained well during annual follow-up, and 7 years after ViV-TAVI, peak/mean THV gradients on TTE were 23/12 mmHg, respectively, DVI was 0.4, and AVA 1.6 cm². Seven months after his annual TTE, a multidetector computerized tomography (MDCT) scan was performed to investigate possible enlargement of his thoracic aorta and an incidental finding of right-sided THV leaflet thickening with extension to the right coronary sinus, Grade 3 reduced leaflet motion (according to DeBakey classification), and a small volume thrombus in the native non-coronary sinus was reported (Figure 1). A simultaneous TTE was not performed. Physical examination revealed mild systolic hypertension and rate-controlled AF. Cardiac examination demonstrated no signs of peripheral or pulmonary oedema and no obvious cardiac murmur. The patient admitted to discontinuing his Apixaban several weeks beforehand and did not wish to recommence so was started on Warfarin [target international normalized ratio (INR) 2.5–3.0]. Follow-up echo 6 weeks later reported peak/mean THV gradients of 23/12 mmHg, respectively, DVI of 0.47, and AVA of 1.79 cm².

Patient 2

A 35-year-old man with Marfan syndrome underwent a modified biological Bentall’s procedure with a 25-mm Perimount (true ID 23 mm) SAVR and interposition tube graft to the ascending aorta in 2006 followed by mitral valve repair for severe mitral regurgitation in 2009. He re-presented in 2012 in acute heart failure secondary to structural deterioration of his SAVR with severe aortic stenosis and severe left ventricular (LV) impairment [TTE peak/mean gradients 125/70 mmHg, DVI 0.1, AVA 0.8 cm², moderate transvalvular AR, LV ejection fraction (LVEF) 25%]. He underwent urgent ViV-TAVI with a 26 mm CoreValve, and post-procedural TTE reported a well-seated THV device with peak/mean gradients of 25/17 mmHg, respectively, DVI 0.34, AVA 2.1 cm², and no PVL. He was discharged on single antiplatelet therapy and no oral anticoagulants and remained well for 3 years but unfortunately was then lost to follow-up. He represented in 2018 with dyspnoea at rest in recurrent acute heart failure. Physical examination on admission revealed normotensive tachycardia (98 b.p.m.) and ankle oedema. Cardiac examination showed bilateral pulmonary crepitations and a rough systolic murmur radiating to both the carotid arteries. Transthoracic echocardiography reported severe biventricular dysfunction (LVEF 14%), thickened THV leaflets with peak/mean THV gradients of 116/66 mmHg, respectively, DVI of 0.40, and AVA 1.87 cm². He underwent urgent ViV-TAVI with a 26-mm self-expanding CoreValve (Medtronic, Minneapolis, MN, USA). Post-procedural transthoracic echocardiography (TTE) reported a well-seated THV device with no paravalvular leak (PVL), peak/mean THV gradients of 15/8 mmHg, respectively, Doppler velocity index (DVI) of 0.40, and aortic valve area (AVA) of 1.87 cm². He was initiated on single antiplatelet therapy and re-commenced on Apixaban for AF. He remained well during annual follow-up, and 7 years after ViV-TAVI, peak/mean THV gradients on TTE were 23/12 mmHg, respectively, DVI was 0.4, and AVA 1.6 cm². Seven months after his annual TTE, a multidetector computerized tomography (MDCT) scan was performed to investigate possible enlargement of his thoracic aorta and an incidental finding of right-sided THV leaflet thickening with extension to the right coronary sinus, Grade 3 reduced leaflet motion (according to DeBakey classification), and a small volume thrombus in the native non-coronary sinus was reported (Figure 1). A simultaneous TTE was not performed. Physical examination revealed mild systolic hypertension and rate-controlled AF. Cardiac examination demonstrated no signs of peripheral or pulmonary oedema and no obvious cardiac murmur. The patient admitted to discontinuing his Apixaban several weeks beforehand and did not wish to recommence so was started on Warfarin [target international normalized ratio (INR) 2.5–3.0]. Follow-up echo 6 weeks later reported peak/mean THV gradients of 23/12 mmHg, respectively, DVI of 0.47, and AVA of 1.79 cm².
calcification and thrombosis (Figure 2B). Unfortunately, the patient died 8 days after redo-SAVR as a result of an embolic stroke following decannulation of extra-corporeal mechanical support.

**Patient 3**

A 69-year-old man with chronic thrombocytopenia, pulmonary sarcoidosis, chronic kidney disease, hypertension, and stable localized thoracic aortic arch aneurysm underwent SAVR in 2008 with a 25-mm (true ID 23 mm) Perimount Magna Ease bioprosthesis (Edwards Lifesciences, Irvine, CA, USA). He re-presented in 2018 with severe transvalvular AR secondary to structural degeneration of his SAVR and underwent ViV-TAVI with 29-mm CoreValve Evolut R. Postoperative TTE reported a well-seated THV device with peak/mean gradients of 15/10 mmHg, respectively, a DVI of 0.45, an AVA of 2.4 cm², and no PVL. He was discharged on single antiplatelet...
therapy. Three months after ViV-TAVI, the patient was re-admitted with orthopnoea and mild chest pain in acute pulmonary oedema. Physical examination on admission revealed hypotension (99/55 mmHg) and tachycardia (94 b.p.m.) with mild peripheral oedema. Cardiac examination showed bilateral pulmonary crepitations and a rough systolic murmur radiating to both the carotid arteries. TTE reported peak/mean THV gradients of 94/50 mmHg, respectively, a DVI of 0.13, and an AVA of 0.4 cm². MDCT confirmed thrombus within the THV leaflets extending to the native sinuses and Grade 4 reduced leaflet motion (Figure 3). The patient was commenced on continuous intravenous heparin while anticoagulation with warfarin was initiated (target INR of 2.5–3.0). Serial TTE documented steady reduction in THV gradients, such that 6-month follow-up TTE reported peak/mean THV gradients of 17/8 mmHg respectively, a DVI of 0.46, and an AVA of 2.01 cm².

Discussion

Transcatheter heart valve thrombosis is an emerging issue following TAVI for both native aortic valve disease and following ViV-TAVI for degenerative SAVR, particularly in patients with either patient–prosthesis mismatch or degenerative porcine SAVR. Diagnosis of THV thrombosis can be problematic, as most cases of reduced THV leaflet motion are diagnosed by advanced imaging studies in asymptomatic patients. While radiological advancements have been made, pre-defined diagnostic criteria (e.g., increased THV gradients >50% from baseline on TTE, hypoattenuation or THV leaflet thickening or abnormal leaflet motion on MDCT) may enhance understanding of the natural history of THV thrombosis.

Traditionally, thrombosis is described by Virchow’s triad (foreign materials, fluid flow, and blood biochemistry). The presence of foreign material, such as THV within a surgical bioprosthesis, may result in platelet activation and Hatoum et al. demonstrated in an in vitro model that implantation of a Medtronic CoreValve or Edwards Sapien THV into a Medtronic Hancock II bioprosthesis resulted in flow reduction and shear stress increasing the risk for leaflet thrombosis. Moreover, blood flow stagnation created by incomplete THV frame expansion within degenerated surgical bioprostheses following ViV-TAVI creates regions of increased blood stasis and platelet activation particularly at the ViV intra-annular attachment to the frame. Relative oversizing could potentiate blood flow stasis and resultant mechanical stresses may disrupt pericardial leaflet collagen patterns leading to early valve degeneration. The ratio of inner surgical diameter to implanted THV device in our series ranged between 0.79 and 0.88, suggesting that relative oversizing was unlikely to be a significant cause of early THV degeneration in our study.

Leaflet thrombosis is usually a relatively early event following TAVI, and indeed one patient in our case series presented 3 months after ViV-TAVI with clinical evidence of THV obstruction. However, both patients with ViV-TAVI for failing stentless SAVR presented several years after the ViV-TAVI procedure. Such late presentation is usually anticipated by progressive THV deterioration and gradual increase in THV gradients, as reported by our group describing THV device degeneration and leaflet thrombosis 10 years after ViV-TAVI for a failing stentless SAVR. However, in our current case series, one patient with late-presenting THV thrombosis was unanticipated (he had been stable for many years on a single antiplatelet agent and Apixaban and only presented with incidental THV thrombosis after temporarily stopping his Apixaban), while the other had been lost to follow-up 3 years after ViV-TAVI, and therefore, the timing of the onset of THV thrombosis in that patient was unclear.

Figure 3 Multidetector computerized tomography demonstrating dense thrombus within the transcatheter device leaflets (A) extending to the neo-sinuses (B).
The 2017 American Heart Association/American College of Cardiology guidelines on valvular heart disease\textsuperscript{13} suggests dual antiplatelet therapy (DAPT) after TAVI (aspirin lifelong plus clopidogrel for 6 months) as ‘reasonable’, recommendation class of llb, level of evidence C, while the latest European Society of Cardiology guidelines on valvular heart disease make no specific recommendations for the duration of DAPT after TAVI, but simply state that a combination of low-dose aspirin and a thienopyridine should be used ‘early’ after TAVI, followed by aspirin or a thienopyridine alone.\textsuperscript{14} A recent meta-analysis suggested the majority of centres performing TAVI for native stenos use DAPT after TAVI\textsuperscript{15}; however, the same meta-analysis demonstrated that DAPT after TAVI conferred no benefit beyond 1 month in terms of stroke rate, overall mortality or major bleeding, and that aspirin monotherapy was as safe and effective as DAPT after TAVI.\textsuperscript{15} Two of our patients had ViV-TAVI in 2011 and 2012, respectively, when we historically discharged patients on a single antiplatelet agent to avoid potentially adverse effects of DAPT; our experience of THV thrombosis since then, including the early THV thrombosis in Patient #3 in our series, has modified our practise such that we now initiate oral anticoagulation before discharge in patients undergoing ViV-TAVI risk-stratified as having a low-risk of bleeding.

For patients with sub-clinical presentation, current literature suggests THV thrombosis may be less likely among patients on oral anticoagulation compared to patients on single antiplatelet therapy\textsuperscript{16} and may be as low as 1.0% for patients taking oral anticoagulation compared to 11.3% in patients not on anticoagulation after ViV-TAVI.\textsuperscript{9} Oral anticoagulants have been shown to be effective after a THV thrombosis diagnosis has been made, with normalization of THV gradients and excellent long-term results.\textsuperscript{17} However, it remains to be clarified whether prophylactic anticoagulants are broadly indicated in this patient group or whether a more patient-specific strategy is appropriate. In the SAVORY and RESOLVE registries, no differences were reported in leaflet motion between direct oral and vitamin K anticoagulants (3% vs. 4%, respectively; \( P = 0.72 \)), although both appeared more effective than no anticoagulation.\textsuperscript{3} Sellers et al. histologically analysed a series of explanted THVs and the associated time-dependent changes in components of structural valve degeneration, including fibrosis and calcification. Their findings suggest a sequential cascade of thrombus formation within hours, fibrosis after 60 days, and calcification after 4 years, which may ultimately contribute to progressive leaflet thickening and structural valve deterioration.\textsuperscript{18} However, an ‘anticoagulation for all’ approach after ViV-TAVI should be approached with caution in patients without an established indication for oral anticoagulation. In particular, administration of a rivaroxaban-based antithrombotic strategy may reduce the risk of thromboembolic complications after TAVI, but is associated with a higher risk of death and thromboembolic complications.\textsuperscript{19}

**Conclusions**

Leaflet thrombosis after ViV-TAVI is an emerging clinical issue, but data on clinical management options remains limited. Our case series underscores the recommendation for regular echocardiographic assessment of THV gradients within the first three post-procedural months and every 6–12-month intervals thereafter. In cases where THV gradients increase, dedicated multidetector computed tomography can direct clinicians in diagnosis and monitoring therapeutic intervention. In cases of confirmed transcatheter valve thrombosis, we recommend patient-specific oral anticoagulation with warfarin with a target INR of 2.5–3.0. The role for prophylactic anticoagulation in patients undergoing ViV-TAVI remains to be determined.

**Lead author biography**

Dincer Aktuerk completed his medical degree in Munich, Germany in 2006. He undertook cardiothoracic higher specialist training in the UK. Following the award of Fellow of Royal College of Surgeons of England, he spent 3 years completing international and national fellowships in Sydney, Australia (Complex Heart Failure Surgery), Stuttgart, Germany (Minimal-Invasive Mitral Valve Surgery) and London, Royal Brompton Hospital (Transcatheter Valve Intervention). Aktuerk has a specialist interest in minimal-invasive surgery and transcatheter therapies of the aortic and mitral valve.

**Supplementary material**

**Supplementary material** is available at *European Heart Journal - Case Reports* online.

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as **Supplementary data**.

**Consent:** The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patients in line with COPE guidance.

**Conflict of interest:** none declared.

**References**

1. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M. et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2017; 376:1321–1331.
2. Chakravarty T, Søndergaard L, Friedman J, De Backer O, Berman D, Koloid F. et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet* 2017; 389:2383–2392.
3. Marwan M, Mekkhal N, Goller M, Rother J, Bitterer D, Schuhbaeck A. et al. Leaflet thrombosis following transcatheter aortic valve implantation. *J Cardiovasc Comput Tomogr* 2018;12:8–13.
4. Abdel- Wahab M, Simonato M, Latib A, Golecki PJ, Aliali A, Kaur J. et al. Clinical valve thrombosis after transcatheter aortic valve-in-valve implantation. *Circ Cardiovasc Interv* 2018;11:e006730.
5. De Backer O, Dangas GD, Jilaihawi H, Lepsic JA, Terkelsen CJ, Malik R. et al. Reduced leaflet motion after transcatheter aortic valve replacement. *N Engl J Med* 2020;382:130–139.
6. Ruparel N, Panoulas VF, Frame A, Sutaria N, Ariff B, Gopalan D. et al. Successful treatment of very early thrombosis of SAPIEN 3 valve with direct oral anticoagulant therapy. *J Heart Valve Dis* 2016;25:211–213.
7. Franzone A, Pilgrim T, Haynes AG, Lenz J, Asami M, Praz F. et al. Transcatheter aortic valve thrombosis: incidence, clinical presentation and long-term outcomes. *Eur Heart J Cardiovasc Imaging* 2018;19:398–404.
8. Puri R, Auftret V, Rodes-Cabau J. Bioprosthetic valve thrombosis. *J Am Coll Cardiol* 2017;69:2193–2211.

9. Hatoum H, Moore BL, Maureira P, Dollery J, Crestanello JA, Dasi LP. Aortic sinus flow stasis likely in valve-in-valve transcatheter aortic valve implantation. *J Thorac Cardiovasc Surg* 2017;154:32–43.

10. Vahidkhah K, Azadani AN. Supra-annular valve-in-valve implantation reduces blood stasis on the transcatheter aortic valve leaflets. *J Biomech* 2017;58:114–122.

11. de Buhr W, Pfeifer S, Slotta-Huspenina J, Wintemantel E, Lutter G, Goetz WA. Impairment of pericardial leaflet structure from balloon-expanded valved stents. *J Thorac Cardiovasc Surg* 2012;143:1417–1421.

12. Duncan A, Mirsadree S, Quarto C, Davies S. Transcatheter aortic valve implantation 10 years after valve-in-valve transcatheter aortic valve implantation for failing aortic valve homograft root replacement. *Catheter Cardiovasc Interv* 2019;doi: 10.1002/ccd.28658.

13. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. American College of Cardiology/American Heart Association Task Force on practice guidelines. AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol* 2017;70:252–289.

14. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012): the joint task force on the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Europace* 2012;14:2451–2496.

15. Ahmad Y, Demir O, Rajkumar C, Howard JP, Shun-Shin M, Cook C, et al. Optimal antplatelet strategy after transcatheter aortic valve implantation: a meta-analysis. *Circulation* 2018;138:e00748.

16. Sondergaard L, De Backer O, Kofod KF, Jilahawi H, Fuchs A, Chakravarty T, et al. Natural history of subclinical leaflet thrombosis affecting motion in bioprosthetic aortic valves. *Europace* 2017;19:2201–2207.

17. Gerckens U, Tamburino C, Bleiziffer S, Bosmans J, Wenaweser P, Brecker S, et al. Final 5-year clinical and echocardiographic results for treatment of severe aortic stenosis with a self-expanding bioprosthesis from the ADVANCE Study. *Europace* 2017;19:2729–2738.

18. Sellers SL, Turner CT, Sathananthan J, Cartlidge TRG, Sin F, Bouchareb R, et al. Transcatheter aortic heart valves: histological analysis providing insight to leaflet thickening and structural valve degeneration. *JACC Cardiovasc Imaging* 2019;12:135–145.

19. Windecker S, Tijssen J, Giustino G, Guimarães AH, Mehran R, Valgimigli M, et al. Trial design: rivaroxaban for the prevention of major cardiovascular events after transcatheter aortic valve replacement: rationale and design of the GALILEO study. *Am Heart J* 2017;184:81–87.