Structural Heart
The Journal of the Heart Team

ISSN: 2474-8706 (Print) 2474-8714 (Online) Journal homepage: https://www.tandfonline.com/loi/ushj20

Clinical or Symptomatic Leaflet Thrombosis Following Transcatheter Aortic Valve Replacement: Insights from the U.S. FDA MAUDE Database

Abdul Moiz Hafiz, Ankur Kalra, Ronnie Ramadan, Marie-France Poulin, Ali Andalib, Colin T. Phillips, Deepak L. Bhatt, Michael J. Reardon, Neal S. Kleiman & Jeffrey J. Popma

To cite this article: Abdul Moiz Hafiz, Ankur Kalra, Ronnie Ramadan, Marie-France Poulin, Ali Andalib, Colin T. Phillips, Deepak L. Bhatt, Michael J. Reardon, Neal S. Kleiman & Jeffrey J. Popma (2017) Clinical or Symptomatic Leaflet Thrombosis Following Transcatheter Aortic Valve Replacement: Insights from the U.S. FDA MAUDE Database, Structural Heart, 1:5-6, 256-264, DOI: 10.1080/24748706.2017.1366086

To link to this article: https://doi.org/10.1080/24748706.2017.1366086

Accepted author version posted online: 29 Aug 2017.
Published online: 19 Sep 2017.

STRUCTURAL HEART
2017, VOL. 1, NOS. 5–6, 256–264
https://doi.org/10.1080/24748706.2017.1366086

ORIGINAL RESEARCH

OPEN ACCESS Check for updates

Clinical or Symptomatic Leaflet Thrombosis Following Transcatheter Aortic Valve Replacement: Insights from the U.S. FDA MAUDE Database

Abdul Moiz Hafiz, MD [a], Ankur Kalra, MD [b], Ronnie Ramadan, MD[c], Marie-France Poulin, MD[d], Ali Andalib, MD[e], Colin T. Phillips, MD [f], Deepak L. Bhatt, MD, MPH [c], Michael J. Reardon, MD[g], Neal S. Kleiman, MD[g], and Jeffrey J. Popma, MD[f]

[a]Southern Illinois University School of Medicine, Springfield, Illinois, USA; [b]Harrington Heart & Vascular Institute, University Hospitals Cleveland Medical Center, Division of Cardiovascular Medicine, Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA; [c]Brigham and Women's Heart & Vascular Center, Harvard Medical School, Boston, Massachusetts, USA; [d]Division of Cardiology, Department of Medicine, Rush University Medical Center, Chicago, Ilinois, USA; [e]St. Michael's Hospital, Toronto, ON, Canada; [f]Division of Interventional Cardiology, Department of Cardiovascular Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA; [g]Houston Methodist DeBakey Heart and Vascular Center, Houston Methodist Hospital, Houston, Texas, USA

ABSTRACT

Background: Data on clinical or symptomatic leaflet thrombosis after transcatheter aortic valve replacement (TAVR) are limited. Whether clinical leaflet thrombosis has significance beyond peri-TAVR stroke or transient ischemic attacks (TIA) is yet to be elucidated.

Methods: Between January 2012 and October 2015, we searched the MAUDE database for all entries with the identifier code, "NPT," designated by the U.S. FDA to identify TAVR-related adverse events (AEs). Selected entries were searched further for the terms "leaflet," "central aortic regurgitation," and "aortic stenosis" to capture all events related to leaflet thrombosis causing structural valve dysfunction (SVD). Presentation of leaflet thrombosis (aortic stenosis or regurgitation or mixed valve lesion), mode of diagnosis (echocardiography, computed tomography, surgical explantation, or autopsy), and timing of presentation after TAVR were recorded. For all AEs of SVD due to leaflet thrombosis, the following outcomes were recorded: stroke or TIA, cardiogenic shock, and death from any cause.

Results: A total of 5691 TAVR-related AEs were reported in the MAUDE database. SVD due to leaflet thrombosis was reported in 30 cases. Most cases (n = 18/30, 60.0%, 95% CI 0.41–0.77) occurred in the first year following TAVR. SVD manifested as either aortic stenosis (n = 16/30, 53.3%, 95% CI 0.34–0.72), or regurgitation (n = 7/30, 23.3%, 95% CI 0.10–0.42), or both (n = 4/30, 13.3%, 95% CI 0.04–0.31). Interventions to address leaflet thrombosis included either escalation of antiplatelet or anticoagulant therapy (n = 9/30, 30.0%, 95% CI 0.15–0.49), valve-in-valve TAVR (n = 5/30, 16.7%, 95% CI 0.06–0.35), or surgery (n = 14/30, 46.7%, 95% CI 0.28–0.66), or their combination. Outcome following leaflet thrombosis included stroke/TIA (n = 3/30, 10.0%, 95% CI 0.02–0.27), cardiogenic shock (n = 2/30, 6.7%, 95% CI 0.01–0.22), and death (n = 9/30, 30.0%, 95% CI 0.15–0.49).

Conclusion: Clinically manifest leaflet thrombosis was associated with serious manifestations that included stroke, cardiogenic shock, and death.

ARTICLE HISTORY Received 27 July 2017; Accepted 28 July 2017

KEYWORDS Anticoagulation; aortic stenosis; leaflet thrombosis; prosthetic valve; TAVR

Introduction

Leaflet thrombosis of transcatheter heart valves is a recently recognized and important mechanism of transcatheter heart valve failure.[1–3] Data from the Assessment of Transcatheter and Surgical Aortic Bioprosthetic Valve Thrombosis and Its Treatment with Anticoagulation (RESOLVE), and Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed with Four-Dimensional Computed Tomography (SAVORY) registries suggest that subclinical leaflet thrombosis, represented by leaflet thickening on computed tomography, is more common with transcatheter valves compared with bioprosthetic surgical valves, and is associated with increased rates of stroke or TIA.[4] However, data on clinical or symptomatic leaflet thrombosis remain limited.[5] Whether clinically manifest leaflet thrombosis has significance beyond peri-TAVR stroke or transient ischemic attacks (TIA) is yet to be elucidated. Specific possibilities include premature structural valve

CONTACT Ankur Kalra, MD, FACP, FACC, FSCAI kalramd.ankur@gmail.com Harrington Heart & Vascular Institute, University Hospitals Cleveland Medical Center, Division of Cardiovascular Medicine, Department of Medicine, Case Western Reserve University School of Medicine, 11100 Euclid Avenue, Mailstop LKS 5038, Cleveland, OH 44106, USA.

Drs. Hafiz and Kalra have contributed equally to this article.
Drs. Kleiman and Popma share senior authorship.

degeneration, central aortic regurgitation, recurrent heart failure, or an increased risk of sudden death.[1]

The Manufacturer and User Facility Device Experience (MAUDE) database houses medical device reports submitted to the U.S. Food and Drug Administration (FDA) by mandatory (manufacturers, importers, and device user facilities) and voluntary (health care professionals, patients, and consumers) reporters, and represents reports of adverse events involving medical devices.[6,7] Although limited by potential selection bias, lack of independent adverse event adjudication, and adverse event underreporting by manufacturers or overreporting by operators, MAUDE provides the opportunity to identify device-related events that may be underrecognized, or previously regarded as infrequent. In this study, we interrogated the MAUDE database to investigate the frequency, management, and outcomes of TAVR-related adverse events due to clinical or symptomatic leaflet thrombosis.

Materials and methods

Data collection

We searched the MAUDE database for all entries between January 2012 and October 2015 with the identifier code, "NPT," which has been designated by the FDA to identify TAVR-related adverse events. Selected adverse event entries were searched further for the terms "leaflet," "central aortic regurgitation," and "aortic stenosis" to capture all events related to leaflet thrombosis causing structural valve dysfunction. These entries were then manually screened one by one to select all cases of leaflet thrombosis that were reported in the study period. When more than one transcatheter valve was deployed in a patient, data were collected for the last valve deployed.

Presentation of leaflet thrombosis (aortic stenosis or regurgitation or mixed valve lesion), mode of diagnosis (echocardiography, computed tomography, surgical explantation, or autopsy), and timing of presentation after TAVR were recorded. Leaflet thrombosis was diagnosed based on acute- or subacute-onset of heart failure or stroke/TIA symptoms with either (1) direct visualization of leaflet thrombosis on echocardiogram, increase in mean gradient > 10 mmHg with no thrombus visible, or regression of elevated mean gradient after oral anticoagulation therapy; or (2) presence of reduced leaflet motion or hypoattenuated leaflet thickening on computed tomography angiogram (CTA); or (3) evidence of device thrombosis at autopsy or via examination of tissue obtained during reoperative surgical aortic valve replacement.[8] Leaflet thrombosis events were stratified based on a recently proposed temporal classification that included a systematic review of published literature: acute (0–3 days after TAVR), subacute (3 days to 3 months after TAVR), late (3 months to 1 year after TAVR), and very late (> 1 year after TAVR).[8] Interventions to address structural valve dysfunction due to leaflet thrombosis, including medical therapy (escalation of antiplatelet or anticoagulant therapy), valve-in-valve TAVR, or surgery were also recorded.

For all adverse event entries of structural valve dysfunction due to leaflet thrombosis, the following outcomes were recorded: stroke or TIA, cardiogenic shock requiring vasopressor or mechanical circulatory support, and death from any cause. Adverse event entries were also stratified by valve type—balloon-expandable (identified by the search terms "Edwards," "Sapien," and "Ascendra") versus self-expanding valves (identified by the search terms "CoreValve," "Medtronic," and "Evolut").

Exclusion criteria

All reports under the "NPT" code category that did not have the term "leaflet dysfunction" were excluded. All cases of structural valve dysfunction caused by procedure-related factors, such as valve embolization or malpositioning, or cases in which structural valve dysfunction could not be classified into either leaflet restriction or malcoaptation (termed "other/unknown") were excluded from the final analysis (Figure 1).

Statistical analysis

Descriptive statistical methods were used to describe medians for continuous variables, and frequency for categorical variables. Data analysis was performed using STATA 14.0 (StataCorp, TX).

Results

Between January 2012 and October 2015, a total of 5691 TAVR-related adverse events were reported in the MAUDE database (Edwards Sapien [Edwards Lifesciences, Irvine, CA, USA] [n = 4252], and Medtronic CoreValve [Medtronic, Inc., Minneapolis, MN, USA] [n = 1437]). Of these, 546 adverse events were segregated based on the pre-specified search terms. Procedure-related structural valve dysfunction (n = 295), and "other/unknown" structural valve dysfunction cases (n = 95) were excluded. The final analysis included 156 adverse events of structural valve dysfunction—leaflet restriction (n = 129), and leaflet malcoaptation (n = 27) (Figure 1).

Structural valve dysfunction due to leaflet thrombosis was reported in 30 cases (Edwards Sapien [Edwards Lifesciences, Irvine, CA, USA] = 20; CoreValve [Medtronic, Inc., Minneapolis, MN, USA] = 10) (Table 1). Most cases (n = 18/30, 60.0%, 95% CI 0.41–0.77) occurred in the first year following TAVR (acute = 4; subacute = 3; late = 11), with variable temporal distribution of cases of very late leaflet thrombosis (n = 12/30, 40.0%, 95% CI 0.23–0.60) (13–60 months) (Figure 2A-2B). Structural valve dysfunction manifested as either aortic stenosis (n = 16/30, 53.3%, 95% CI 0.34–0.72), or regurgitation (n = 7/30, 23.3%, 95% CI 0.10–0.42), or both (n = 4/30, 13.3%, 95% CI 0.04–0.31). The remainder of the three cases of leaflet thrombosis that did not present as either aortic stenosis or regurgitation had clinically manifest stroke/TIA. Recognition of aortic stenosis and regurgitation due to leaflet thrombosis occurred at a mean of 15.5 ± 12.2 months and 10.1 ± 10.9 months after TAVR, respectively. Figure 2C and 2D represent temporal distribution of aortic stenosis and regurgitation due to leaflet thrombosis, respectively. Interventions to address leaflet thrombosis included either escalation of antiplatelet or anticoagulant therapy (n = 9/30, 30.0%, 95% CI 0.15–0.49), valve-in-valve TAVR (n = 5/30, 16.7%, 95% CI 0.06–0.35), or surgery (n = 14/30, 46.7%, 95% CI 0.28–0.66), or their combination. Other interventions included catheter manipulation and aspiration of thrombus (n = 1), balloon aortic valvuloplasty (n = 1), and escalation of diuretic therapy for treatment of

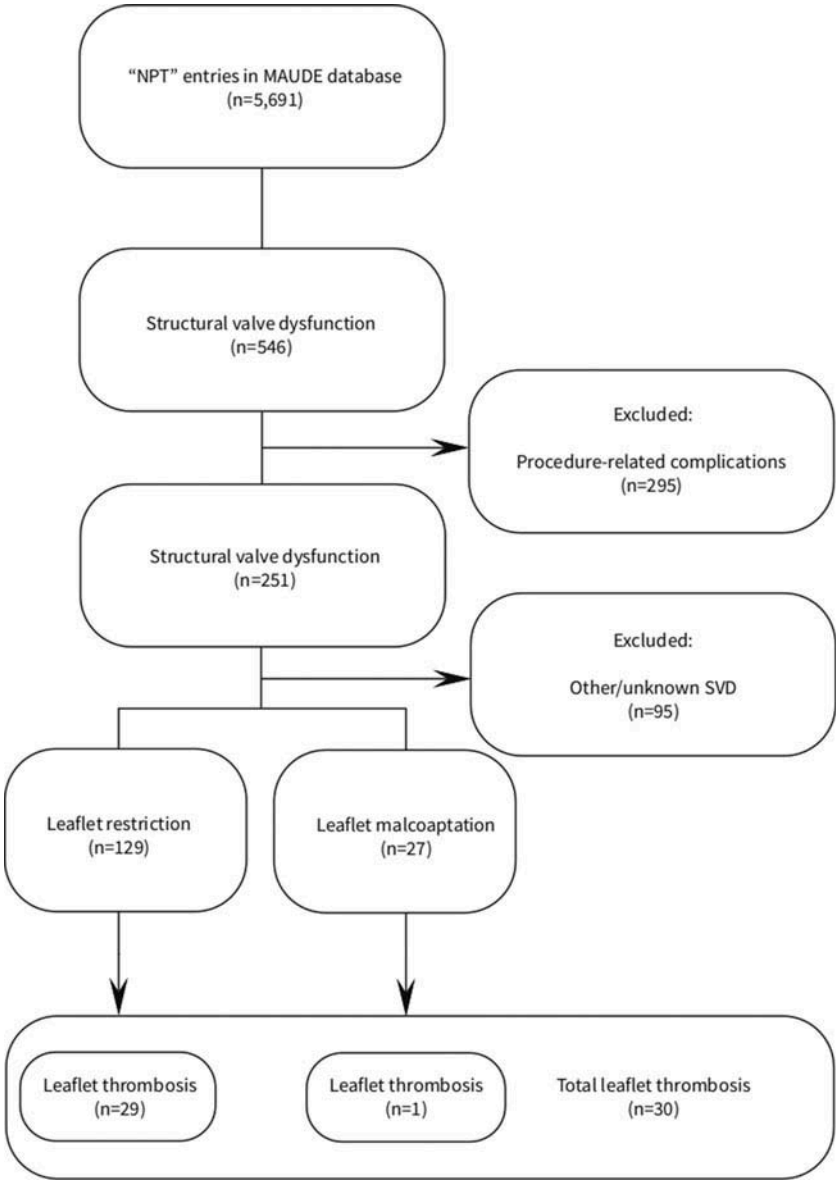

Figure 1. CONSORT flow diagram demonstrating methodology of search for cases of leaflet thrombosis in the MAUDE database. SVD, structural valve dysfunction.

heart failure symptoms (n = 1). Two patients had no intervention performed. Outcome following leaflet thrombosis included stroke/TIA (n = 3/30, 10.0%, 95% CI 0.02–0.27), cardiogenic shock (n = 2/30, 6.7%, 95% CI 0.01–0.22), and death (n = 9/30, 30.0%, 95% CI 0.15–0.49) (Table 2).

Discussion

In this study, clinical or symptomatic leaflet thrombosis occurred in 30 cases, and represented at least 0.53% (95% CI 0.00–0.01) of all TAVR-related adverse events that were reported in the MAUDE database. Most cases (18/30, 60.0%) of leaflet thrombosis occurred within the first year following TAVR, and presented as either aortic stenosis (53.3%) or regurgitation (23.3%). Although prosthetic valve degeneration more commonly presents as regurgitation due to leaflet calcification and decreased leaflet mobility, prosthetic valve thrombosis may also be associated with new-onset regurgitation.[10] In a study by Egbe and colleagues comparing clinical and echocardiographic predictors of bioprosthetic heart valve thrombosis and degeneration in 397 consecutive explanted bioprostheses, 11% (5/46) cases of prosthetic heart valve thrombosis presented with isolated regurgitation.[11] In cases that did not present with either aortic stenosis or regurgitation (3/30, 10.0%), the manifesting symptoms were that of a stroke in all 3 patients. Interventions to address clinical leaflet thrombosis included either medical therapy (escalation of antiplatelet or anticoagulant therapy) (n = 8/30, 26.7%), valve-in-valve TAVR (n = 3/30, 10.0%), or surgery (n = 14/30, 46.7%). Although infrequently reported, clinically manifest leaflet thrombosis was associated with a poor prognosis—stroke/TIA in 10.0% (3/30) cases, cardiogenic shock in 6.7% (2/30) cases, and death in 30.0% (9/30) cases. Death occurred in 7/9 cases despite interventions to address clinical leaflet thrombosis (escalation of medical therapy = 1; post balloon aortic valvuloplasty = 1; valve-in-valve TAVR = 3; surgery = 3).

Table 1. Leaflet thrombosis following transcatheter aortic valve replacement: Presentation, temporal classification, type of intervention, and outcome.

Presentation	Number of cases (%)	Duration of onset after TAVR (months) (mean ± SD)	Mode of diagnosis[a]	Temporal classification[b]	Valve type	Intervention[c]	Outcome	Mode of diagnosis if death occurred[a]
Aortic stenosis	16/30 (53.3%)	15.5 ± 12.2	Echo (n = 5); surgical explantation (n = 7); autopsy (n = 2); CT: (n = 1); unknown (n = 1)	Acute (n = 0); subacute (n = 1); late (n = 9); very late (n = 6)	Balloon-expandable (n = 12); self-expanding (n = 4)	Wire manipulation (n = 0); post BAV (n = 1); ViV TAVR (n = 1); surgery (n = 7); medical therapy (n = 6); no intervention (n = 1)	Cardiogenic shock (n = 0); stroke (n = 1); death (n = 3)	Echo (n = 1); autopsy (n = 2)
Aortic regurgitation	7/30 (23.3%)	10.1 ± 10.9	Echo (n = 2); surgical explantation (n = 4); autopsy (n = 0); angiography (n = 1)	Acute (n = 2); subacute (n = 1); late (n = 1); very late (n = 3)	Balloon-expandable (n = 5); self-expanding (n = 2)	Wire manipulation (n = 1); post BAV (n = 0); ViV TAVR (n = 1); surgery (n = 4); medical therapy (n = 0); no intervention (n = 1)	Cardiogenic shock (n = 1); stroke (n = 0); death (n = 3)	Echo (n = 1); Surgical explantation (n = 2)
Mixed	4/30 (13.3%)	21.3 ± 26.6	Echo (n = 1); surgical explantation (n = 1); autopsy (n = 1); CT (n = 1)	Acute (n = 0); subacute (n = 1); late (n = 1); very late (n = 2)	Balloon-expandable (n = 1); self-expanding (n = 3)	Wire manipulation (n = 0); post BAV (n = 0); ViV TAVR (n = 1); surgery (n = 2); medical therapy (n = 1); no intervention (n = 0)	Cardiogenic shock (n = 0); stroke (n = 0); death (n = 2)	Echo (n = 1); autopsy (n = 1)
No stenosis or regurgitation	3/30 (10%)	7.3 ± 12.7	Echo (n = 1); surgical explantation (n = 1); autopsy (n = 1); unknown (n = 0)	Acute (n = 2); subacute (n = 0); late (n = 0); very late (n = 1)	Balloon-expandable (n = 2); self-expanding (n = 1)	Wire manipulation (n = 0); post BAV (n = 0); ViV TAVR (n = 0); surgery (n = 1); medical therapy (n = 1); no intervention (n = 1)	Cardiogenic shock (n = 1); stroke (n = 2); death (n = 1)	Autopsy (n = 1)

Notes. [a]Modes of diagnoses were either echocardiography, surgical explantation or autopsy; in a series of 13 cases of prior TAVR who underwent a post-mortem examination or who had a TAVR device surgically explanted, four cases of leaflet thrombosis were diagnosed only on pathological examination.[9]
[b]Leaflet thrombosis was stratified according to a recently published temporal classification, based on a systematic review of published literature.[8]
[c]More than one intervention was performed in some patients to address leaflet thrombosis.
BAV, balloon aortic valvuloplasty; TAVR, transcatheter aortic valve replacement; ViV, valve-in-valve

With expanding indications for TAVR, there has been an exponential increase in the number of TAVR procedures in the U.S., with 24,808 TAVRs performed in 2015, compared with 4627 procedures in 2012.[12] The frequency of leaflet thrombosis in prior studies by Latib and co-workers and Córdoba-Soriano and co-workers was low in comparison with the frequency reported in the two recent registry studies (7% in the Danish registry, and 13% in the RESOLVE and SAVORY registries).[3,13–15] However, a diagnosis of leaflet thrombosis in the latter two studies also included the finding of hypoattenuated leaflet thickening on multidetector computed tomography without any clinical manifestations, believed to represent subclinical leaflet thrombosis. In the study by Latib and colleagues of 4266 patients undergoing TAVR in 12 centers, of the 26 (0.61%) prosthetic valve thrombosis cases diagnosed by echocardiography, deaths occurred in 3 patients (11.5%). In our study, 9/30 (30%) patients died—the diagnosis of leaflet thrombosis in 7/9 (77.8%) patients was confirmed by either pathological examination of surgically explanted transcatheter valve (n = 3) or autopsy (n = 4) (Tables 1 and 2). While these data do not provide the frequency of these events, and undoubtedly the clinical events often led to the recognition of leaflet thrombosis, they are useful in that they establish definitive evidence of its occurrence.

This study has several inherent limitations commonly seen with data extraction from a self-reported, publicly available database with regard to ascertainment bias and lack of independent verification of each report. The adverse event entries in the MAUDE database only report the index adverse event, and further clinical information with regard to final management of the adverse event. If additional details become available later, they are entered under the identical "MDR Report Key Number," enabling data collation. However, time lapse and interim management decisions between the occurrence of adverse events and final interventions to address them are not available. For example, we

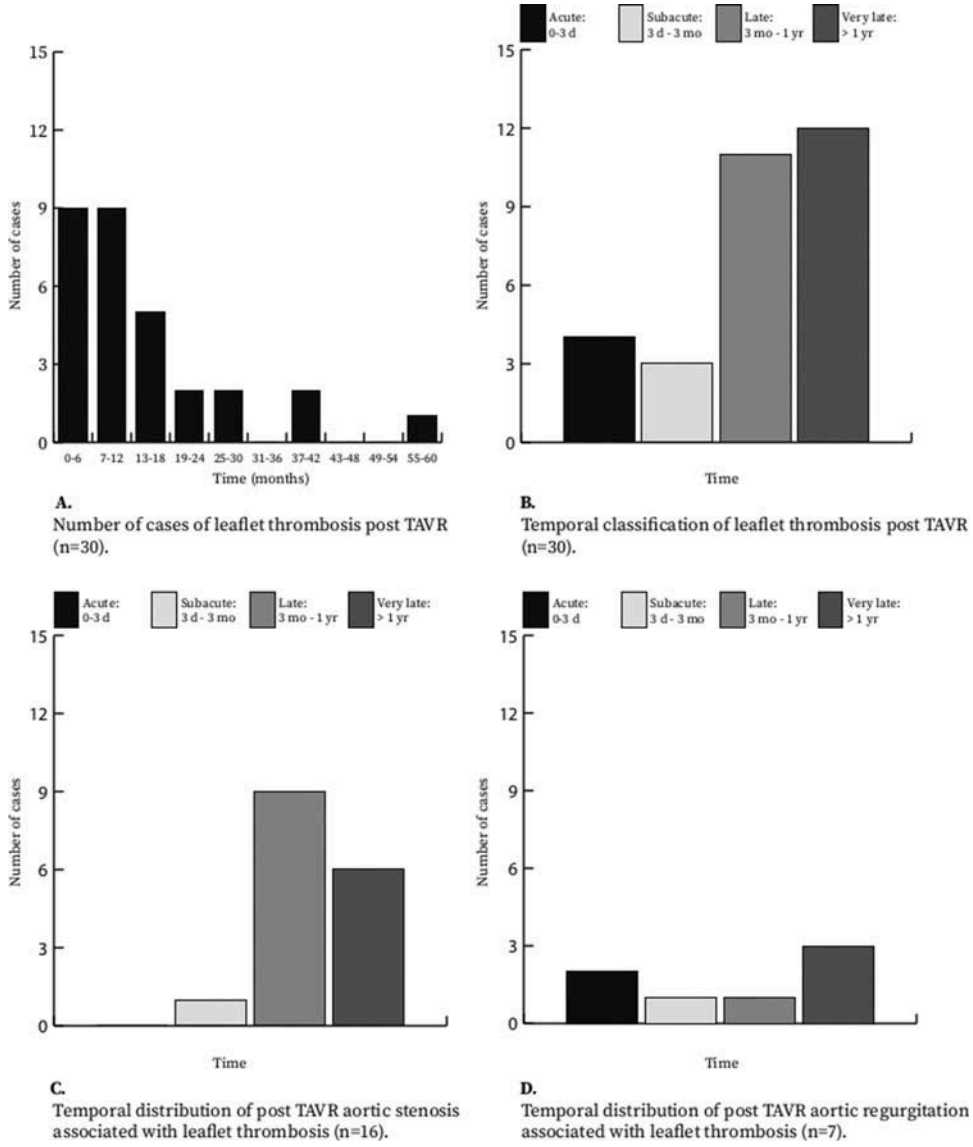

Figure 2. Number of cases of leaflet thrombosis, temporal classification of leaflet thrombosis, and aortic stenosis and regurgitation due to leaflet thrombosis post-TAVR.

reported that more patients had surgery as a final intervention after leaflet thrombosis was diagnosed, compared with escalation of antiplatelet of anticoagulant therapy (47% vs. 30%). Whether escalation of medical therapy was attempted prior to surgery or valve-in-valve TAVR cannot be ascertained. Alternatively, it is plausible that a different diagnosis (for e.g. infective endocarditis) other than leaflet thrombosis was considered in patients that had surgery. In addition, there is surely incomplete capture of all events of leaflet thrombosis due to lack of standard definitions during the study period, leading to missed diagnoses, and under-reporting by manufacturers. However, all adverse events in the MAUDE database were reported by industry representatives, conforming to device-related event reporting requirements. Although our search terms did not include "stroke/TIA" to capture cases of leaflet thrombosis that may have presented as stroke or TIA, the broader search term "leaflet" was likely successful in capturing such adverse event entries (3/3 patients without aortic stenosis or regurgitation had stroke as the manifesting symptom). Also, there was uncertainty with regard to appropriate adjudication of stroke/TIA events in the TAVR population due to leaflet thrombosis by using "NPT" and "stroke/TIA" as a search strategy for MAUDE interrogation.

Despite these limitations and our obvious inability to ascertain the frequency of leaflet thrombosis using this database, this study demonstrates clearly that clinical or symptomatic leaflet thrombosis following TAVR should not be regarded casually as a benign event, and needs to be addressed seriously.

Conclusion

Clinical or symptomatic leaflet thrombosis is an uncommon but serious adverse event following TAVR that portends a grave prognosis. In cases reported in the FDA MAUDE database, most occurred in the first year following TAVR, presented as either aortic stenosis or regurgitation, and required surgery in 47% of cases. Clinically manifest leaflet thrombosis in the MAUDE database was associated with serious clinical

Table 2. Case description of patients with clinical or symptomatic leaflet thrombosis following transcatheter aortic valve replacement.

#	Leaflet thrombosis: clinical presentation	Diagnostic modality	Management	Adverse clinical event (stroke/TIA, cardiogenic shock and/or death)	Time to clinical event	Additional findings & event summary
1	Heart failure	Echocardiogram	Diuretics for HF	None reported	N/A	1 month post TAVR; new-onset heart failure due to moderate central and trace paravalvular regurgitation; intra-procedure cine and echocardiographic images reviewed by manufacturer suggested presence of an echogenic lesion in the non-coronary sinus of Valsalva & left coronary cusp; leaflet dysfunction consistent with bulky calcification or thrombus.
2	Symptomatic; increasing gradients on follow-up echocardiograms	CT; TEE	Valve-in-valve TAVR	None reported	N/A	1 year post TAVR; patient became symptomatic; serial echocardiograms demonstrated gradual increase in transaortic gradients. On CT, the leaflets were thickened with possibly some thrombotic material at the base of the left and right prosthetic leaflets. Imaging review by the manufacturer summarized that the TEE was suggestive of the presence of thrombus, likely attached to the aortic aspect of the Sapien (Edwards Lifesciences, Irvine, CA, USA) valve.
3	Severe central AI immediately post TAVR on echocardiogram	Echocardiogram & angiogram	Catheter manipulation & aspiration	None reported	N/A	20–30 minutes post TAVR; severe central AI was noted; pigtail catheter was used to manipulate the non-moving non-coronary leaflet. An angiogram showed a perivalvular aortic hematoma with thrombus in the Sapien (Edwards Lifesciences, Irvine, CA, USA) valve. The physician attempted to remove the clot with multipurpose and AL1 guiding catheters, and a small amount was removed as seen on the catheter tip upon removal. During the procedure, the ACT was above 250 seconds. A TEE 2 days post TAVR showed no thrombus.
4	Symptomatic; post procedure hemodynamic instability; same day echocardiogram showed moderate-severe AI	Explant: stuck leaflet; there were some blood clots affixed to the aortic side of the leaflets	SAVR	**Cardiogenic shock** and **death**	Death occurred several weeks post TAVR	Same day presentation; 23-mm Sapien (Edwards Lifesciences, Irvine, CA, USA) valve was positioned and implanted in a 60:40 ventricular position, with the non-coronary cusp side slightly more ventricular compared with the left coronary side. The final result was mild-moderate regurgitation. Later during SAVR, the valve was noted to be adequately positioned within the annulus, but was explanted and native bicuspid valve resected.
5	Severe AS on follow-up imaging at 6 months	Explant: thrombus on outflow	SAVR	None reported	N/A	8 months post valve-in-valve TAVR in a stenotic non-Medtronic (Medtronic, Inc., Minneapolis, Minnesota) bioprosthetic valve; both valves were explanted. At 6 months post-procedure visit, an echocardiographic evaluation determined that there was severe aortic stenosis.
6	Chest pain and heart failure	Explant: thrombotic-appearing host tissue filled and stiffened all leaflets on the outflow	SAVR	**Death**	Death occurred 13 months post TAVR	11 months post TAVR, patient exhibited acute chest pain, and moderate aortic regurgitation on cardiac catheterization. A TEE confirmed moderate AI. Two months later, patient developed congestive heart failure symptoms and was found to have significant prosthetic aortic insufficiency. Death occurred 5 days post reoperation due to right-sided heart failure. No autopsy was performed.
7	Severe AS on follow-up with a 58 mmHg mean gradient	Echocardiogram	DAPT + warfarin initiated	None reported	N/A	6 months post TAVR, the leaflets were noted to be thickened, and it was determined that the patient had valve thrombosis; the patient's cardiologist had taken the patient off clopidogrel, 30 days post TAVR.
8	Symptoms and signs: shortness of breath, confusion, pulmonary edema and electrocardiographic changes.	TEE: thrombi around the sinuses of the aortic valve; two of the leaflets were fused	Anticoagulation	**Hemorrhagic CVA** and **death**	7 months post TAVR	7 months post TAVR; CT of the brain showed a linear band of hypoattenuation in the left parietal lobe, suggestive of an acute infarct. MRI of the brain showed acute infarcts in the left parietal lobe as well as left frontal lobe. TEE revealed vegetation noted on the mitral valve. It was reported that there was a recent Streptococcal endocarditis of the mitral valve, and the cerebral emboli were plausibly its sequela.

(*Continued*)

Table 2. Case description of patients with clinical or symptomatic leaflet thrombosis following transcatheter aortic valve replacement. (Continued).

#	Leaflet thrombosis: clinical presentation	Diagnostic modality	Management	Adverse clinical event (stroke/TIA, cardiogenic shock and/or death)	Time to clinical event	Additional findings & event summary
9	Symptomatic; severe AS on echocardiogram with a mean gradient of 70 mmHg	Echocardiogram: one leaflet of the valve was not functioning	Anticoagulation	None reported	N/A	2 years and 3 months post TAVR, severe AS was noted. The Sapien XT (Edwards Lifesciences, Irvine, CA, USA) valve was initially implanted inside a 23-mm Mitroflow (Sorin Group USA Inc., Arvada, CO, USA) valve with a final result of a 30 mmHg mean gradient. The patient was asymptomatic at that time. No other treatment was provided.
10	Symptomatic; chest pain and shortness of breath. Severe AS on echocardiogram; mean gradient 67 mmHg	Echocardiogram	Anticoagulation with warfarin	None reported	N/A	8 months after the implantation of a 26-mm Sapien XT (Edwards Lifesciences, Irvine, CA, USA) valve, the patient was re-admitted to the hospital with symptoms. It was concluded that there may be a thrombus on the valve. The patient was transitioned to warfarin with plans to be reevaluated in 3 months.
11	Heart failure; severe AI on TEE	TEE: markedly thickened functional non-coronary cusp and left coronary cusp > right coronary cusp	Valve-in-valve TAVR	**Death**	15 months post TAVR	15 months post TAVR, TEE revealed mild-moderate paravalvular leak, mild-moderate central AI, and thickened Sapien (Edwards Lifesciences, Irvine, CA, USA) valve leaflets; readmitted 2 months later with severe AI and heart failure. A 31 mm CoreValve® (Medtronic, Inc., Minneapolis, MN, USA) was implanted; the patient died due to heart and multiple organ failure on postoperative day 10. Manufacturer conclusion after review of imaging data: "Thickening of the leaflet suggested either structural valve deterioration or non-structural dysfunction (pannus formation) or valve thrombus. Differentiation among these would necessitate either visual inspection during reoperation or autopsy."
12	Chest pain; severe AS on TTE; mean gradient 72 mmHg	CT: extensive nearly symmetric aortic valve thickening Explant: thrombotic occlusion of Sapien XT (Edwards Lifesciences, Irvine, CA, USA) valve	Balloon aortic valvuloplasty	**Death**	16 months post TAVR	16 months post TAVR; a cardiac CT reported an extensive, nearly symmetric aortic valve thickening. Post CT cardiac arrest; balloon aortic valvuloplasty was performed, and Impella® (Abiomed, Inc., Danvers, MA, USA) placed. Patient died from cardiopulmonary failure. Explant pathology report: thrombotic occlusion of Sapien XT (Edwards Lifesciences, Irvine, CA, USA) valve by extensive fibrin-platelet thrombus involving the three prosthetic sinuses of Valsalva; all three prosthetic leaflets were stiff and covered by thick, tan-red thrombus on the aortic surface; the right coronary cusp was folded and retracted secondary to thrombus deposition.
13	Heart failure, found to have severe AI with decreased EF	Explant: thrombotic material on the device frame	SAVR	None reported	N/A	Over the first year after device implant, the patient developed severe aortic regurgitation. Patient was receiving dual antiplatelet therapy from the time of the device implant until reoperation.
14	Recurrent heart failure	Explant: thrombotic material on the device frame	SAVR + CABG	None reported	N/A	Over a 5-year period after the device implant, the patient developed severe aortic stenosis and progressive coronary artery disease, resulting in cardiac decompensation. Patient had an uneventful postoperative course.
15	Dyspnea	Explant: thrombotic material on Sapien XT (Edwards Lifesciences, Irvine, CA, USA) leaflets causing stenosis	Valve-in-valve TAVR, followed by SAVR	None reported	N/A	2 years and 3 months post TAVR, stenosis of the aortic valve was diagnosed. Self-expanding valve-in-valve was implanted in Sapien (Edwards Lifesciences, Irvine, CA, USA) valve. During the valve-in-valve procedure, the balloon pushed the thrombotic material into the coronary ostia, totally occluding the right coronary artery, necessitating open sternotomy with SAVR.
16	Symptomatic, severe AS, mean gradient of 70 mmHg	Explant: thrombus formation was observed	SAVR	None reported	N/A	2 years post TAVR; patient was on dual platelet therapy after the implant. It was noted that two leaflets were not moving.
17	Dyspnea and "increased mean gradient"	Explant: device thrombosis with pannus restricting leaflet mobility	SAVR	None reported	N/A	12 months post TAVR; no subsequent adverse patient effects were reported following surgical device replacement. Assessment revealed thickened valve leaflets covered with thrombotic host tissue and pannus along the frame, and partially along the free margins.

(*Continued*)

Table 2. Case description of patients with clinical or symptomatic leaflet thrombosis following transcatheter aortic valve replacement. (Continued).

#	Leaflet thrombosis: clinical presentation	Diagnostic modality	Management	Adverse clinical event (stroke/TIA, cardiogenic shock and/or death)	Time to clinical event	Additional findings & event summary
18	Angina and "very high gradient"	Explant: thrombus was observed on the outflow aspect on all three leaflets	SAVR	None reported	N/A	2 weeks post implant of a Sapien XT valve inside a St. Jude Epic valve (St. Jude Medical, Inc., St. Paul, MN, USA). Thrombi restricted mobility in all three leaflets and led to stenosis.
19	Hemodynamic instability and heart failure	Explant: thrombi were observed on all three leaflets on the outflow aspect	SAVR	**Cardiogenic shock**	N/A	TAVR inside a degenerated surgical Sorin (LivaNova, PLC, London, UK) valve; immediate post-procedure presentation.
20	Chest pain, shortness of breath, abdominal pain, and heart failure; echocardiogram: mean gradient of 31 mmHg	Autopsy + explant: leaflets were stiff due to coagulated blood on the outflow	None	**Death**	42.5 months post TAVR	42 months post TAVR; pannus noted in inflow and outflow.
21	Increasing valve gradients post TAVR	Explant: all three leaflets covered by fibrin/thrombus	SAVR	None reported	N/A	13 months post TAVR; valve explanted.
22	AI: moderate-severe	Explant: thrombotic material/ vegetation was observed	SAVR	None reported	N/A	30 months post TAVR; thrombotic deposits appeared to be sufficiently severe to be largely responsible for the reported insufficiency. There is no specific evidence from the histology analysis to suggest reason(s) for the development of thrombosis.
23	Severe AS on follow-up over 6–12 months post TAVR	Explant: thrombus	SAVR	None reported	N/A	6 months post TAVR; increasing transaortic gradients. Explant revealed immobile leaflets due to the presence of a brown thrombotic host tissue and pannus.
24	Stroke followed by death	Autopsy: limited mobility of all leaflets due to fibrin thrombus	None	**CVA** and **death**	Death 15 days post TAVR	1 hour post implant, the patient lost sensation and movement on his left side. A CT scan demonstrated a left occipital cerebral infarction. Autopsy showed thrombus most significant on the right coronary cusp.
25	Severe AS: mean gradient 43 mmHg, 1 month post TAVR	Autopsy: thrombus on first and second THVs	Valve-in-valve TAVR	**Death**	6.5 months after 1st TAVR; 15 days after 2nd valve-in-valve TAVR	6 months post TAVR; severe AS (mean gradient increased to 50 mmHg) and moderate AI. Autopsy revealed the first bioprosthetic valve with thrombus in the area of the valve leaflets, most significant on the non-coronary leaflet. The second bioprosthetic valve had mural thrombus on the aortic surface involving the right and the non-coronary leaflets, which limited their mobility.
26	Increased gradients on follow-up echocardiogram post TAVR	CT: thrombus on two leaflets	Anticoagulation with warfarin	None reported	N/A	1.5 months post TAVR; CT performed which confirmed leaflet thrombosis.
27	Severe AS: mean gradient 55 mmHg; asymptomatic	Clinical suspicion; diagnostic modality not reported	Anticoagulation	None reported	N/A	42 months post TAVR; severe AS; there was a reduction in the gradient post anticoagulation.
28	CVA	Echocardiogram + CT: thickened immobile leaflet suggestive of very late thrombosis	Anticoagulation	**CVA**	22 months post TAVR	22 months post TAVR, the patient presented with a CVA; had been on aspirin monotherapy; post initiation of anticoagulation, some regression was noted on serial echocardiographic imaging.
29	Dyspnea	CT: leaflet thickening and thrombus seen	Aspirin + clopidogrel for 6 months	None reported	N/A	1 year post TAVR hospitalization; CT showed homogeneous thickening of all three leaflets, identified as thrombus, and considered to be the cause of dyspnea.
30	Heart failure	Autopsy: diffuse fibrin-platelet thrombus adhered to the valve cusps of the non-Medtronic bioprosthetic valve	Valve-in-valve TAVR with anticoagulation for 15 months; SAVR 2 months post valve-in-valve TAVR	**Death**	Death occurred 17 months post valve-in-valve TAVR	4 years post TAVR; severe AI on angiography; non-Medtronic valve implanted in Medtronic (Medtronic, Inc., Minneapolis, MN, USA) valve (valve-in-valve); 17 months post valve-in-valve, echocardiogram demonstrated high gradients, thickened leaflets, and mild-to-moderate central AI.

Note. ACT, activated clotting time; AI, aortic insufficiency; AS, aortic stenosis; CVA, cerebrovascular accident; CT, computed tomography; MRI, magnetic resonance imaging; TAVR, transcatheter aortic valve replacement; TEE, transesophageal echocardiogram; THV, transcatheter heart valve; TIA, transient ischemic attack; TTE, transthoracic echocardiogram.

manifestations that included stroke, cardiogenic shock, and death. As indications for TAVR expand to include patients at intermediate and perhaps low risk for perioperative mortality following surgery, an early diagnosis of leaflet thrombosis may be crucial for planning appropriate management and optimizing clinical outcome of this patient subset.

Key messages

Leaflet thrombosis of transcatheter heart valves is a recently recognized and important mechanism of transcatheter heart valve failure. Whether clinically manifest leaflet thrombosis has significance beyond peri-TAVR stroke or transient ischemic attacks (TIA) is yet to be elucidated.

In this study, clinically manifest leaflet thrombosis was associated with serious clinical manifestations that included stroke, cardiogenic shock, and death.

Clinical or symptomatic leaflet thrombosis following TAVR should not be regarded casually as a benign event, and needs to be addressed seriously. As indications for TAVR expand, an early diagnosis of leaflet thrombosis may be crucial for planning appropriate management and optimizing clinical outcome.

Disclosure statements

Dr. Deepak L. Bhatt discloses the following relationships: Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute (including for serving as DMC Chair for the PORTICO trial funded by St. Jude, now Abbott), Mayo Clinic, Mount Sinai School of Medicine, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, *Clinical Trials and News*, ACC.org), Belvoir Publications (Editor in Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott); Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, PLx Pharma, Takeda.

Dr. Reardon reports personal fees from Medtronic, Inc.

Dr. Popma discloses the following relationships: Institutional Grants: Medtronic, Inc., Boston Scientific, Abbott Vascular; Medical Advisory Board: Boston Scientific, Abbott Vascular; Consultant: Direct Flow Medical.

None of the other authors report any conflicts of interest or have any disclosures to make.

ORCID

Abdul Moiz Hafiz http://orcid.org/0000-0003-0668-5015
Ankur Kalra http://orcid.org/0000-0003-0080-1660
Colin T. Phillips http://orcid.org/0000-0002-6543-0234
Deepak L. Bhatt http://orcid.org/0000-0002-1278-6245

References

1. Mylotte D, Andalib A, Thériault-Lauzier P, et al. Transcatheter heart valve failure: a systematic review. *Eur Heart J*. 2015;36:1306–1327. doi:10.1093/eurheartj/ehu388.
2. Holmes DR, Mack MJ. Uncertainty and possible subclinical valve leaflet thrombosis. *N Engl J Med*. 2015;373:2080–2082. doi:10.1056/NEJMe1511683.
3. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med*. 2015;373:2015–2024. doi:10.1056/NEJMoa1509233.
4. Chakravarty T, Søndergaard L, Friedman J, et al. for the RESOLVE; SAVORY investigators. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet*. 2017;389:2383–2392. doi:10.1016/S0140-6736(17)30757-2.
5. Jose J, Sulimov DS, El-Mawardy M, et al. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics, and treatment outcomes. *JACC Cardiovasc Interv*. 2017;10:686–697. doi:10.1016/j.jcin.2017.01.045.
6. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm#fn1. Accessed April 30, 2017.
7. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/ucm127891.htm. Accessed April 30, 2017
8. Dangas GD, Weitz JI, Giustino G, et al. Prosthetic heart valve thrombosis. *J Am Coll Cardiol*. 2016;68:2670–2689. doi:10.1016/j.jacc.2016.09.958.
9. Mangione FM, Jatene T, Gonçalves A, et al. Leaflet thrombosis in surgically explanted or post-mortem TAVR valves. *JACC Cardiovasc Imaging*. 2017;10:82–85. doi:10.1016/j.jcmg.2016.11.009.
10. Habets J, Budde RP, Symersky P, et al. Diagnostic evaluation of left-sided prosthetic heart valve dysfunction. *Nat Rev Cardiol*. 2011;8:466–478. doi:10.1038/nrcardio.2011.71.
11. Egbe AC, Pislaru SV, Pellikka PA, et al. Bioprosthetic valve thrombosis versus structural failure: clinical and echocardiographic predictors. *J Am Coll Cardiol*. 2015;66:2285–2294. doi:10.1016/j.jacc.2015.09.022.
12. Grover FL, Vemulapalli S, Carroll JD, et al. STS/ACC TVT Registry. 2016 annual report of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy registry. *J Am Coll Cardiol*. 2017;69:1215–1230. doi:10.1016/j.jacc.2016.11.033.
13. Latib A, Naganuma T, Abdel-Wahab M, et al. Treatment and clinical outcomes of transcatheter heart valve thrombosis. *Circ Cardiovasc Interv*. 2015;8:e001779. doi:10.1161/CIRCINTERVENTIONS.114.001779.
14. Córdoba-Soriano JG, Puri R, Amat-Santos I, et al. Valve thrombosis following transcatheter aortic valve implantation: a systematic review. *Rev Esp Cardiol (Engl Ed)*. 2015;68:198–204. doi:10.1016/j.recesp.2014.10.004.
15. Hansson NC, Grove EL, Andersen HR, et al. Transcatheter aortic valve thrombosis: incidence, predisposing factors, and clinical implications. *J Am Coll Cardiol*. 2016;68:2059–2069. doi:10.1016/j.jacc.2016.08.010.