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STATE-OF-THE-ART REVIEW

Thrombotic Risk and Antithrombotic Strategies After Transcatheter Mitral Valve Replacement

Matteo Pagnesi, MD,[a] Francesco Moroni, MD,[a] Alessandro Beneduce, MD,[a] Francesco Giannini, MD,[b] Antonio Colombo, MD,[b] Giora Weisz, MD,[c,d] Azeem Latib, MD[c,e]

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CME/MOC/ECME Objectives for This Article: Upon completion, the reader should be able to: 1) recognize the thrombotic risk after TMVR; and 2) discuss the antithrombotic treatment strategies after TMVR.

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From the [a]Cardio-Thoracic-Vascular Department, San Raffaele Scientific Institute, Milan, Italy; [b]Interventional Cardiology Unit, GVM Care and Research Maria Cecilia Hospital, Cotignola, Italy; [c]Department of Cardiology, Montefiore Medical Center, Bronx, New York; [d]Cardiovascular Research Foundation, New York, New York; and the [e]Division of Cardiology, Department of Medicine, University of Cape Town, Cape Town, South Africa. Dr. Latib has served on the advisory board for Medtronic, Abbott Vascular, and Cardiovalve. Dr. Weisz has served on the medical advisory board for Corindus, Eco Fusion, Filterlex, Medivizor, and Trisol; and has received institutional research grants from Abbott Vascular, Corindus, Cardiovascular Systems, Inc., CSL Behring, RenalGuard, and Svelte. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Matteo Pagnesi, MD,[a] Francesco Moroni, MD,[a] Alessandro Beneduce, MD,[a] Francesco Giannini, MD,[b] Antonio Colombo, MD,[b] Giora Weisz, MD,[c,d] Azeem Latib, MD[c,e]

ABSTRACT

Severe mitral regurgitation (MR) is fairly common in the general population and is associated with significant morbidity and mortality. Although surgical mitral valve (MV) repair and replacement are well established treatment options for MV disease, as much as one-half of patients with severe, symptomatic MR are not referred for surgery due to prohibitive procedural risk. Novel transcatheter alternatives are therefore being developed to provide an alternative treatment for these patients. A growing experience with transcatheter MV replacement (TMVR) strategies is accumulating and promising early results have been reported. However, the risk of transcatheter heart valve (THV) thrombosis seems to be relevant after TMVR, potentially higher than that observed after transcatheter aortic valve replacement, and routine anticoagulant therapy appears to be necessary to mitigate this risk. Hereafter, the authors: 1) review available evidence on thrombotic risk after TMVR (including new dedicated THVs for native MV, valve-in-valve, valve-in-ring, and valve-in-mitral annular calcification); and 2) discuss the antithrombotic treatment strategies after TMVR.
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Mitral regurgitation (MR) is a fairly common valve disease in developed countries, affecting 1.7% of the general population, with its prevalence increasing in more advanced ages, reaching up to approximately 10% in subjects >75 years of age (1,2). Independently from the etiology, untreated symptomatic severe MR carries a dismal prognosis, with mortality reaching up to 50% and 90% of surviving patients being hospitalized for decompensated heart failure at 5-year follow-up (3). Surgical mitral valve (MV) repair represents the first-line therapeutic option in patients with severe symptomatic MR, particularly in cases of degenerative MR and high likelihood of successful repair; surgical MV replacement is an alternative to repair when MV intervention is indicated and the likelihood of successful and durable repair is low (4,5). However, up to one-half of patients with severe symptomatic MR are not referred to surgery, mainly due to prohibitive surgical risk (6). Therefore, less invasive transcatheter techniques have been developed over the last decade (7). Although a consolidated experience nowadays exists for MV repair (8), a growing experience with transcatheter MV replacement (TMVR) has been accumulated over the last few years, with a number of novel dedicated transcatheter heart valves (THVs) entering the clinical scenario (9). Furthermore, transcatheter approaches represent a new treatment option in patients with degenerated bioprostheses (valve-in-valve [ViV]), failed annuloplasty rings (valve-in-ring [ViR]), and severe mitral annular calcification (valve-in-mitral annular calcification [ViMAC]) at high risk for conventional MV surgery (10–12). Eventually, all these subjects treated with percutaneous bioprostheses, similar to surgical patients, are exposed to an increased risk of valve thrombosis and thromboembolic events. Although many therapeutic regimens have been proposed, currently no evidence-based antithrombotic treatment can be recommended. Aim of the present review is to provide an updated picture of current evidence concerning thrombotic risk after TMVR (new dedicated THVs for native MV, ViV, ViR, and ViMAC), and discuss the antithrombotic treatment strategies in this setting.

THROMBOTIC RISK AND ANTITHROMBOTIC STRATEGIES AFTER SURGICAL BIOPROSTHETIC MV REPLACEMENT

Decades of clinical experience have led to consolidated practice in the management of thromboembolic risk after surgical MV replacement, and current surgical practice provides potential lessons for the newly developed transcatheter options. The risk of thromboembolic events is increased in the early postoperative period after surgical bioprosthetic valve replacement (13,14). Early observational experience suggested an overall risk of thromboembolic events of approximately 2.3% per year after aortic or mitral bioprosthesis implantation, with the large majority of events occurring in the first 90 days (14). More recent

ABBREVIATIONS AND ACRONYMS

CT = computed tomography

INR = international normalized ratio

MR = mitral regurgitation

MV = mitral valve

TAVR = transcatheter aortic valve replacement

THV = transcatheter heart valve

TMVR = transcatheter mitral valve replacement

ViMAC = valve-in-mitral annular calcification

ViR = valve-in-ring

ViV = valve-in-valve

VKA = vitamin K antagonist

data from the large Society of Thoracic Surgeons Adult Cardiac Surgery National Database reported a very low rate of embolic events at 90 days (0.9%) after bioprosthetic aortic valve replacement, showing also a significantly reduced risk of death (relative risk reduction 20%) and embolic events (relative risk reduction 48%) among patients treated with aspirin plus warfarin compared with aspirin-only therapy (15). Furthermore, prolonging duration of anticoagulation up to 6 months after bioprosthetic aortic valve replacement was associated with improved survival and lower incidence of stroke and thromboembolic events, albeit at the expense of higher bleeding events (16). Although no robust evidence on bioprosthetic MV replacement exists, the risk of mitral bioprosthesis thrombosis seems to be higher to that observed for aortic bioprosthetic valves (17–19), and oral anticoagulation with vitamin K antagonist (VKA) after surgery was associated with a lower risk of thromboembolic events (14).

The rationale for anticoagulation in the first months after bioprosthesis implantation is to decrease the risk of thromboembolic events until the prosthetic valve is fully endothelialized (5); furthermore, local blood flow perturbations around the valve prosthesis (that could be even more relevant in the mitral position compared with the aortic one) and patient-related risk factors (atrial fibrillation, suboptimal anticoagulation, history of prior thromboembolic events, left ventricular dysfunction, known hypercoagulable condition) may play a crucial pathogenetic role in bioprosthetic valve thrombosis (18,20). Of note, as a result of atrial manipulation in patients with long-standing MR, the incidence of new onset atrial fibrillation is particularly high after MV surgery (21), thus increasing the risk of postprocedural thromboembolic events. Despite the lack of evidence from randomized controlled trials, current European and American guidelines (4,5) recommend the use of oral anticoagulation with a VKA for 3 months and 3 to 6 months, respectively, after surgical bioprosthetic MV replacement (**Table 1**). The need for anticoagulant therapy must be carefully balanced with the risk of bleeding, extending anticoagulant therapy duration up to 6 months in patients considered at low bleeding risk after surgery (5); this aspect could be even more relevant among patients that are currently considered for transcatheter MV interventions, who are deemed inoperable or at high surgical risk and may have several comorbidities potentially increasing the bleeding risk. Furthermore, aside from the early thromboembolic risk, late valve thrombosis has been recognized as a leading mechanism of long-term bioprosthetic valve dysfunction, potentially occurring years after surgery (17,22–25). In a recent large observational study, Egbe et al. (17) reported a median time to explantation for bioprosthetic valve thrombosis of 24 months, with 15% of cases occurring more than 5 years after surgery. Hence, beyond the first 3 to 6 months after surgery, serial clinical and imaging follow-up (long-term surveillance) seems to be warranted, and future studies are needed to better understand the mechanisms and preventive strategies for late bioprosthetic valve thrombosis.

HIGHLIGHTS

- The risk of THV thrombosis seems to be relevant after TMVR.
- Routine anticoagulant therapy and serial clinical and imaging follow-up is suggested to mitigate this risk.
- Future dedicated studies are needed to better investigate THV thrombosis and refine antithrombotic strategies after TMVR.

CURRENT EVIDENCE ON THROMBOTIC RISK AFTER TMVR

TMVR IN NATIVE MV. New THVs specifically designed for TMVR of the native diseased MV have been developed in the last few years to provide a less-invasive treatment option in inoperable or high-risk patients (9). Such devices have been evaluated in early feasibility studies or are currently under clinical investigation. **Table 2** reports available data with these novel TMVR systems, specifying details on antithrombotic therapy, THV thrombosis, mortality, and cerebrovascular and bleeding events (26–33). As shown, information on antithrombotic strategy at discharge was reported in only 3 studies, consisting of VKA with or without antiplatelet therapy in most patients (26,27,32). A relatively high rate of THV thrombosis (6% to 8%) was observed at different time points after Tendyne (Abbott Vascular, Abbott Park, Illinois), HighLife (HighLife Medical, Irvine, California), and Fortis (Edwards Lifesciences, Irvine, California) device implantation:

- 6 cases of Tendyne thrombosis were reported at 1-year follow-up (6 of 100 patients, rate 6.0%), all observed in the early part of the study (first 35

cases), when post-operative medical therapy consisted solely of antiplatelet therapy (aspirin); after a protocol change implementing the use of mandatory warfarin therapy (target international normalized ratio [INR] 2.5 to 3.5) for at least 3 months, no further instances of THV thrombosis were observed (26).

- 1 case of HighLife thrombosis was reported at 30 days (1 of 14 patients, rate 7.1%), related to subtherapeutic anticoagulation (INR <2.0) (30).
- 1 case of probable Fortis thrombosis was reported early after TMVR (1 of 13 patients at 2 years, rate 7.7%), in a patient on VKA plus aspirin therapy (32); furthermore, in May 2015, Edwards Lifesciences stopped the Fortis THV program because of issues related to device thrombosis (34).

Interestingly, no cases of clinically overt THV thrombosis at 1 year were reported after Intrepid valve (Medtronic Inc., Redwood City, California) implantation as a result of the antithrombotic strategy with VKA (target INR 2.5 to 3.5) plus single antiplatelet therapy for at least 3 months, at the expense of a relatively high rate (18%) of 30-day major bleeding (27). These findings seem to indirectly confirm the protective role of an intense antithrombotic strategy (anticoagulation with a high target INR plus antiplatelet therapy) on thrombotic complications after TMVR, but also highlight the negative impact of this strategy on bleeding events in a high or extreme risk population currently referred for transcatheter MV interventions. Compared with surgical MV replacement or transcatheter aortic valve replacement (TAVR), procedural peculiarities of TMVR could theoretically enhance thrombogenicity (e.g., substantially larger implants to fill MV annulus or the presence of more prosthetic material in mitral THVs); furthermore, specific structural device features (Online Table 1) could impact on the thrombotic risk and determine differences in the rates of thrombotic complications between TMVR devices. Similarly, the access type (transapical vs. transseptal) could be potentially associated with periprocedural thrombosis. However, to date, no dedicated study has evaluated these pathophysiological aspects.

Of note, the proportion of patients with known atrial fibrillation at baseline was high in these early feasibility studies, ranging from 33% to 62% of included patients (27,28,31,32), thus potentially determining an independent indication for anticoagulant therapy (not related to the TMVR procedure *per se*) in a relevant proportion of treated patients. Similarly, the reported incidence of new onset atrial fibrillation after TMVR was 2% to 14% in these studies (26,27,29,32).

TABLE 1 Current European and American Guidelines Recommendations on Antithrombotic Treatment After Surgical Bioprosthetic Mitral Valve Replacement

Guidelines Year (Ref. #)	Recommendation	Class	Level of Evidence
ESC/EACTS 2017 (4)	Oral anticoagulation using a VKA should be considered for the first 3 months.	IIa	B
	Oral anticoagulation is recommended lifelong for patients who have other indications for anticoagulation.*	I	C
AHA/ACC 2017 (5)	Anticoagulation with a VKA to achieve an INR of 2.5 is reasonable for at least 3 months and for as long as 6 months in patients at low risk of bleeding.	IIa	B
	Aspirin 75–100 mg per day is reasonable in all patients with a bioprosthetic valve.	IIa	B

*Atrial fibrillation, venous thromboembolism, hypercoagulable state or, with a lesser degree of evidence, severely impaired left ventricular dysfunction (ejection fraction <35%).

ACC = American College of Cardiology; AHA = American Heart Association; EACTS = European Association for Cardio-Thoracic Surgery; ESC = European Society of Cardiology; INR = international normalized ratio; VKA = vitamin K antagonist.

TRANSCATHETER MITRAL ViV AND ViR. Transcatheter mitral ViV and ViR procedures have recently emerged as valid therapeutic options for degenerated bioprosthetic valves and failed annuloplasty rings in patients deemed at prohibitive or high surgical risk (10,12). The largest amount of evidence regarding mitral ViV and ViR is derived from observational studies using THVs originally designed for aortic valve replacement (**Table 3**) (12,35–55), mainly the balloon-expandable SAPIEN valves (Edwards Lifesciences). The growing experience with these interventions and early reports of clinically overt or subclinical THV thrombosis have led to increased awareness regarding the risk of thrombotic complications after mitral ViV and ViR (56–59). It is noteworthy that there is a lack of standardization in antithrombotic strategies prescribed after such interventions, with thrombotic events and antithrombotic therapy remaining unreported in several available studies (**Table 3**). Although the large multicenter VIVID (Valve-in-Valve International Data) registry has not yet reported data on antithrombotic treatment and THV thrombosis after mitral ViV and ViR (35), relevant insights come from the recently published multicenter TMVR registry (12). This study included 322 ViV and 141 ViR patients treated with different THVs, reporting information on antithrombotic therapy at discharge and THV thrombosis in 411 of 521 patients. Among this subgroup, 71.8% of patients received anticoagulant therapy and the remaining

TABLE 2 Studies Evaluating TMVR in Native Mitral Valve Disease

Study (Ref. #)	Study Design	N	THV	Approach	Age (yrs)	Antithrombotic Therapy at Discharge
Tendyne global feasibility study (26)	Multicenter Prospective	100	Tendyne	TA	75 ± 8	Initially ASA only; after a protocol change, VKA (target INR 2.5–3.5) for at least 3 months
Intrepid global pilot study (27)	Multicenter Prospective	50	Intrepid	TA	73 ± 9	VKA (target INR 2.5–3.5) + SAPT for at least 3 months
TIARA-I early feasibility study + TIARA-II European CE mark study + SAP/compassionate use (28)	Multicenter Prospective	58	Tiara	TA	73 ± 10	Not reported
PRELUDE study + SAP (29)	Multicenter Prospective	17	Caisson	TS	81 (median)	Not reported
HighLife safety and feasibility study + compassionate use (30)	Multicenter Prospective	15	HighLife	TA/TS	69 (50–79)	Not reported
SAPIEN M3 early feasibility study (31)	Multicenter Prospective	15	SAPIEN M3	TS	76 ± 12	Not reported
Fortis compassionate use program (32)	Multicenter Consecutive patients	13	Fortis	TA	71 ± 8	5 VKA + ASA 2 VKA 1 VKA + DAPT 1 ASA
CardiAQ early TS experience (33)	Multicenter Consecutive patients	12	CardiAQ	TS	80 ± 8	Not reported

Values are mean ± SD, n/N (%), or median (range), unless otherwise indicated. Observational studies reporting data on TMVR for native mitral valve disease (with new dedicated devices) were selected for inclusion in the present Table; studies with <3 patients were excluded. Pooled rates of THV thrombosis: cumulative event rate 8/192 (4.2%); pooled estimated rate 2.9% (95% confidence interval 0.3 to 5.4%), calculated using a weighted meta-analysis of single-arm studies with a binary random-effects model. Low heterogeneity was found among studies ($Q = 4.4$, $p_{heterogeneity} = 0.361$, I^2=8.1). Analyses were performed with Meta-analyst Beta 3.13 (Tufts Medical Center, Boston, Massachusetts).

ASA = aspirin; BARC = Bleeding Academic Research Consortium; CT = computed tomography; CVE = cerebrovascular event; INTERLUDE = Clinical Investigation of the Caisson Transcatheter Mitral Valve Replacement System for Percutaneous Mitral Valve Replacement in Patients With Symptomatic Mitral Regurgitation; PRELUDE = Percutaneous Mitral Valve Replacement EvaLuation Utilizing IDE Early Feasibility Study; SAP = Special Access Program; SAPT = single antiplatelet therapy (aspirin or clopidogrel); TA = transapical; THV = transcatheter heart valve; TIARA-I = Early Feasibility Study of the Neovasc Tiara Mitral Valve System; TIARA-II = Tiara Transcatheter Mitral Valve Replacement Study; TMVR = transcatheter mitral valve replacement; TS = transseptal; other abbreviations as in Table 1.

28.2% received antiplatelet therapy. THV thrombosis occurred in 10 cases (9 ViV and 1 ViR), with a timing varying significantly from the first days to 2 years after TMVR. Interestingly, the cumulative 1-year rate of THV thrombosis was significantly higher in patients without anticoagulation compared with those with anticoagulation (6.6% vs. 1.6%; log-rank p = 0.019), supporting the protective role of an anticoagulation-based strategy on the risk of thrombotic complications after mitral ViV and ViR (12). Furthermore, a recent single-center prospective study reported a 2-year cumulative rate of THV thrombosis of 14.4% among 91 patients treated with ViV, ViR, or ViMAC; all patients were asymptomatic and THV thrombosis resolved in all cases with VKA (37).

Although often being considered together, mitral ViV and ViR are different procedures with specific technical and anatomic features that could theoretically contribute to the thrombotic risk. For instance, in ViR procedures, the relative position of THV with respect to the failed annuloplasty ring could determine a perivalvular low-flow space on the atrial side of the bioprosthesis or at the interface between THV and native MV apparatus, potentially altering flow dynamics, creating a low shear stress area, and enhancing local thrombogenicity. On the other hand, ViV determines a different geometrical interplay between prosthetic valves and native structures, where the presence and the specific type of a degenerated surgical bioprosthesis could play a role in the local thrombotic risk. In the TMVR registry (12), although ViR patients had lower left ventricular ejection fraction as compared with ViV (representing a lower-flow condition), the vast majority of THV thrombosis events occurred after ViV (90.9%); furthermore, THV thrombosis after mitral ViV was more frequently observed in previous stented porcine valves (n = 9) as compared with pericardial valves (n = 1), consistently with previous data on surgical aortic valve replacement and transcatheter aortic ViV (60–62).

TMVR IN SEVERE MITRAL ANNULAR CALCIFICATION. TMVR with aortic THVs has been recently developed as a percutaneous therapeutic option for patients with native MV disease and severe mitral annular calcification (ViMAC). Available studies evaluating mitral ViMAC are shown in **Table 4** (11,12,36,37,39,63–65). Guerrero et al. (11) recently

TABLE 2 Continued

Follow-Up Timing	Mortality	Cerebrovascular Events	Bleeding Events	THV Thrombosis	Comments on THV Thrombosis
1 yr	26%	Disabling stroke 3%	BARC 2, 3, or 5 bleeding 32%	6/100 (6)	THV thrombosis involving leaflets (4 cases), the tether (1 case), or the cuff (1 case). All thrombosis cases observed before the protocol change requiring mandatory VKA therapy.
1 yr	23.5%	30-day disabling stroke 0% 30-day nondisabling stroke 4%	30-day major bleeding 18%	0/50 (0)	–
90 days	21.8%	Procedural CVE 3%	Not reported	Not reported	–
30 days	18.2%	Any stroke 0%	Reoperation for bleeding 0%	Not reported	–
30 days	21.4%	Any stroke 0%	Not reported	1/14 (7.1)	1 case of THV thrombosis related to subtherapeutic anticoagulation (INR <2.0).
30 days	0%	Any stroke 6.7%	Life-threatening bleeding 0%	0/15 (0)	–
2 yrs	54%	30-day any stroke 0%	30-day life-threatening bleeding 0%	1/13 (7.7)	Probable THV thrombosis in 1 patient 13 days after TMVR (under VKA + ASA therapy), who died 2 days later (sudden death). In May 2015, Edwards Lifesciences stopped the Fortis program in response to issues of periprocedural THV thrombosis.
30 days	17%	Not reported	Not reported	Not reported	–

reported 1-year results of the multicenter TMVR in MAC Global Registry, which represents the largest ViMAC experience including 116 extreme surgical risk patients. In this real-world registry, information on medical therapy at discharge was available in 67.2% of patients, with oral anticoagulation prescribed in most patients (73.1%) with known discharge therapy. THV thrombosis was observed in 2 of 106 patients at 1 year (rate 1.8%) who were receiving warfarin therapy without aspirin (with INR of 2.2 and <2, respectively), and was the cause of death in both cases (11). No cases of THV thrombosis were observed in other relatively large studies at short-term or mid-term follow-up, even though details on antithrombotic therapy at discharge were not described (12,39,63). Interestingly, a relatively high rate of THV thrombosis was reported by Urena et al. (37) (3 of 27 patients at 30 days, rate 11.1%): all patients were asymptomatic and valve thrombosis resolved with VKA in all cases.

DIAGNOSIS OF THV THROMBOSIS AFTER TMVR

Considering the wide timeframe of device thrombosis after TMVR (12), serial echocardiographic surveillance and clinical follow-up is fundamental to promptly detect and treat thrombotic THV dysfunction. In cases of clinical suspicion (new-onset heart failure symptoms with acute or subacute presentation, new thromboembolic events) and suggestive transthoracic echocardiographic features of THV thrombosis (direct visualization of thrombus in rare cases, 50% mean gradient increase, thickened cusps, restricted leaflet mobility), prompt evaluation with transesophageal echocardiography (**Figure 1**) or computed tomography (CT) scan is indicated, with specific treatment according to clinical presentation and patients' profile in cases of confirmed THV thrombosis (initiation or intensification of anticoagulation, thrombolysis, surgery, or transcatheter ViV) (18,20).

Besides the occurrence of clinically overt THV thrombosis, recent studies performing systematic imaging follow-up with 4-dimensinoal CT after TAVR have pointed out a significant risk of subclinical THV thrombosis, a phenomenon that was less frequent in patients receiving anticoagulants (vs. antiplatelets) after valve replacement, generally resolved at follow-up after initiation of anticoagulation, and was associated with higher rates of neurological events in some reports (although the latter finding is inconclusive) (66–71). However, questions remain regarding the actual clinical relevance of subclinical THV thrombosis (68,70,71), the optimal timing of post-implantation imaging, and the possible occurrence of image artefacts (72); hence, routine screening with CT cannot presently be justified after any TAVR or TMVR, reserving CT for cases with high suspicion of a THV thrombotic process arising during serial clinical and echocardiographic surveillance (20).

TABLE 3 Studies Evaluating Transcatheter Mitral ViV and ViR Procedures

Study (Ref. #)	Study Design	n	THV	Approach	Age (yrs)	Antithrombotic Therapy at Discharge	Follow-Up Timing	Mortality (%)
Mitral VIVID Registry (35)	Multicenter Retrospective	349 ViV 88 ViR	347 SAPIEN/XT 28 Melody 17 SAPIEN 3 18 others	345 TA 81 TS 11 TAtr	ViV 75 ± 12 ViR 69 ± 14	Not reported	30 days	ViV 7.7% ViR 11.4%
TMVR Registry (12)	Multicenter Retrospective	322 ViV 141 ViR	247 SAPIEN 3 175 SAPIEN/XT 21 Lotus 16 Direct Flow 4 Melody	284 TA 175 TS 4 TAtr	ViV 73 ± 13 ViR 72 ± 10	195 VKA 94 VKA + SAPT/DAPT 92 DAPT 24 SAPT 6 DOAC	1 yr	ViV 14.0% ViR 30.6%
Eleid et al. (36)	Multicenter Retrospective	60 ViV 15 ViR	SAPIEN/XT/3	TS	ViV 75 ± 11 ViR 72 ± 8	VKA (target INR 2–3) + SAPT for indefinite duration	1 yr	ViV 14% ViR 18%
Urena et al. (37)	Single center Prospective	34 ViV 30 ViR	32 SAPIEN XT 31 SAPIEN 3	62 TS 2 TA	ViV 73 [52–84] ViR 70 [48–84]	VKA (target INR 2–3) + ASA for at least 3 months, then VKA discontinued†	30 days	ViV 5.9% ViR 6.7%
Kamioka et al. (38)	Multicenter Retrospective	62 ViV	SAPIEN/XT 21 SAPIEN 3 41	48 TS 14 TA	75 ± 9	49 VKA 38 ASA 14 $P2Y_{12}$-i 5 DOAC	1 yr	11.3%
MITRAL trial (39)	Multicenter Prospective	26 ViV 30 ViR	SAPIEN XT/3	TS	ViV 83 (mean) ViR 72 ± 9	Not reported	30 days	ViV 4% ViR 6.8%
Ye et al. (40)	Single center Consecutive patients	31 ViV	SAPIEN/XT	TA	79 ± 9	VKA + ASA for indefinite duration	2.5 yrs (median)	30-day 1.4% 5-yr 59.5%
Frerker et al. (41)	Single center Retrospective	14 ViV 10 ViR	16 SAPIEN/XT 8 SAPIEN 3	13 TA 11 TS	72 ± 13	Not reported	30 days	12.5%
Himbert (42)	—	28 ViR	17 SAPIEN XT 10 SAPIEN 3	TS	67 (38–76)	Not reported	1-yr	13.1%
Cheung et al. (43)	Single center Consecutive patients	23 ViV	SAPIEN/XT	TA	81 ± 6	15 VKA + SAPT for 6 months 7 DAPT for 6 months 1 VKA	753 (376–1,119) days	9.6%
Bouleti et al. (44)	Single center Retrospective	6 ViV 11 ViR	SAPIEN XT	TS	61 ± 24	Not reported	18 months	32%
Descoutures et al. (45)	Multicenter Retrospective	17 ViR	SAPIEN XT	9 TA 8 TS	70 ± 16	Not reported	13 ± 5 months	38%
Eng et al. (46)	Singe-center Retrospective	8 ViV 5 ViR	SAPIEN/XT/3	TA-TS	75 ± 6	10 VKA 3 DAPT	135 [35–123] days	8%
Wilbring et al. (47)	Single center Retrospective	10 ViV 2 ViR	SAPIEN XT	TA	75 ± 5	Not reported	In-hospital	15.4%
Schäfer et al. (48)	Single center Case series	8 ViV 4 ViR	SAPIEN/XT	7 TA 5 TS	69 ± 13	DAPT for 1 month, then ASA alone	30 days	0%
Whisenant et al. (49)	Single center Case series	7 ViV 2 ViR	SAPIEN/XT	7 TA 2 TS	—	5 SAPT 2 DAPT 2 VKA	In-hospital	0%
Cullen et al. (50)	Single center Case series	9 ViV	Melody	TS	75 ± 11	Not reported	In-hospital	0%
Latib et al. (51)	Multicenter Retrospective	8 ViR	Direct Flow	TA	75 ± 5	Not reported	30 days	25%
Seiffert et al. (52)	Single center Case series	6 ViV	SAPIEN/XT	TA	75 ± 15	Not reported	70 (26–358) days	16.7%
Kliger et al. (53)	Single center Case series	5 ViV	Melody	TA-TS	73 ± 12	Not reported	In-hospital	0%
Cerillo et al. (54)	Single center Case series	3 ViV	SAPIEN	TA	68 ± 21	Not reported	In-hospital	33.3%
Cheung et al. (55)	Multicenter Case series	3 ViR	Tiara	TA	74 (68–81)	Not reported	30 days	0%

Values are mean ± SD, n/N (%), median [interquartile range], or median (range), unless otherwise indicated. Observational studies reporting data on transcatheter mitral ViV and ViR were selected for inclusion in the present Table; studies with <3 patients were excluded. Pooled rates of THV thrombosis: cumulative event rate 27/725 (3.7%); pooled estimated rate 3.1% (95% confidence interval 1.9% to 4.4%), calculated using a weighted meta-analysis of single-arm studies with a binary random-effects model. Low heterogeneity was found among studies ($Q = 9.8$, $p_{heterogeneity} = 0.833$, $I^2 = 0.0$). Analyses were performed with Meta-analyst Beta 3.13 (Tufts Medical Center, Boston, Massachusetts). *Information on antithrombotic therapy and THV thrombosis was available in 411 of 521 patients included in the TMVR registry; however, the exact number of ViV, ViR, and ViMAC cases available for this subanalysis was not specified. †In the absence of THV thrombosis (assessed by transesophageal echocardiography) or another indication. ‡Considering an overall sample size of 91 patients (34 ViV, 30 ViR, and 27 ViMAC).

DOAC = direct oral anticoagulant; GI = gastrointestinal; ICH = intracranial hemorrhage; MV = mitral valve; $P2Y_{12}$-i = $P2Y_{12}$ receptor inhibitor; TAtr = transatrial; TIA = transient ischemic attack; ViMAC = valve-in-mitral annular calcification; ViR = valve-in-ring; ViV = valve-in-valve; VIVID = Valve-in-Valve International Data; other abbreviations as in Tables 1 and 2.

TABLE 3 Continued

Cerebrovascular Events	Bleeding Events	THV Thrombosis	Comments on THV Thrombosis
Procedural major stroke: ViV 2.9%, ViR 1.1%	Not reported	Not reported	–
30-day any stroke: ViV 2.3%, ViR 0%	30-day life-threatening or fatal bleeding: ViV 2.3%, ViR 6.7% 30-day major or extensive bleeding: ViV 4.6%, ViR 3.9%	ViV 10, ViR 1*	1-yr THV thrombosis higher in patients without anticoagulation (6.6% vs. 1.6%; log-rank p = 0.019).*
Not reported	Major bleeding: ViV 7%, ViR 13%	ViV 1/60 (1.7) ViR 1/15 (1.7)	1 case of THV leaflet dysfunction 2 months after ViV (despite therapeutic INR). 1 case of THV thrombosis 15 months after ViR (despite therapeutic VKA and ASA therapy; died of complications related to THV thrombosis).
Any stroke: ViV 5.9%, ViR 0% Major stroke: ViV 0%, ViR 0%	Life-threatening or fatal bleeding: ViV 5.9%, ViR 3.3%	ViV 3/34 (8.8) ViR 2/30 (6.7)	Cumulative 2-yr rate of THV thrombosis 14.4%.‡ All patients were asymptomatic and thrombosis resolved in all cases with VKA. VKA indicated life-long after thrombosis.
In-hospital any stroke 0%	In-hospital life-threatening bleeding 6.5% In-hospital major bleeding 8.1% In-hospital minor bleeding 8.1%	Not reported	–
Ischemic stroke: ViR 0%	ICH: ViR 3.4%	ViR 0/29 (0.0)	–
30-day disabling stroke 3.2%	30-day life-threatening bleeding 3.2% 30-day major bleeding 19.4%	2/31 (6.5)	THV thrombosis in 2 patients who were in DAPT, which resolved with VKA therapy.
Procedural any stroke 4.2%	Procedural life-threatening bleeding 8.3%	Not reported	–
Any stroke 0%	30-day major-to-fatal bleeding 14.3%	1/28 (3.6)	–
Major stroke 4.4% Minor stroke 0% TIA 0%	Life-threatening bleeding 0% Major bleeding 26.1% Minor bleeding 0%	0/23 (0.0)	–
30-day stroke or TIA 0%	30-day major bleeding 5.9% 30-day minor bleeding 0%	Not reported	–
Not reported	Not reported	Not reported	–
Major stroke 8% Minor stroke 0%	Life-threatening bleeding 0% Major bleeding 8%	2/13 (15.4)	2 cases of symptomatic THV thrombosis (heart failure, elevated gradients) at 99 ± 34 days after ViV and ViR; both patients were in DAPT; anticoagulation was effective in 1 case and not tolerated in the other case (due to GI bleeding). Suspected subclinical THV thrombosis in 1 ViR patient who was in DAPT.
Stroke 0% TIA 0%	Bleeding complications 0%	2/12 (16.7)	Beginning THV thrombosis in 2 ViV patients who were in ASA therapy (at 8 weeks and 3 months, respectively). VKA was initiated (target INR 2.5) with complete regression of thrombosis.
Procedural major stroke 8.3%	Procedural major bleeding 0%	Not reported	–
Procedural any stroke 0%	Procedural significant bleeding 0%	2/9 (22.2)	THV thrombosis in 2 ViV patients who were in SAPT (at 17 months and 11 days, respectively): 1 patient underwent surgical MV replacement; 1 patient was treated with VKA with resolution of thrombosis.
Any stroke 0%	Not reported	0/9 (0.0)	–
Not reported	Not reported	0/4 (0.0)	–
In-hospital adverse neurological events 0%	In-hospital apical bleeding 33.3%	0/6 (0.0)	–
Not reported	Not reported	0/5 (0.0)	–
Not reported	Not reported	0/3 (0.0)	–
Stroke or TIA 0%	Bleeding complication 0%	0/3 (0.0)	–

TABLE 4 Studies Evaluating TMVR in Severe MAC

Study (Ref. #)	Study Design	N	THV	Approach	Age (yrs)	Antithrombotic Therapy at Discharge	Follow-Up Timing
TMVR in MAC Global Registry (11)	Multicenter Retrospective	116	57 SAPIEN/XT 57 SAPIEN 3 2 Inovare	46 TA 23 TAtr 47 TS	73 ± 12	39 VKA + ASA 13 VKA 11 DAPT 10 ASA 3 VKA + DAPT 2 DOAC	1 yr
STS/ACC TVT Registry (63)	Multicenter Retrospective	100	50 SAPIEN 3 50 SAPIEN/XT or others	43 TS 42 TA 2 TAtr 13 unknown	77 [65–83]	Not reported	30 days
TMVR Registry (12)	Multicenter Retrospective	58	41 SAPIEN 3 9 Lotus 6 SAPIEN XT 2 Direct Flow	31 TS 26 TA 1 TAtr	75 ± 11	Not reported*	1 yr
MITRAL Trial (39)	Multicenter Prospective	30	SAPIEN XT/3	15 TAtr 14 TS 1 TA	75 ± 8	Not reported	30 days
Urena et al. (37)	Single center Prospective	27	5 SAPIEN XT 22 SAPIEN 3	22 TS 5 TA	73 [68–81]	VKA (target INR 2–3) + ASA for at least 3 months, then VKA discontinued†	30 days
Eleid et al. (36)	Multicenter Retrospective	12	SAPIEN/XT/3	TS	79 ± 9	VKA (target INR 2–3) + SAPT for indefinite duration	1 yr
Praz et al. (64)	Multicenter Prospective	26	24 SAPIEN 3 2 SAPIEN XT	TAtr	78 ± 7	VKA (target INR 2–3) + ASA for indefinite duration	30 days
Russell et al. (65)	Single center Retrospective	8	SAPIEN 3	TAtr	76 ± 6	VKA (target INR 2–3) + ASA for at least 3 months, then ASA alone	30 days

Values are mean ± SD, n/N (%), or median [interquartile range], unless otherwise indicated. Observational studies reporting data on TMVR in severe MAC were selected for inclusion in the present Table; studies with <3 patients were excluded. Pooled rates of THV thrombosis: cumulative event rate 5/277 (1.8%); pooled estimated rate 1.4% (95% confidence interval 0.1 to 2.8%), calculated using a weighted meta-analysis of single-arm studies with a binary random-effects model. Low heterogeneity was found among studies ($Q = 3.8$, $p_{heterogeneity} = 0.700$, $I^2 = 0.0$). Analyses were performed with Meta-analyst Beta 3.13 (Tufts Medical Center, Boston, Massachusetts). *It was not specified the exact number of ViMAC patients included in the subanalysis of the TMVR registry on antithrombotic therapy and THV thrombosis; however, no cases of THV thrombosis after ViMAC were observed. †In the absence of THV thrombosis (assessed by transesophageal echocardiography) or another indication.

MAC = mitral annular calcification; MITRAL = Mitral Implantation of TRAnscatheter vaLves; STS = Society of Thoracic Surgeons; TVT = Transcatheter Valve Therapy; other abbreviations as in Tables 1–3.

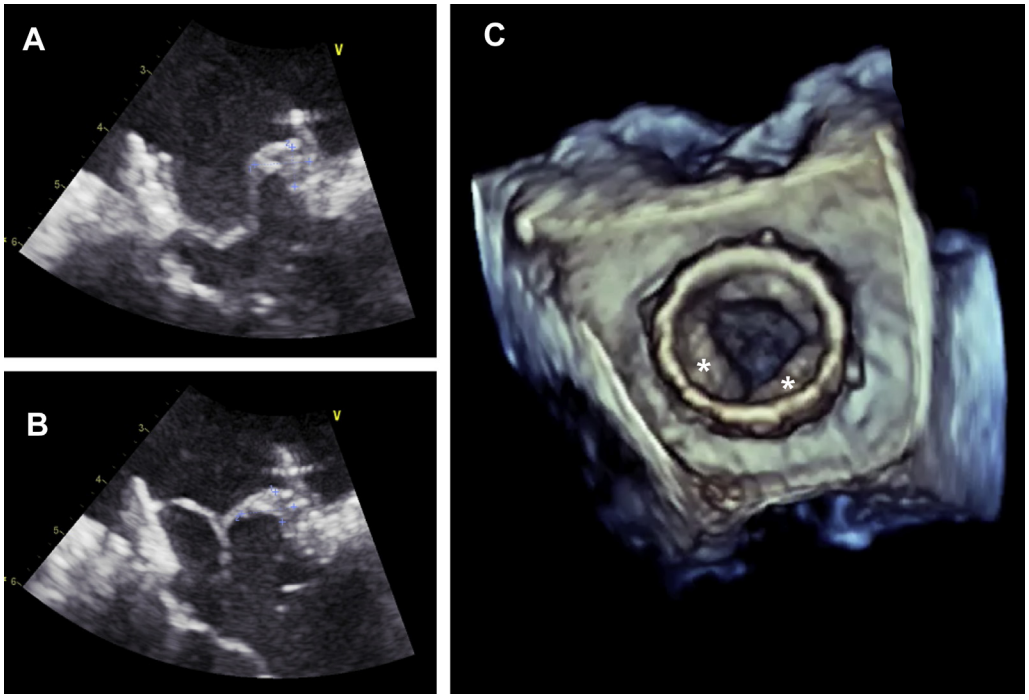
VIEWPOINT: ANTITHROMBOTIC STRATEGIES AFTER TMVR

THV thrombosis is a complex multifactorial phenomenon (**Central Illustration**), arising from the interplay between valve-related and patient-related factors (18,20). Early experience with TMVR suggests a non-negligible risk of clinically overt THV thrombosis at short-term and mid-term follow-up, potentially higher than that observed after TAVR (73). The lower rate of THV thrombosis observed by Yoon et al. (12) among patients treated with anticoagulant therapy, as well as indirect evidence obtained from early experience with new TMVR devices (Tendyne, Intrepid) (26,27), suggest that anticoagulation thromboprophylaxis may be beneficial after TMVR procedures, in line with current clinical practice after surgical bioprosthetic MV replacement (4,5). Hence, it seems reasonable to prescribe oral anticoagulation with VKA in the first months after any TMVR procedure in patients who do have not an indication for long-term anticoagulation, to mitigate the risk of THV thrombosis. The duration of anticoagulant therapy and the eventual association of antiplatelet therapy could be tailored through a careful evaluation of the patient's individual bleeding risk, even though this strategy is empirical and not based on dedicated studies. Although no specific bleeding risk score has been developed for patients undergoing TMVR, existing scores validated in patients with atrial fibrillation on chronic VKA therapy (HAS-BLED [Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol], HEMORR$_2$HAGES [Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, ReBleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke], and ATRIA [Anticoagulation and Risk Factors in Atrial Fibrillation]) might also be applicable in this setting, since they include common and well-known risk factors for bleeding events (74). Furthermore, because specific structural device features could impact on thrombogenicity (e.g., material, flow patterns, size), the intensity of the prescribed antithrombotic regimen would ideally be tailored to the

TABLE 4 Continued

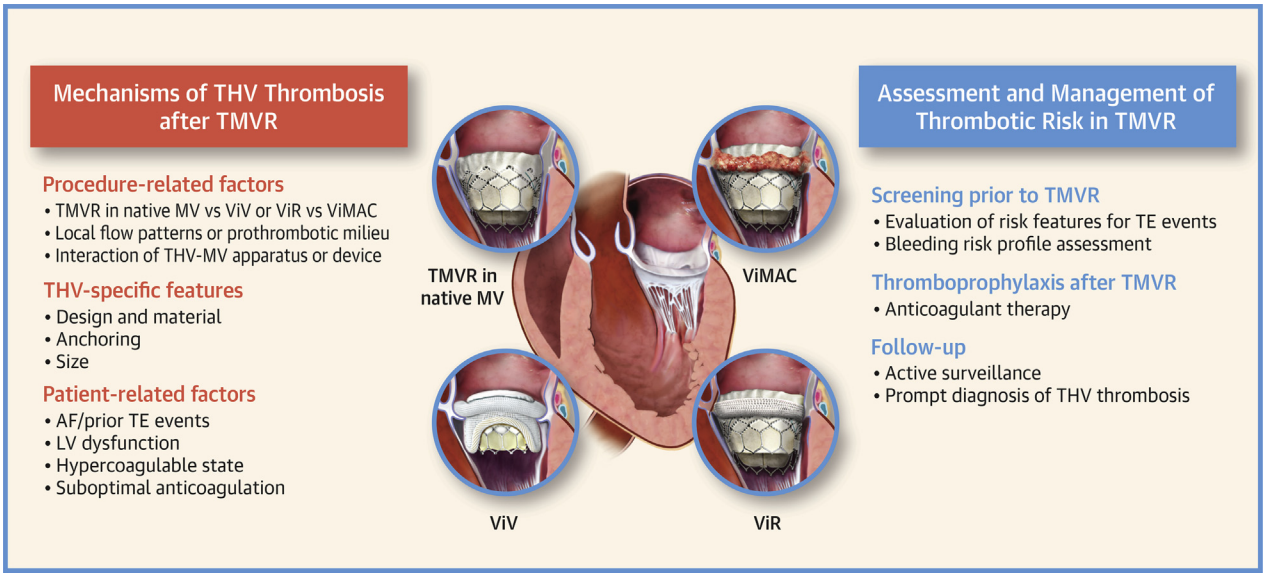
Mortality	Cerebrovascular Events	Bleeding Events	THV Thrombosis	Comments on THV Thrombosis
53.7%	Any stroke 6.6% Fatal stroke 1.8%	Fatal bleeding 2.8%	2/106 (1.8)	Both patients were receiving warfarin (INR of 2.2 and <2, respectively) and died because of THV thrombosis.
21.7%	Ischemic stroke 5.6%	ICH 0%	0/72 (0.0)	–
62.8%	30-day any stroke 3.9%	30-day life-threatening or fatal bleeding 4.5% 30-day major or extensive bleeding 1.8%	0%*	–
19.2%	Ischemic stroke 3.8%	Any bleeding 7.7% ICH 0%	0/26 (0.0)	–
11.1%	Any stroke 7.4% Major stroke 7.4%	Life-threatening or fatal bleeding 3.7%	3/27 (11.1)	All patients were asymptomatic and thrombosis resolved in all cases with VKA. VKA indicated life-long after thrombosis.
43%	Not reported	Major bleeding 25%	0/12 (0.0)	–
26.9%	Any stroke 3.8% Disabling stroke 0%	Major bleeding 7.7%	0/26 (0.0)	–
0%	Any stroke 0%	Not reported	0/8 (0.0)	–

FIGURE 1 Transesophageal Echocardiographic Images of Transcatheter Heart Valve Thrombosis After Transcatheter Mitral Valve Replacement



(A, B) Bidimensional transesophageal images of the thrombosis of a 26-mm SAPIEN 3 transcatheter heart valve (Edwards Lifesciences, Irvine, California) implanted inside a failed mitral annuloplasty ring (30-mm Carpentier-Edwards ring [Edwards Lifesciences]). The valve leaflets appear thickened due to the apposition of hyperechoic material (i.e., thrombus). **(C)** Three-dimensional reconstruction of the prosthesis in the same subject. **Asterisks** mark the thickened, dysfunctional leaflets.

CENTRAL ILLUSTRATION **Thrombotic Risk After TMVR**



Pagnesi, M. et al. J Am Coll Cardiol Intv. 2019;12(23):2388-401.

According to available early evidence, the thrombotic risk seems to be relevant after transcatheter mitral valve replacement (TMVR), with multiple mechanisms implicated in transcatheter heart valve (THV) thrombosis involving procedure-, device-, and patient-related factors. A detailed pre-procedural screening is important to identify patients with particularly high thrombotic risk features and evaluate the patient's individual bleeding risk. An anticoagulation-based antithrombotic strategy should be considered to prevent THV thrombosis and thromboembolic (TE) events after TMVR, tailoring the intensity and duration of the prescribed antithrombotic regimen to the individual bleeding and thrombotic risk profile. Serial clinical and imaging follow-up is suggested to promptly detect and treat thrombotic THV dysfunction. AF = atrial fibrillation; LV = left ventricular; MV = mitral valve; ViMAC = valve-in-mitral annular calcification; ViR = valve-in-ring; ViV = valve-in-valve.

type of THV implanted; however, no device-specific recommendations can be provided presently in the absence of dedicated studies.

Serial clinical and imaging follow-up (either before and after the interruption of anticoagulant therapy), with a careful balance of individual thromboembolic and hemorrhagic risk profiles, may dynamically guide the intensity and duration of antithrombotic therapy after TMVR. Furthermore, in the absence of dedicated randomized studies in the TMVR field, lessons can be learned from the recently interrupted GALILEO (Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes) trial. This trial evaluated a direct oral anticoagulant-based strategy after TAVR in subjects without an established indication for long-term oral anticoagulation, randomizing patients to rivaroxaban 10 mg once daily plus aspirin 75 to 100 mg for 3 months followed by rivaroxaban alone versus dual antiplatelet therapy (clopidogrel 75 mg plus aspirin 75 to 100 mg) for 3 months followed by aspirin alone (75). The GALILEO trial was terminated early because of an increased risk of mortality, thromboembolic events, and bleeding in patients randomized to the rivaroxaban arm (76); these preliminary findings could lead to several conflicting speculations, on the one hand raising suspicions of a suboptimal thromboprophylactic effect of low-dose rivaroxaban, but on the other hand suggesting an increased bleeding risk with an anticoagulant plus antiplatelet strategy in elderly patients undergoing TAVR. Unlike TAVR, oral anticoagulation with VKA seems to be necessary for thromboprophylaxis after TMVR and, at the same time, bleeding risk concerns are particularly relevant in high-risk or inoperable patients currently referred for TMVR. Hence, avoiding combined antithrombotic therapy or prolonged anticoagulation in patients at high bleeding risk could be beneficial, reserving intense anticoagulation (high INR target and prolonged duration) or combined anticoagulant and antiplatelet therapy in patients at low bleeding risk or with particularly high thrombotic risk features (e.g., patients with prior thromboembolic event or after mitral ViV in degenerated stented porcine valves). Of note,

available evidence on thromboprophylaxis after TMVR is almost exclusively based on oral anticoagulation with VKA, with an extremely low number of patients treated with direct oral anticoagulants in early available studies. In patients deemed to be at very high (prohibitive) bleeding risk, with an expected risk of anticoagulant-related bleeding events potentially higher and more concerning than the THV-related thromboembolic risk, the adoption of an antiplatelet-only strategy without anticoagulation seems to be inevitable; in these cases, we recommend a strict clinical and imaging follow-up to exclude the occurrence of THV thrombosis. Of note, in a relevant proportion of patients currently treated with TMVR, antithrombotic therapy is primarily guided by underlying comorbidities, particularly atrial fibrillation (potentially determining an independent indication for anticoagulation). Furthermore, since concomitant left atrial appendage closure (LAAC) during surgical MV replacement has demonstrated to reduce the incidence of thromboembolic events at follow-up (77), percutaneous LAAC could theoretically be beneficial in a subgroup of patients currently undergoing TMVR; however, no dedicated studies are available to date on the additive role of LAAC in this specific population.

FUTURE PERSPECTIVES

Available evidence on thrombotic risk and antithrombotic strategies after TMVR is still limited, as there is only a small number of published studies providing prospective data, these endpoints are not homogeneously reported in several observational studies, and a robust assessment of predictors and prognostic implication of THV thrombosis is still lacking. We hope that ongoing and future TMVR studies will consistently report THV thrombosis as a key endpoint, possibly using a homogeneous definition as recommended by the Mitral Valve Academic Research Consortium, clearly differentiating between major (clinically overt) and minor (subclinical) device thrombosis (78). More evidence is also needed on procedure- and THV-related thrombotic risk (e.g., by means of large dedicated studies separately evaluating ViV and ViR or specifically assessing temporal and imaging features of THV thrombosis after each type of TMVR intervention). Furthermore, extensive evaluation of protective and predicting factors of THV thrombosis after TMVR would be relevant, with a focus on the preventive role of tailored antithrombotic strategies.

CONCLUSIONS

According to available early evidence, the risk of THV thrombosis seems to be relevant after TMVR. An anticoagulation-based antithrombotic strategy should be considered to prevent the risk of valve thrombosis and thromboembolic events after any TMVR procedure (TMVR in native MV disease, ViV, ViR, and ViMAC), tailoring the intensity and duration of the prescribed antithrombotic regimen on the individual bleeding and thrombotic risk profile of any treated patient. Serial clinical and imaging follow-up is suggested to promptly detect and treat thrombotic THV dysfunction. However, future dedicated studies are needed to define the optimal antithrombotic strategies after TMVR.

ADDRESS FOR CORRESPONDENCE: Dr. Azeem Latib, Department of Cardiology, Montefiore Medical Center, 111 East 210th Street, Bronx, New York 10467. E-mail: alatib@gmail.com.

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

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