Clinical Therapeutics xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Therapeutics

journal homepage: www.elsevier.com/locate/clinthera

Review

Antithrombotic Treatment After Transcatheter Valve Interventions: Current Status and Future Directions

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ARTICLE INFO

Key words:
Antiplatelet
Oral anticoagulation
Transcatheter aortic valve replacement
Transcatheter edge-to-edge repair
Transcatheter mitral valve replacement
Transcatheter tricuspid valve replacement

ABSTRACT

Purpose: The optimal antithrombotic strategy after transcatheter valve interventions is a subject of ongoing debate. Although there is evidence from randomized trials in patients undergoing transcatheter aortic valve replacement (TAVR), current evidence on optimal antithrombotic management after transcatheter mitral or tricuspid valve interventions is sparse. This article appraises the current evidence on this topic.

Methods: This narrative review presents key research findings and guideline recommendations, as well as highlights areas for future research.

Findings: After TAVR, randomized trial evidence suggests that single antiplatelet therapy is reasonable for patients without pre-existing indications for oral anticoagulation (OAC). If there is a concurrent indication for OAC, the addition of antiplatelet therapy increases bleeding risk. Whether direct oral anticoagulants achieve better outcomes than vitamin K antagonists is uncertain in this setting. Although OAC has been shown to reduce subclinical leaflet thrombosis (which may progress to structural valve degeneration), bleeding events are unacceptably high. There is a lack of randomized trial data comparing antithrombotic strategies after transcatheter mitral or tricuspid valve replacement or after mitral or tricuspid transcatheter edge-to-edge repair. Single antiplatelet therapy after mitral or tricuspid transcatheter edge-to-edge repair may be appropriate, whereas at least 3 months of OAC is suggested after transcatheter mitral valve replacement or transcatheter tricuspid valve replacement.

Implications: Randomized studies are warranted to address the knowledge gaps in antithrombotic therapy after transcatheter valve interventions and to optimize outcomes.

Introduction

Transcatheter valve interventions carry a risk for both thrombotic and bleeding events, which is a challenge for antithrombotic management. The rationale for antithrombotic therapy after transcatheter aortic valve replacement (TAVR) is in part due to thrombogenicity of the transcatheter heart valve metallic frame, which is greatest before endothelialization is complete (ie, 3 months' post procedure).[1] Bioprostheses implanted in the mitral position have a higher thromboembolic risk than those implanted in the aortic position.[1–3] Contributing mechanisms for valve thrombosis after transcatheter mitral valve replacement (TMVR) include the relatively large size of the transcatheter mitral valve compared with the aortic valve[4–6] and the higher incidence of atrial fibrillation after TMVR compared with TAVR.[7,8] It is assumed that transcatheter tricuspid valve interventions might have an even higher thrombotic risk, due to the lower pressure circulation on the right side of the heart than on the left.[9]

Uncertainty remains about the optimal antithrombotic regimen needed to balance thrombotic risk and bleeding after transcatheter valve interventions[10] (Figure 1). The current narrative review explores the evidence surrounding antithrombotic therapy after TAVR, TMVR, transcatheter tricuspid valve replacement (TTVR), and mitral or tricuspid transcatheter edge-to-edge repair (M-TEER and T-TEER, respectively).

Determinants of Thrombotic and Bleeding Risk

Comorbidities associated with increased risk of thromboembolic events include older age,[11] history of cerebrovascular events,[11] left ventricular dysfunction,[2,12] and atrial fibrillation (occurs in ~33% of patients after TAVR,[13] in ~75% of patients undergoing M-TEER,[14] and in 85% of patients undergoing transcatheter tricuspid valve interventions[15]). Furthermore, obesity, chronic renal disease, and anaemia are associated with a hypercoagulable state[5] and are common in patients undergoing TAVR.[16–18]

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https://doi.org/10.1016/j.clinthera.2023.09.028
Accepted 29 September 2023
Available online xxx

Please cite this article as: A. Maznyczka and T. Pilgrim, Antithrombotic Treatment After Transcatheter Valve Interventions: Current Status and Future Directions, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2023.09.028

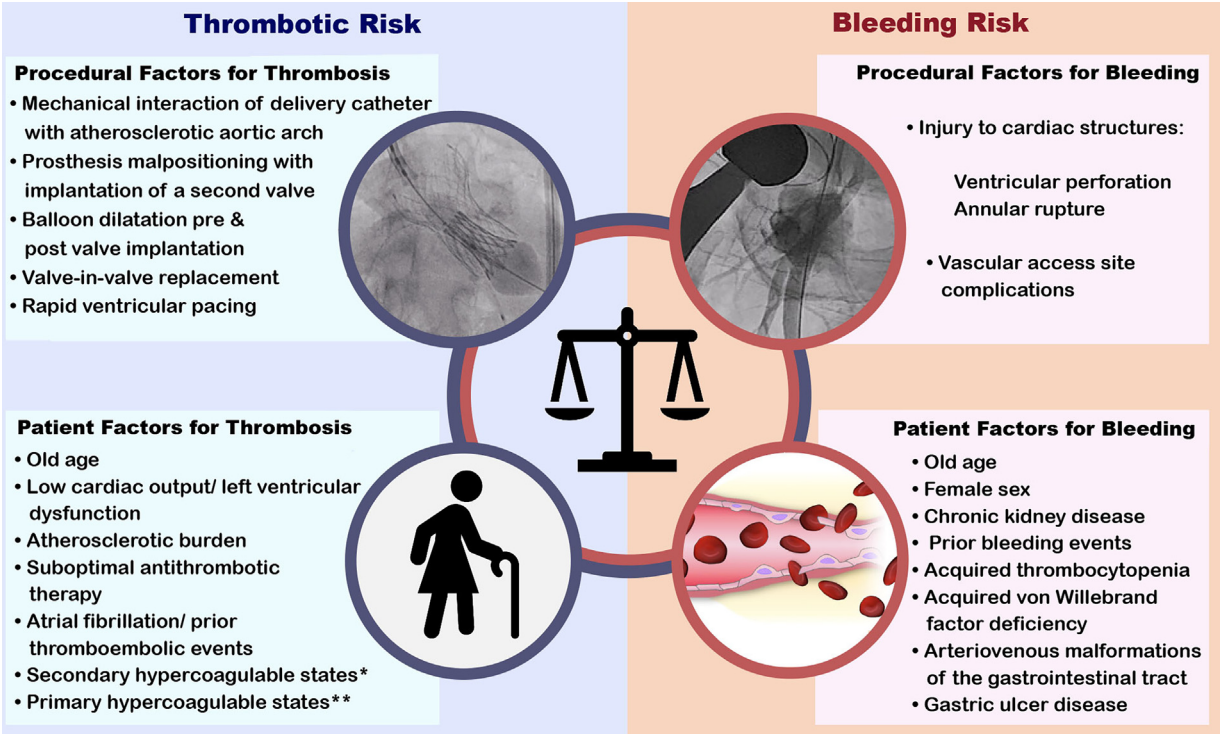

Figure 1. Balancing the risk of bleeding and thrombosis after transcatheter valve interventions. *Secondary hypercoagulable states (eg, smoking, anaemia, obesity, chronic kidney disease). †Primary hypercoagulable states (eg, factor V Leiden, deficiency of protein C or protein S, or antithrombin).

Patient characteristics associated with increased risk of bleeding include old age, frailty, renal or hepatic impairment, and acquired thrombocytopenia (eg, due to platelet destruction at the valve site secondary to shear stress).[19] There is also an association between aortic stenosis and arteriovenous malformations of the gastrointestinal tract, or acquired von Willebrand factor deficiency, which can further contribute to increased bleeding risk.[20,21] In addition, percutaneous procedures can be associated with vascular bleeding complications related to large-bore catheter use for access, particularly in patients with peripheral arterial disease.

Of note, trials in TAVR populations have tended to include elderly patients with comorbidities associated with both increased risk of bleeding and thromboembolic events. The expansion of TAVR to younger patients with a lower risk profile may shift the balance of bleeding and ischaemic events.

Transcatheter Aortic Valve Intervention

Thrombotic Complications After TAVR

TAVR is indicated for managing symptomatic severe aortic stenosis in low-risk,[22,23] intermediate-risk,[24,25] and high-risk[26,27] patients. Obstructive valve thrombosis after TAVR affects ~0.5% of patients per year[6] and can be defined as a mean trans-prosthetic gradient ≥10 mmHg change from baseline or an absolute transvalvular gradient >20 mmHg.[28] Obstructive valve thrombosis manifests clinically as recurrent symptoms of aortic stenosis, heart failure, or thromboembolism.

Conversely, subclinical leaflet thrombosis is more common, occurring in 7% to 15% of post-TAVR patients.[5,29–32] Subclinical leaflet thrombosis is defined as hypoattenuated leaflet thickening (HALT) at the base of the valve leaflets, with or without reduced leaflet motion (RLM), on four-dimensional computed tomography (CT) imaging.[30,33,34] Observational studies indicate a possible association between subclinical leaflet thrombosis after TAVR and strokes or transient ischemic attacks[30,35]; clarity regarding the impact on clinical outcomes is lacking, however.[34]

Other thromboembolic complications after TAVR include periprocedural myocardial infarction (MI) (~1%)[22,26] and stroke (~2%–3%).[36–39] Thromboembolic MI must be differentiated from other causes of coronary obstruction after TAVR, including coronary obstruction by the dislocated cusp[40,41] or coronary ostium dissection.[41] Most strokes post-TAVR occur within the first day, and the stroke risk peaks within the first week after TAVR.[42,43] This is likely related to emboli from the interaction between the transcatheter valve system and the diseased aorta and aortic valve.[44] Balloon post-dilatation of the TAVR valve has also been associated with increased risk of cerebrovascular events.[11,45]

Guideline Recommendations for Antithrombotic Therapy After TAVR

The combination and duration of antiplatelet therapy and/or oral anticoagulation (OAC) after TAVR vary widely.[46] An expert consensus from the European Society of Cardiology (ESC) recommends lifelong single antiplatelet therapy post-TAVR (preferably with aspirin, but clopidogrel may be used) in patients with no pre-existing indication for OAC and no recent coronary stents (Class I, Level of Evidence A)[47] (Table 1, Figure 2). However, a recent consensus statement from a Delphi panel of experts in the United Kingdom and Ireland recommends that the optimal duration of single antiplatelet therapy should be based on an individual patient's risk profile and cannot be generalized to the whole TAVR population.[48] This Delphi consensus recommended 3 to 12 months of single antiplatelet therapy after TAVR (perhaps most relevant to patients at high bleeding risk) but highlighted that concomitant coronary artery disease could indicate the need for a longer duration of single antiplatelet therapy.

The 2021 ESC consensus document recommends that in patients with coronary stenting within 3 months of TAVR, and no pre-existing indication for OAC, dual antiplatelet therapy (DAPT) (aspirin and clopidogrel) should be continued for 1 to 6 months, followed by lifelong use of single antiplatelet therapy[49] (Figure 2). The reason for shorter DAPT in this setting is because post-TAVR patients tend to have a higher underlying bleeding risk due to comorbidities. ESC guidelines for patients with high bleeding risk undergoing percutaneous coronary intervention

Table 1
European and US guidelines for the management of antithrombotic therapies in patients undergoing transcatheter valve interventions.

Procedure	European Guidelines	Class of Recommendation	Level of Evidence	US Guidelines	Class of Recommendation	Level of Evidence
TAVR	If no concomitant indication for OAC, lifelong single antiplatelet therapy (preferably aspirin) is recommended[47]	I	A	If no concomitant indication for OAC, single antiplatelet therapy with aspirin (75–100 mg daily) is reasonable[51]	IIa	B
	If concomitant indication for OAC, continue OAC lifelong[47]	I	B	For patients at low risk of bleeding, and no concomitant indication for OAC, DAPT (aspirin and clopidogrel) may be reasonable for 3–6 months after TAVR[51]	IIb	B
	If recent coronary stenting (<3 months) and no concomitant indication for OAC, consider DAPT (aspirin and clopidogrel) for 1–6 months, and then single antiplatelet therapy (aspirin or clopidogrel) lifelong[49]	Not provided in guideline publication	Not provided in guideline publication	For patients at low bleeding risk, and no concomitant indication for OAC, OAC with vitamin K antagonist may be reasonable for at least 3 months after TAVR[51]	IIb	B
	If recent coronary stenting (<3 months) and concomitant indication for OAC, continue OAC lifelong and consider a single antiplatelet drug (aspirin or clopidogrel) for 1–6 months[49]	Not provided in guideline publication	Not provided in guideline publication			
TMVR	No recommendation made in ESC guidelines			No recommendation made in ACC/AHA guidelines		
Mitral or tricuspid TEER	No recommendation made in ESC guidelines			No recommendation made in ACC/AHA guidelines		
TTVR	No recommendation made in ESC guidelines			No recommendation made in ACC/AHA guidelines		

ACC/AHA = American College of Cardiology/American Heart Association; DAPT = dual antiplatelet therapy; ESC = European Society of Cardiology; OAC = oral anticoagulation; TAVR = transcatheter aortic valve replacement; TEER = transcatheter edge-to-edge repair; TMVR = transcatheter mitral valve replacement; TTVR = transcatheter tricuspid valve replacement.

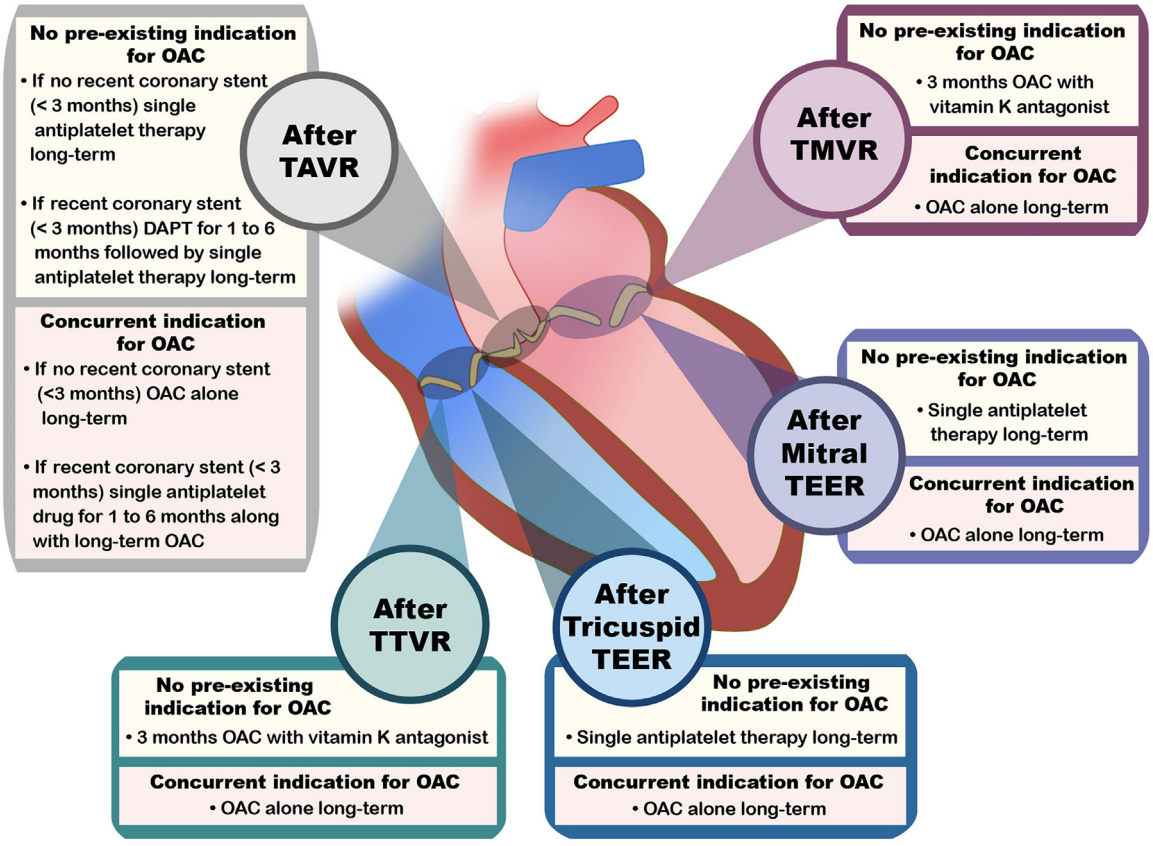

Figure 2. Suggested antithrombotic strategies after transcatheter valve interventions. DAPT = dual antiplatelet therapy; OAC = oral anticoagulation; TAVR = transcatheter aortic valve replacement; TEER = transcatheter edge-to-edge repair; TMVR = transcatheter mitral valve replacement; TTVR = transcatheter tricuspid valve replacement.

recommend 1 to 3 months of DAPT for chronic coronary syndromes or 3 to 6 months of DAPT for acute coronary syndromes.[50]

For patients with a pre-existing indication for OAC undergoing TAVR, the ESC/European Association for Cardio-Thoracic Surgery guidelines recommend OAC alone long term (without concurrent antiplatelet therapy) (Class I, Level of Evidence B).[47] In patients with a concurrent indication for OAC and recent coronary stenting (within 3 months of TAVR), a single antiplatelet drug for 1 to 6 months is recommended along with long-term OAC (warfarin or a direct oral anticoagulant [DOAC]).[50]

Similarly, the 2020 American Heart Association/American College of Cardiology guidelines state that lifelong single antiplatelet therapy should be considered after TAVR[51] (Table 1). However, in contrast to European recommendations, the US guidelines state that DAPT (aspirin and clopidogrel) or warfarin (but not DOAC) may be considered for 3 to 6 months after TAVR in patients with low bleeding risk.[51]

Antiplatelet Strategies After TAVR in Patients Without Concurrent Indication for OAC

The present article provides evidence from randomized trials supporting the aforementioned recommendations. Four open-label, randomized trials compared the effect of different antiplatelet strategies on clinical outcomes after TAVR in patients without a pre-existing indication for OAC[52–55] (Table 2). The ARTE (Aspirin Versus Aspirin and Clopidogrel Following TAVR) trial included 222 patients (mean age, 79 years; 58% male) who had TAVR with a balloon-expandable valve (92% SAPIEN XT [Edwards Lifesciences, Irvine, CA, USA]).[52] There was a threefold higher incidence of major/life-threatening bleeds with DAPT (aspirin [80–100 mg/d] and clopidogrel [75 mg/d]) compared with aspirin monotherapy, with no difference in the risk of death, MI, or stroke at 3 months' post-TAVR. All bleeding events occurred within the first month after TAVR, and the majority (56%) were due to vascular or access-site complications.

These findings were corroborated by the larger (N = 665) POPular TAVI (Antiplatelet Therapy for Patients Undergoing TAVR) trial (cohort A), which included patients with a mean age of 80 years (51% male).[53] The main valve types used were: SAPIEN 3 (Edwards Lifesciences), 45%; CoreValve Evolut R (Medtronic, Minneapolis, MN, USA), 26%; CoreValve Evolut Pro (Medtronic), 11%; Lotus (Boston Scientific, Boston, MA, USA), 4%; and Accurate Neo (Boston Scientific), 4%. POPular TAVI (cohort A) reported fewer bleeds at 1 year with aspirin monotherapy compared with 3 months of DAPT (aspirin [80–100 mg/d] and clopidogrel [75 mg/d]) followed by aspirin monotherapy post-TAVR, without increasing ischaemic events (Table 2). Of all bleeds, the most common cause was access site bleeding.

The SAT-TAVI (single antiplatelet therapy for TAVR) pilot randomized study compared aspirin monotherapy versus DAPT (aspirin and clopidogrel) for 6 months in 120 patients (mean age, 81 years; 33% male) after TAVR with the SAPIEN XT valve.[54] There was no difference in cardiovascular mortality at 6 months; however, at 30 days, vascular complications were more frequent with DAPT compared with aspirin monotherapy (Table 2). A smaller randomized trial (N = 79) compared aspirin monotherapy versus 3 months of DAPT (aspirin and clopidogrel) after TAVR and found no difference in mortality, MI, stroke, emergency conversion to surgery, or life-threatening bleeds.[55]

Follow-up CT imaging was not performed in the ARTE,[52] POPular-TAVI,[53] or SAT-TAVI[54] trial. Therefore, the occurrence of subclinical leaflet thrombosis after TAVR was not evaluated in those trials.

OAC After TAVR in Patients Without a Pre-existing Indication for OAC

Four open-label, randomized trials investigated the effect of OAC on clinical outcomes after TAVR in patients without an established indication for OAC[56–59] (Table 3). The largest (N = 1644) was the GALILEO (Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After TAVR to Optimise Clinical Outcomes) trial.[56] GALILEO had an open-label design and randomized TAVR patients to receive low-dose rivaroxaban (10 mg daily) in combination with aspirin (75–100 mg) for 3 months followed by rivaroxaban monotherapy versus DAPT (aspirin [75–100 mg] and clopidogrel [75 mg]) for 3 months followed by aspirin monotherapy. The mean age was 80 years (51% male), 6% had valve-in-valve (ViV) TAVR, and the most frequently used valve types were SAPIEN 3 (44%), CoreValve Evolut R (26%), Accurate Neo (10%), Lotus (5%), and Portico (Abbott, Abbott Park, IL, USA) (5%). At 17 months, the rivaroxaban group had a higher incidence of death, thromboembolic complications, and major bleeds compared with the antiplatelet therapy group.

The ATLANTIS (Antithrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Haemorrhagic Events After TAVR for Aortic Stenosis) trial investigated an even more powerful antithrombotic regimen of apixaban 5 mg BID after successful TAVR.[57] The mean age was 82 years (47% male), and 5% had ViV TAVI. The ATLANTIS trial stratum 2 (n = 1049) included patients without an established indication for OAC, and study participants were randomized to receive 1 year of apixaban versus antiplatelet therapy (single antiplatelet therapy or DAPT [aspirin and clopidogrel] with doses left to the physician's discretion). In ATLANTIS stratum 2, there was no difference in the composite of thromboembolic or bleeding events (major, disabling, or life-threatening) between apixaban versus antiplatelet therapy at 1 year (Table 3). Interestingly, in ATLANTIS stratum 2, apixaban was associated with a lower incidence of obstructive valve thrombosis and a higher incidence of non-cardiovascular death compared with antiplatelet therapy (Table 2). However, these findings should be interpreted with caution due to the risk of a type I statistical error with multiple statistical analyses.

Both the GALILEO[56] and ATLANTIS[57] trials had four-dimensional CT substudies to detect subclinical TAVR leaflet thrombosis. In the GALILEO trial substudy,[60] cardiac CT imaging was performed at a mean of 3 months after TAVR, and the primary end point was at least one prosthetic leaflet with >50% RLM. There was a lower incidence of RLM with rivaroxaban compared with DAPT (2.1% vs 10.9%; $P = 0.01$), even though death, thromboembolic events, and bleeds were worse with rivaroxaban in the GALILEO trial.[56] In the ATLANTIS trial substudy,[61] cardiac CT imaging was performed 3 to 6 months' post-TAVR, and the primary end point was at least one prosthetic leaflet with >50% RLM or HALT grade ≥4. Among the 558 patients without an established indication for OAC who had CT imaging performed, there was a reduction in the primary end point with apixaban compared with antiplatelet therapy (odds ratio, 0.51; 95% CI, 0.30–0.86; $P = 0.01$). However, this did not translate to a reduction in death, MI, stroke, or pulmonary embolism in the main ATLANTIS trial.[57]

Another notable study is the ADAPT-TAVR (Anticoagulant Versus Dual Antiplatelet Therapy for Preventing Leaflet Thrombosis and Cerebral Embolization After TAVR) trial.[58] The results of ADAPT-TAVR reaffirm findings from the ATLANTIS[61] and GALILEO[60] CT substudies, in terms of DOAC therapy reducing the risk of subclinical leaflet thrombosis, without reducing stroke rates. Specifically, in 229 patients (mean age, 80 years; 42% male) with CT imaging performed 6 months after TAVR (89% SAPIEN 3 valves), there was a trend toward reduced incidence of leaflet thrombosis with edoxaban (60 mg or 30 mg once daily) compared with DAPT with aspirin (100 mg daily) and clopidogrel (75 mg daily) (9.8% vs 18.4%; absolute difference, –8.5% [95% CI, –17.8 to 0.8; $P = 0.076$]).[58] There was no difference in the incidence of new cerebral thromboembolism on magnetic resonance imaging between the 2 groups (Table 3). However, ADAPT-TAVR was underpowered to detect differences in clinical events.

In the LRT 2.0 (Low Risk TAVR) trial,[59] warfarin in combination with low-dose aspirin was shown to reduce HALT compared with aspirin alone. LRT 2.0 was a small randomized trial (N = 94) of low-risk TAVR patients, with a mean age of 73 years (70% male). Warfarin was not associated with an increased risk of bleeding (Table 3). Unfortunately, the LRT 2.0 trial was underpowered to evaluate whether warfarin in

Table 2
Published randomized studies of antiplatelet treatment strategies for transcatheter aortic valve replacement (TAVR) patients without a concurrent indication for oral anticoagulation (OAC).

Study	Year	Sample Size	Groups Compared	Follow-up	Inclusion Criteria	Main Exclusion Criteria	Primary End Point	Main Findings
ARTE,[52] NCT01559298 NCT02640794	2017	222	Aspirin monotherapy vs aspirin + clopidogrel after TAVR	3 months	TAVR to native valve with balloon-expandable valve SAPIEN XT (92%), SAPIEN 3 (8%)	Indication for chronic OAC Major bleed ≤3 months' pre-TAVR PCI with drug-eluting stent ≤ 1year pre-TAVR Prior intracranial bleed	Composite of death, MI, stroke, transient ischemic attack, or major/life-threatening bleed	No difference in primary end point with DAPT vs aspirin (15.3% vs 7.2%; odds ratio, 2.31 [95% CI, 0.95–5.62]; $P = 0.065$) DAPT ↑ risk of major/life-threatening bleeds compared with aspirin monotherapy (10.8% vs 3.6%; odds ratio, 3.22 [95% CI, 1.01–10.34]; $P = 0.038$) without being associated with ↓ risk of death (6.3% vs 3.6%; $P = 0.37$), MI (3.6% vs 0.9%; $P = 0.18$), or stroke (2.7% vs 0.9%; $P = 0.31$)
POPular-TAVI Cohort A,[53] NCT02247128	2020	665	Aspirin monotherapy vs aspirin + clopidogrel for 3 months' post-TAVR then aspirin monotherapy thereafter	12 months	TAVR to native valve SAPIEN 3 (45%), CoreValve Evolut R (26%), CoreValve Evolute Pro (11%), Lotus (4%), Accurate Neo (4%), other (10%)	Indication for chronic OAC PCI with drug-eluting stent ≤3 months or with bare metal stent ≤1 month pre-TAVR	Two primary end points: All bleeding (minor, major, life-threatening, or disabling) Nonprocedure-related bleeding (including bleeding at the puncture site)	Aspirin monotherapy ↓ risk of bleeding of any type compared with DAPT (15.1% vs 26.6%; risk ratio, 0.57 [95% CI, 0.42–0.77]; $P = 0.001$) Aspirin monotherapy ↓ risk of nonprocedure-related bleeds compared with DAPT (15.1% vs 24.9%; risk ratio, 0.61 [95% CI, 0.44–0.83]; $P = 0.005$) No difference between aspirin monotherapy and DAPT for death from cardiovascular causes, stroke, or MI (9.7% vs 9.9%)
SAT-TAVI[54]	2014	120	Aspirin monotherapy vs aspirin + clopidogrel for 6 months' post-TAVR then aspirin monotherapy thereafter	6 months	TAVR to native valve with SAPIEN-XT	Indication for chronic OAC Untreated coronary artery disease requiring revascularization PCI with drug-eluting stent ≤6 months Severe aortic or mitral regurgitation, or prosthetic valve (any location)	Primary end point not specified. Adverse cardiovascular events were reported, including cardiovascular death, stroke, major, and minor vascular complications	At 30 days, vascular complications were ↓ with aspirin monotherapy compared with DAPT (5% vs 13.3%; $P < 0.05$) No difference in cardiovascular death or stroke between the aspirin monotherapy and DAPT groups
Ussia et al[55]	2011	79	Aspirin monotherapy vs aspirin + clopidogrel for 3 months' post-TAVR then aspirin monotherapy thereafter	6 months	TAVR to native valve with CoreValve	Indication for chronic OAC Previous PCI or MI requiring DAPT	Composite of all-cause death, MI, stroke, urgent or emergency conversion to surgery, or life-threatening bleed	No difference between aspirin monotherapy and DAPT for the primary end point (15% vs 18%; $P = 0.85$)

ARTE = Aspirin Versus Aspirin and Clopidogrel Following TAVR; DAPT = dual antiplatelet therapy; MI = myocardial infarction; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; POPular TAVI = Antiplatelet Therapy for Patients Undergoing TAVR; SAT-TAVI = single antiplatelet therapy for TAVR.

Table 3
Published randomized studies of oral anticoagulation for transcatheter aortic valve replacement (TAVR) patients without established indication for oral anticoagulation.

Study	Year	Sample Size	Groups Compared	Follow-up	Inclusion Criteria	Main Exclusion Criteria	Primary End Point	Main Findings
GALILEO,[56] NCT02556203	2020	1644	Rivaroxaban 10 mg long-term + aspirin for the first 3 months vs aspirin long-term + clopidogrel for the first 3 months	17 months	Successful TAVR for aortic stenosis either native or ViV SAPIEN 3 (44%), CoreValve Evolut R (26%), Accurate Neo (10%), Lotus (5%), Portico (5%), other (9%)	Known bleeding diathesis Any absolute indication for DAPT Clinically overt stroke within the previous 3 months Severe renal or hepatic impairment	Efficacy outcome: death or thromboembolic event (ie, stroke, MI, symptomatic valve thrombosis, non–central nervous system systemic embolism, pulmonary embolism, or deep vein thrombosis) Safety outcome: major, life-threatening, or disabling bleed	↑ deaths or thromboembolic events in the rivaroxaban group vs antiplatelet only group (incidence, 9.8 vs 7.2 per 100 person-years; hazard ratio, 1.35 [95% CI, 1.01 to 1.81]; $P = 0.04$) Trend to ↑ primary safety outcome bleeds in the rivaroxaban group than the antiplatelet-only group (incidence, 4.3 vs 2.8 per 100 person-years; hazard ratio, 1.50 [95% CI, 0.95 to 2.37]; $P = 0.08$) Incidence of major bleeds ↑ in the rivaroxaban group (2.8 vs 1.4 per 100 person-years; hazard ratio, 2.02 [95% CI, 1.09 to 3.76])
GALILEO-4D,[60] NCT02833948	2020	231	Rivaroxaban 10 mg long-term + aspirin for the first 3 months vs aspirin long-term + clopidogrel for the first 3 months	3 months	Successful TAVR for aortic stenosis either native or ViV	Known bleeding diathesis Any absolute indication for DAPT Clinically overt stroke within the previous 3 months Severe renal or hepatic impairment	≥1 prosthetic leaflet with >50% RLM, detected on 4D CT imaging	Incidence of RLM ↓ in the rivaroxaban group vs antiplatelet-only group (2.1% vs 10.9%; $P = 0.01$)
ATLANTIS stratum 2,[57] NCT02664649	2022	1049	Apixaban 5 mg BID vs single antiplatelet therapy or DAPT (aspirin and/or clopidogrel)	12 months	Successful TAVR Balloon-expanding valve (48%), self-expanding valve (52%)	Concomitant use of ticagrelor or prasugrel Previous intracranial haemorrhage Creatinine clearance <15 mL/min or dialysis	Composite of death, MI, stroke, or transient ischaemic attack, non– central nervous system embolism, pulmonary embolism, intracardiac or valve thrombosis, deep vein thrombosis, life-threatening, disabling, or major bleeding	No difference in the primary end point for apixaban vs antiplatelet therapy (16.9% vs 19.3%; hazard ratio, 0.88 [95% CI, 0.66 to 1.17]) Incidence of obstructive valve thrombosis ↓ in the apixaban group vs antiplatelet group (1.1% vs 6.1%; odds ratio, 0.19 [95% CI, 0.08 to 0.46]) Non-cardiovascular death ↑ in the apixaban group (2.7% vs 1.0%; hazard ratio, 2.99 [95% CI, 1.07 to 8.36]) No difference in cardiovascular deaths for apixaban vs antiplatelet group (3.2% vs 2.5%; hazard ratio, 1.42 [95% CI, 0.69 to 2.95]) No difference in bleeding for apixaban vs antiplatelet group (21.9% vs 21.4%; hazard ratio, 1.05 [95% CI, 0.81 to 1.36])

(*continued on next page*)

Table 3 (*continued*)

Study	Year	Sample Size	Groups Compared	Follow-up	Inclusion Criteria	Main Exclusion Criteria	Primary End Point	Main Findings
ATLANTIS-4D-CT Stratum 2,[61] NCT02664649	2022	558	Apixaban 5 mg BID vs single antiplatelet therapy or DAPT (aspirin and/or clopidogrel)	3–6 months	Successful TAVR	Concomitant use of ticagrelor or prasugrel Previous intracranial haemorrhage Creatinine clearance <15 mL/min or dialysis	≥1 prosthetic leaflet with >50% RLM or HALT grade ≥4, detected on 4D CT imaging	Primary end point ↓ in the apixaban vs antiplatelet group (odds ratio, 0.51 [95% CI, 0.30 to 0.86]; $P = 0.01$) RLM ↓ in the apixaban vs antiplatelet group (odds ratio, 0.12 [95% CI, 0.03 to 0.40])
ADAPT-TAVR,[58] NCT03284827	2022	229	Edoxaban 60 mg vs DAPT (aspirin + clopidogrel)	6 months	Successful TAVR SAPIEN 3 (89%), CoreValve Evolut R (5%), other (6%)	Any absolute indication for DAPT (eg, recent PCI) Severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2 body surface area)	Incidence of valve leaflet thrombosis detected on 4D CT imaging	Trend toward ↓ incidence of leaflet thrombosis in the edoxaban group vs DAPT group (9.8% vs 18.4%; absolute difference, –8.5% [95% CI, –17.8 to 0.8]; $P = 0.076$) No difference in the % of new cerebral lesions on magnetic resonance imaging in patients with edoxaban vs DAPT (25.0% vs 20.2%; absolute difference, 4.8% [95% CI, –6.4 to 16.0]; $P = 0.40$)
LRT 2.0,[59] NCT03557242	2021	94	Warfarin + aspirin vs aspirin	30 days	TAVR Society of Thoracic Surgeons Predicted Risk of Mortality score ≤3%	Aortic stenosis secondary to bicuspid aortic valve Prior bioprosthetic surgical aortic valve End-stage renal disease Left ventricular ejection fraction <20% Recent stroke (<6 months) or MI (<30 days)	Composite of HALT, ≥moderate RLM, hemodynamic dysfunction (mean aortic valve gradient ≥20 mm Hg, effective orifice area ≤1.0 cm^2, dimensionless valve index <0.35, ≥moderate aortic regurgitation, stroke, or transient ischaemic attack	Primary end point ↑ with aspirin vs warfarin + aspirin (26.5% vs 7.0%; odds ratio, 4.8 [95% CI, 1.3 to 18.3]; $P = 0.014$) No difference in bleeding between the 2 groups In the as-treated-analysis, HALT was ↑ with aspirin vs warfarin + aspirin (16.7% vs 3.1%; odds ratio, 6.3 [95% CI, 1.3 to 30.6]; $P = 0.011$)

4D CT = four-dimensional computed tomography; ADAPT-TAVR = Anticoagulant Versus Dual Antiplatelet Therapy for Preventing Leaflet Thrombosis and Cerebral Embolization After TAVR; ATLANTIS = Antithrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Haemorrhagic Events After TAVR for Aortic Stenosis; DAPT = dual antiplatelet therapy; GALILEO = Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After TAVR to Optimise Clinical Outcomes; HALT = hypoattenuated leaflet thickening; LRT 2.0 = Low Risk TAVR; MI = myocardial infarction; PCI = percutaneous coronary intervention; RLM = reduced leaflet motion; ViV = valve-in-valve.

Table 4
Published randomized studies of antithrombotic treatment strategies for transcatheter aortic valve replacement (TAVR) patients with a concurrent indication for oral anticoagulation (OAC).

Study	Year	Sample Size	Groups Compared	Follow-up	Inclusion Criteria	Main Exclusion Criteria	Primary End Point	Main Findings
POPular-TAVI Cohort B,[62] NCT02247128	2020	326	OAC alone vs clopidogrel + OAC for 3 months' post-TAVR	12 months	TAVR in patients receiving OAC for another indication	PCI with drug-eluting stent ≤3 months or with bare metal stent ≤1 month pre-TAVR	Two primary end points: All bleeding (minor, major, life-threatening or disabling) Nonprocedure-related bleeding (including bleeding at the puncture site)	OAC alone ↓ risk of bleeding of any type vs OAC + clopidogrel (21.7% vs 34.6%; risk ratio, 0.63 [95% CI, 0.43–0.90]; $P = 0.01$) OAC alone ↓ risk of nonprocedure-related bleeds vs OAC + clopidogrel (21.7% vs 34.0%; risk ratio, 0.64 [95% CI, 0.44–0.92]; $P = 0.02$) No difference in cardiovascular deaths, MI, or ischemic stroke with OAC alone vs OAC + clopidogrel (13.4% vs 17.3%; risk ratio, 0.77 [95% CI for superiority, 0.46–1.31])
ATLANTIS stratum 1,[57] NCT02664649	2022	451	Apixaban 5 mg BID vs vitamin K antagonist	12 months	Successful TAVR in patients receiving OAC for another indication	Concomitant use of ticagrelor or prasugrel Previous intracranial haemorrhage Creatinine clearance <15 mL/min or dialysis	Composite of death, MI, stroke, or transient ischaemic attack, non–central nervous system embolism, pulmonary embolism, intracardiac or valve thrombosis, deep vein thrombosis, and life-threatening, disabling, or major bleeding	No difference in the primary end point for apixaban vs vitamin K antagonist (22.0% vs 21.9%; hazard ratio, 1.02 [95% CI, 0.69–1.51]) No difference in incidence of obstructive valve thrombosis for apixaban vs vitamin K antagonist (0.9% vs 1.3%; odds ratio, 0.68 [95% CI, 0.11–4.08]) No difference in mortality between apixaban vs vitamin K antagonist groups (10.3% vs 10.1%; hazard ratio, 1.04 [95% CI, 0.58–1.86]) No difference in bleeding between apixaban vs vitamin K antagonist groups (26.5% vs 25.4%; hazard ratio, 1.05 [95% CI, 0.73–1.51])
ENVISAGE-TAVI AF,[13] NCT02943785	2021	1426	Edoxaban (60 mg or 30 mg) vs vitamin K antagonist (antiplatelet therapy administered at the clinician's discretion)	Mean 18 months	Successful TAVR for severe aortic stenosis, in patients receiving OAC for another indication	Co-existing conditions that confer higher risk of bleeding	Composite of all-cause death, MI, ischaemic stroke, systemic thromboembolism, valve thrombosis, or major bleeding	Edoxaban noninferior to vitamin K antagonist for the primary end point (17.3 per 100 person-years vs 16.5 per 100 person-years; hazard ratio, 1.05 [95% CI, 0.85–1.31]; $P = 0.01$ for noninferiority) Risk of major gastrointestinal bleed ↑ with edoxaban vs vitamin K antagonist (5.4 per 100 person-years vs 2.7 per 100 person-years; hazard ratio, 2.03 [95% CI, 1.28–3.22])

ATLANTIS = Antithrombotic Strategy to Lower All Cardiovascular and Neurologic Ischaemic and Haemorrhagic Events After TAVR for Aortic Stenosis; ENVISAGE-TAVI AF = Edoxaban Versus Vitamin K Antagonists After TAVR in Patients with Atrial Fibrillation; MI = myocardial infarction; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; POPular TAVI = Antiplatelet Therapy for Patients Undergoing TAVR.

combination with aspirin post-TAVR might reduce thromboembolic events or mortality in this population of relatively younger, low-risk patients.

TAVR in Patients With an Established Indication for Chronic OAC

Three open-label randomized trials investigated the optimal antithrombotic strategy in TAVR patients with a coexisting indication for long-term OAC[13,57,62] (Table 4).

POPular TAVI Cohort B was a trial of 326 TAVR patients (mean age, 81 years; 55% male) who were receiving OAC for another indication (27% were taking DOAC and 73% were taking vitamin K antagonists).[62] These patients were randomized to receive 3 months of clopidogrel (75 mg daily) versus no antiplatelet drug. OAC alone was associated with lower incidence of bleeds compared with OAC plus clopidogrel (Table 4). The TAVR access site was the most common location of bleeding. There was no difference in cardiovascular deaths, MI, or ischaemic stroke between the 2 groups.

Another notable trial was ATLANTIS stratum 1,[57] which included 451 patients with an established indication for OAC, randomized to receive apixaban versus vitamin K antagonist. ATLANTIS stratum 1 showed that apixaban 5 mg BID, compared with a vitamin K antagonist, had similar rates of the composite end point of thromboembolic events or bleeding, and no difference in the rate of obstructive valve thrombosis (Table 4).

The ENVISAGE-TAVI AF (Edoxaban Versus Vitamin K Antagonists After TAVR in Patients with Atrial Fibrillation) trial enrolled 1426 patients (mean age, 82 years; 53% male), almost all with atrial fibrillation as the indication for OAC after successful TAVR.[13] Edoxaban (60 mg or 30 mg) was compared with a vitamin K antagonist, and antiplatelet therapy was administered at the clinician's discretion. The primary end point was a composite of all-cause death, MI, ischaemic stroke, systemic thromboembolism, valve thrombosis, or major bleeding. Edoxaban was noninferior to the vitamin K antagonist for the primary end point of net adverse events (Table 4). An increased risk of major gastrointestinal bleeding was observed with edoxaban; however, the bleeding outcomes may have been affected by subtherapeutic international normalized ratio values and a higher incidence of drug discontinuation in the vitamin K antagonist group.

The attraction of DOACs, over vitamin K antagonists, is that monitoring of the international normalized ratio is not required, and DOACs are less influenced by food or other medications than warfarin. A meta-analysis of 8 studies (2 randomized[13,57] and 6 observational[63–68] [mean age, 81 years]), which compared vitamin K antagonists versus DOAC after TAVR in patients with atrial fibrillation, showed no difference in all-cause mortality, stroke, or major bleeds.[69] However, risk of any bleeding was lower with DOAC compared with vitamin K antagonists. The findings suggest that DOACs are a safe alternative to vitamin K antagonists in this setting, although larger randomized trials are warranted to confirm the results.

Transcatheter Mitral Valve Intervention

Antithrombotic Therapy After TMVR

TMVR is an option for patients with severe primary mitral regurgitation, with contraindications for surgery, or prohibitive surgical risk, who are not suitable candidates for M-TEER.[47] There is lack of randomized trial data on the management of antithrombotic therapy after TMVR; consequently, considerable antithrombotic treatment variation exists in clinical studies and practice.[70,71]

Observational study data suggest a lower incidence of valve thrombosis when anticoagulation is used after TMVR compared with antiplatelet therapy.[70] In the surgical arena, the ENAVLE (Explore the Efficacy and Safety of Edoxaban in Patients After Heart Valve Repair or Bioprosthetic Valve Replacement) trial included patients with and without atrial fibrillation undergoing surgical aortic or mitral bioprosthetic valve replacement or repair.[72] In 220 patients, edoxaban was noninferior to warfarin in terms of thromboembolic and bleeding events at 3 months (0% vs 3.7%; risk difference, –0.0367 [95% CI, –0.0720 to –0.0014]; $P < 0.0001$ for noninferiority). The findings are supported by the open-label RIVER (Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation) trial, which included 1005 patients with atrial fibrillation undergoing surgical bioprosthetic mitral valve replacement.[73] Although rivaroxaban (20 mg daily) was shown to be noninferior to warfarin, with respect to the composite of cardiovascular death or thromboembolic events at 12 months' follow-up (3.4% vs 5.1%; hazard ratio, 0.65; 95% CI, 0.35 to 1.20), only 20% of patients were enrolled before the third postoperative month. There was also no difference in major bleeds between rivaroxaban versus warfarin in the RIVER trial (1.4% vs 2.6%; hazard ratio, 0.54 [95% CI, 0.21 to 1.35]). It remains to be determined how the findings from surgical patients undergoing mitral valve replacement apply to patients treated by using transcatheter therapies. Future randomized trials are warranted to clarify the role of DOACs after TMVR.

Due to lack of evidence-based data for antithrombotic therapy after TMVR, there are no European or US guideline recommendations in this setting. For the purpose of the present review, suggestions for antithrombotic therapy after TMVR were extrapolated from current recommendations in patients undergoing surgical bioprosthetic mitral valve replacement. In patients with no pre-existing indication for OAC, the ESC guidelines recommend considering 3 months of OAC with a vitamin K antagonist (target international normalized ratio, 2.5) after surgical bioprosthetic mitral valve replacement (Class IIa, Level of Evidence C).[47] The US guidelines state that 3 to 6 months of OAC with a vitamin K antagonist is reasonable after surgical bioprosthetic mitral valve replacement in patients who are at low bleeding risk.[51] The US guidelines also state that aspirin monotherapy (75–100 mg daily) can be considered as an alternative to vitamin K antagonists after surgical bioprosthetic mitral valve replacement in the absence of other indications for OAC.[51,74] Based on the high incidence of atrial fibrillation in patients who have TMVR[8] and the thrombogenicity of the non-endothelialized mitral replacement device components, OAC for 3 months after TMVR should be favored[1] (Figure 2). It has been suggested in expert opinion articles that even though OAC is reasonable in the first months after TMVR, the duration on OAC could be tailored to an individual patient's bleeding risk; however, such a strategy is not based on dedicated research studies.[75] In patients with other indications for OAC, long-term OAC should be continued after TMVR without the addition of antiplatelet therapy. Future randomized trials are needed to define the optimal antithrombotic strategies after TMVR.

Antithrombotic Therapy After M-TEER

M-TEER is recommended in patients with chronic severe symptomatic mitral regurgitation who are receiving optimal medical therapy and have appropriate anatomy on transesophageal echocardiography, with a left ventricular ejection fraction between 20% and 50%, left ventricular end systolic diameter ≤70 mm, and pulmonary artery systolic pressure ≤70 mmHg (Class IIa, Level of Evidence B).[51] The antithrombotic strategies differed in the 3 major trials that investigated the safety and efficacy of M-TEER with a MitraClip (Abbott).[76–78]

In the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial,[76] patients without a pre-existing indication for OAC received aspirin (81 mg daily) and/or clopidogrel (75 mg daily) for ≥6 months after M-TEER. In contrast, for the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial,[78] patients received either DAPT (aspirin and clopidogrel) for 3 months, followed by aspirin monotherapy, or in patients with a pre-existing indication for OAC, aspirin was added to OAC for 3 months. In the EVEREST II (Pivotal Study of a Percutaneous Mitral Valve Repair System) trial,[77] however, patients received DAPT with aspirin (325 mg daily) and clopidogrel (75 mg daily) for 30 days, followed by aspirin monotherapy for 6 months; in patients with a pre-existing indication for OAC, antiplatelet therapy was not added after M-TEER.

There are no published randomized trials comparing antithrombotic regimens after M-TEER, and there is a lack of standardization in antithrombotic strategies in this setting. A retrospective study in Germany showed that after M-TEER, 22% of patients received antiplatelet monotherapy, 19% received OAC monotherapy, 21% received OAC and antiplatelet therapy, 21% received no antithrombotic therapy, 12% received DAPT, and 3% received OAC and DAPT.[79]

Observational data suggest a higher risk of death or thromboembolism with no antithrombotic treatment after M-TEER, compared with antiplatelet monotherapy.[79] Furthermore, observational data in patients without atrial fibrillation suggest that the risk of thromboembolism is similar with aspirin or OAC after M-TEER.[80] In patients with a pre-existing indication for OAC, observational data suggest that OAC monotherapy is associated with lower risk of mortality; thus, adding antiplatelet therapy to OAC in this setting may worsen outcomes.[14]

Overall, based on observational data,[14,79,80] it seems reasonable to suggest single antiplatelet therapy after M-TEER in patients with no pre-existing indication for OAC, whereas if there is a pre-existing indication for warfarin or DOAC, adding antiplatelet drugs is not necessary (Figure 2). Guidelines for antithrombotic therapy after M-TEER are required but should be formulated on appropriately sized robust trials.

Transcatheter Tricuspid Valve Intervention

Transcatheter tricuspid valve interventions, including annuloplasty devices, T-TEER, or valve replacement, have a Class IIb recommendation in the ESC guidelines for patients with symptomatic, secondary, severe tricuspid regurgitation who are inoperable.[47] Currently, however, data are lacking to support evidence-based antithrombotic regimens in patients undergoing transcatheter tricuspid valve interventions. Extrapolating recommendations from surgical bioprostheses, in the absence of concomitant indications for long-term OAC, one could consider 3 months of OAC with vitamin K antagonist after TTVR, whereas after T-TEER, one could consider single antiplatelet therapy. However, long-term OAC is often already indicated in this setting, given that the majority of patients undergoing transcatheter tricuspid valve interventions have atrial fibrillation.[15] Future research is needed to estab-

lish the optimal anticoagulation duration after transcatheter tricuspid interventions.

Discussion

Overall, randomized trials support a less potent antithrombotic strategy post-TAVR (ie, single antiplatelet therapy in patients without an established indication for OAC). If a patient has a pre-existing indication for warfarin or DOAC, the evidence supports continuing OAC without the addition of antiplatelet therapy. The net clinical benefit of this strategy in randomized trials is driven mainly by a lower risk of bleeding events. Vascular access site complications and gastrointestinal bleeds were the most common cause of bleeding post-TAVR.[13,52,53,62]

Of note, all the randomized trials in Tables 2 to 4 had an open-label design and were therefore potentially subject to reporting and ascertainment bias. Furthermore, the duration of follow-up for detecting adverse clinical events was relatively short, ranging from 30 days to 18 months. The trials tended to include elderly patients, which reflects the traditional practice whereby TAVR has been performed in older, frail patients with comorbidities that are associated with increased risk of bleeding and thromboembolic events. However, the risk profile among patients referred for TAVR is decreasing, as a result of expanding indications. Therefore, the trial findings might not be applicable to younger, lower risk TAVR patients.

Another important consideration is that transcatheter approaches represent a new treatment option in patients with degenerated bioprostheses (ie, ViV aortic or mitral valve replacement) and failed mitral annuloplasty rings (ie, valve-in-ring [ViR] mitral valve replacement). However, such patients are not included or are underrepresented in the aforementioned randomized trials. The risk of leaflet thrombosis seems to be higher after ViV implantation than after native valve implantation,[81] likely due to geometric confinement of transcatheter heart valves by the degenerated bioprosthesis, and these patients may also have a higher risk of stroke.[48] ViR mitral valve replacement may also be associated with higher risk of valve thrombosis because the position of the transcatheter heart valve relative to the failed annuloplasty ring could determine a perivalvular low-flow space, potentially enhancing thrombogenicity.[75]

Even though studies have shown that OAC (but not DAPT) after TAVR reduced the incidence of subclinical leaflet thrombosis,[59–61,82] this has not translated to a reduction in cerebral thromboembolic events, or reduction in mortality, in randomized trials.[56,57] Therefore, based on the currently available evidence, routine CT imaging after TAVR to detect subclinical leaflet thrombosis is not indicated. An observational study with the longest follow-up to date showed that at 3.25 years, HALT was not associated with stroke or mortality but was associated with symptomatic valve deterioration (9.4% with HALT vs 1.5% without HALT; $P < 0.001$).[83] The long-term natural history and significance of subclinical leaflet thrombosis remains incompletely understood.[84]

Future Perspectives

Several unanswered questions remain. First, the duration of antiplatelet therapy after TAVR is not well established. Second, future research is warranted to investigate the hypothesis that low-dose OAC might reduce thromboembolic events and mortality, without being associated with increased bleeding, in lower risk TAVR patients, who are younger and with fewer high bleeding risk characteristics. Another evidence gap is the impact of HALT on thrombotic complications after TAVR. Studies with longer follow-up are warranted to further evaluate whether subclinical leaflet thrombosis progresses to structural valve degeneration over time[85] and whether it is associated with stroke and other thromboembolic events in the long run. Importantly, the optimal antithrombotic strategy remains unclear in subsets of patients undergoing transcatheter ViV aortic or mitral valve replacement, or ViR or valve-in-mitral annular calcification TMVR. Future research should address this topic to enable evidence-based consensus recommendations in these subpopulations. Given the paucity of randomized trial data to guide antithrombotic therapy after M-TEER, T-TEER, TMVR, or TTVR, further research is warranted. In particular, future randomized studies should clarify the efficacy and safety of DOACs in the early postprocedure phase after TMVR in patients without a pre-existing indication for OAC.

Ongoing Studies

A notable ongoing randomized trial is ACASA-TAVI (Anticoagulation versus AcetylSalicylic Acid after TAVR) (NCT05035277), which is comparing OAC with DOAC (rivaroxaban 20 mg daily, apixaban 5 mg BID, or edoxaban 60 mg daily) versus single antiplatelet therapy after TAVR.[86] The co-primary end points of the ACASA-TAVI trial are: (1) incidence of HALT; and (2) the composite of Valve Academic Research Consortium 3[28] bleeding events, MI, stroke and death from any cause at 1 year. Another ongoing trial is AVATAR (Anticoagulation Alone Versus Anticoagulation and Aspirin Following TAVI) (NCT02735902), which is recruiting TAVR patients with an underlying indication for long-term OAC; the goal is to investigate the 12-month net clinical benefit of OAC with a vitamin K antagonist or DOAC compared with OAC with the addition of aspirin.

Conclusions

After TAVR, evidence from randomized trials suggests single antiplatelet therapy for patients without concurrent indication for OAC and continuation of OAC (without the addition of antiplatelet therapy) in patients with a pre-existing indication for warfarin or DOAC. After M-TEER or T-TEER, single antiplatelet therapy may be considered in patients with no pre-existing indication for OAC; if there is a coexisting indication for OAC, adding antiplatelet drugs is not necessary, although evidence-based guidelines are needed. After TMVR or TTVR, data extrapolated from studies in patients having surgical bioprosthetic valve replacement suggest that OAC is indicated for at least 3 months in patients without prior indication for OAC. Randomized studies are warranted to address the knowledge gaps in antithrombotic therapy after transcatheter valve interventions and to optimize outcomes.

Declaration of Competing Interest

None declared.

Acknowledgements

There are no funders to report for the manuscript. All contributors to the manuscript are in the author list. AM's role involved writing the first draft of the manuscript, performing the literature search, interpreting data and creating the figures and tables. TP's role involved manuscript writing, intellectual content of the manuscript and data interpretation.

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