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REVIEW

TAVI

Thrombo-embolic prevention after transcatheter aortic valve implantation

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Transcatheter aortic valve implantation (TAVI) has emerged as a valuable treatment alternative to surgical aortic valve replacement among patients with symptomatic aortic stenosis at increased surgical risk. The rapid technological evolution from early to current-generation TAVI systems with low-profile delivery catheters, bioprosthetic valves with proven midterm durability, and improved positioning and retrieval features have made important contributions to the widespread clinical use of this minimal invasive therapy. Although peri-procedural and long-term thrombotic and bleeding events after TAVI remain a relevant concern, the optimal antithrombotic strategy and duration to mitigate these risks remain unclear. This review provides an overview of recent insights in this field, and highlights current and future antithrombotic trials focusing on optimizing outcomes in patients undergoing TAVI.

Keywords Aortic valve • TAVI • Anticoagulation

Rationale for antithrombotic therapy after aortic valve implantation

Calcific aortic stenosis (AS) is the most common type of valvular heart disease leading to intervention and represents a major health-care burden.[1] Symptomatic severe AS has a poor prognosis when treated medically and inevitably leads to functional deterioration, heart failure, and death.[2]

In recent years, transcatheter aortic valve implantation (TAVI) has been introduced as a less invasive treatment to prosthetic surgical replacement of the valve (SAVR) among high-risk and intermediate-risk patients particularly if transfemoral access is feasible.[3–6] TAVI has been rapidly embraced, and it is estimated that >250 000 TAVI procedures have been performed in >65 countries worldwide (by the end of 2016). A wide spectrum of devices are currently in use (*Figure 1*).

Despite improving experience and techniques, ischaemic and bleeding complications after TAVI remain prevalent and impair survival (*Table 1*). These complications are related to both the procedure itself but also over the long-term because of underlying risk factors (*Figure 2*).

Mechanisms of thrombosis in patient undergoing transcatheter aortic valve implantation

The implanted bioprosthetic valve and the stent structure to which it is attached may add an additional prothrombotic environment contributing to cardioembolic risk in patients who are already at increased baseline risk of thrombo-embolic events.[10–12] Insertion of a prosthesis without removal of the calcified aortic valve creates an irregular zone around the valve frame with turbulent and often low shear flow patterns that may predispose to fibrin deposition, thrombus formation, and embolization beyond processes involved in normal healing.[10–12] Long-term data from bioprosthetic valve studies have indicated that neointimal tissue growth and endothelialization of the valve stent

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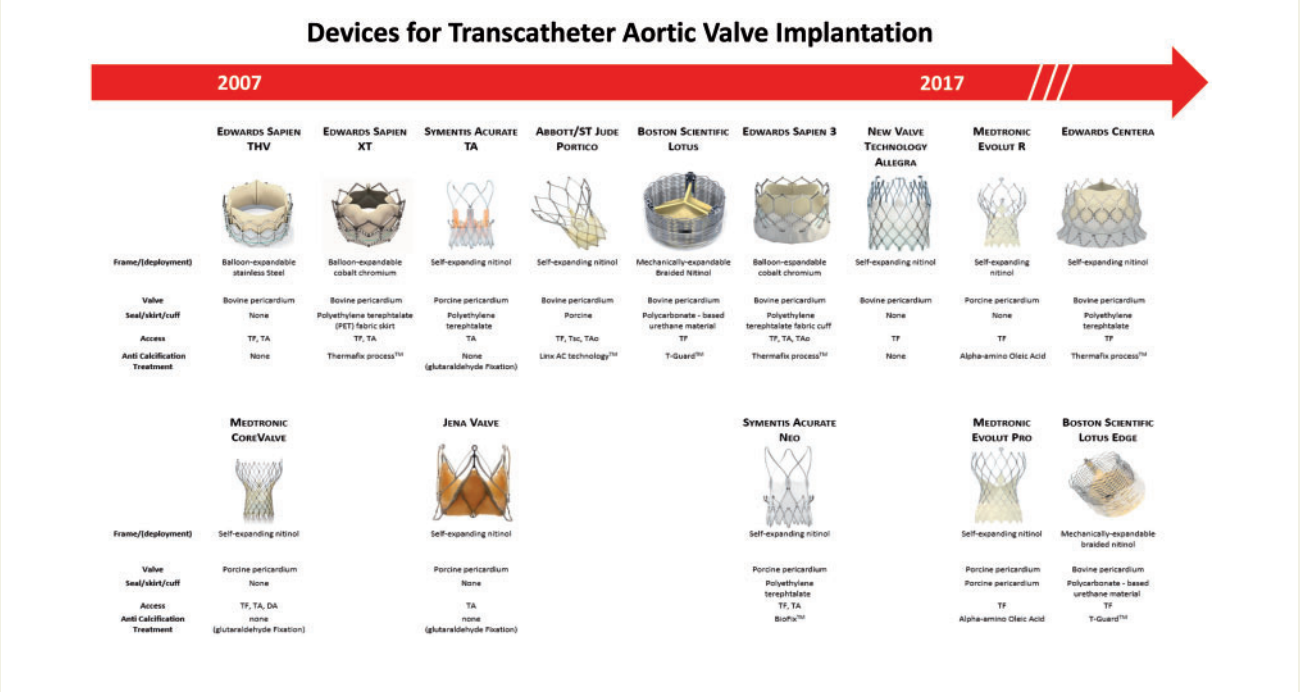

Figure 1 Different types of transcatheter valves for the aortic position that are available. TA, transapical; TAo, transaortic; TF, transfemoral; Tsc, transsubclavian.

Table 1 Ischaemic and bleeding complications in patients after transcatheter aortic valve implantation

	<30 days	1 year	2 years
Life-threatening/or disabling; or major bleeding complications[a] (%)	10.2 (±3.5)	15.95 (±0.9)	17.6 (±0.7)
Stroke (%)	4.1 (±0.7)	7.0 (±1.7)	8.5 (±2.3)
Disabling stroke (%)	2.4 (±1.3)	4.1 (±1.8)	4.9 (±2.1)
Nondisabling stroke (%)	1.6 (±0.6)	3.2 (±0.5)	3.9 (±0.6)
TIA (%)	1.1 (±0.4)	2.1 (±0.5)	3.5 (±0.9)
Systemic embolism	Unreported	Unreported	Unreported
Deep vein thrombosis	Unreported	Unreported	Unreported
New onset atrial fibrillation (%)	11.2 (±1.9)	13 (±4.1)	15.4 (±5.7)
Valve thrombosis (clinical)	0.03–0.07%/year		
Myocardial infarction (%)	0.9 (±0.1)	2.1 (±0.3)	2.7 (±0.8)
Coronary obstruction requiring intervention (%)	0.3 (±0.1)	0.3 (±0.1)	0.3 (±0.1)
All-cause mortality (%)	2.8 (± 0.6)	10.3 (± 3.7)	15.9 (± 5.6)
Cardiovascular mortality (%)	2.6 (± 0.6)	7.1 (± 2.9)	10.7 (± 4.1)

Rates of events were calculated as the number of events divided by the number of treated patients with available data for the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI), the Placement of Aortic Transcatheter Valves (PARTNER) 2 cohort and the US CoreValve high risk study.[3,6–8] Results are presented as weighted mean ± 1 standard deviation.[9]

TIA, transient ischaemic attack.

[a]According to the modified Valve Academic Research Consortium definitions.

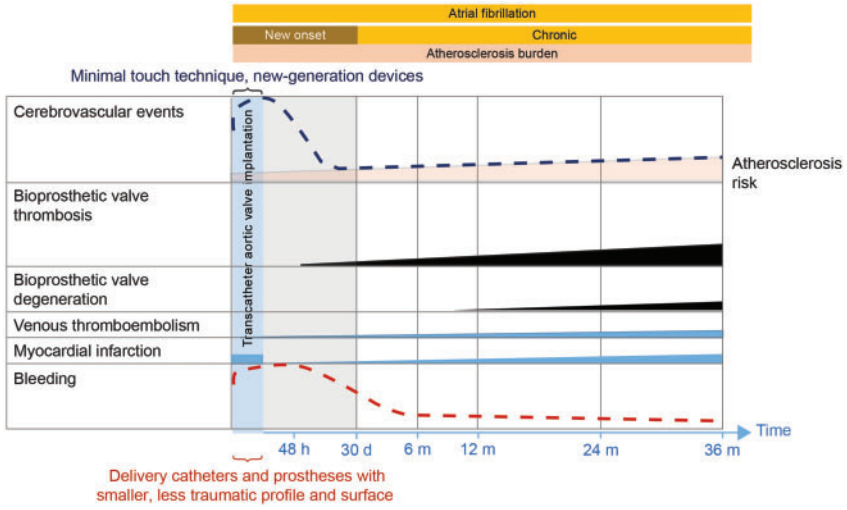

Figure 2 Risk of thrombotic and bleeding events according to time after transcatheter aortic valve implantation (the blue dotted line indicates the risk of a cerebrovascular event, and the red dotted line indicates the risk of bleeding).

probably occur about 3 months after implantation, when the risk of stroke shows a corresponding decline thereafter.[13,14]

The elevated thrombo-embolic risk extends well beyond the procedure and persists during follow-up (*Figure 2* and *Table 1*).

Cerebrovascular events

Ischaemic stroke may occur during or after TAVI, either in the first days or during long-term follow-up and are associated not only with considerable morbidity but also offset the prognostic gain of aortic valve intervention compared with patients without stroke.[3–5,15–18]

Although the highest risk of clinically apparent stroke is 'front loaded' (within 48 h) after TAVI, the risk remains elevated for up to 3 months.[12,19] Actually, one in four cerebrovascular events (CVEs) occur after 30 days and sometimes also after many months (*Table 1*). Early events are mainly procedural and related to device manipulation, post-valve deployment balloon dilation, and repeated prosthesis placement.[12,20,21] In fact, debris captured within embolic protection devices, during TAVI procedures, consist of thrombus, fibrin, calcified material, and tissue from the aortic wall or native leaflets.[22–24] Subacute and late episodes are mainly of thrombo-embolic origin, which could arise from the stent of the implanted valves, but more frequently from atrial fibrillation (AF) occurrence.

The prevalence of AF in elderly TAVI patients amounts to ~30–50%. Moreover, 10–15% of patients develop new-onset AF (which is often clinically silent or unrecognized) after the procedure.[3,25] New-onset AF has been identified as one of the strongest procedure-related predictors for CVEs within 30 days after the procedure.[25,26] The baseline cardioembolic risk of patients undergoing TAVI is high (mean $CHADS_2$ score ~3).[25,27]

Acknowledging that clinical stroke after TAVI can be a devastating complication, it may be only the tip of the iceberg of cardioembolic sequelae.[28] Silent CVEs after TAVI are the hidden part of this iceberg, occurring in three-quarters of cases, irrespective of the device or vascular access used. The prognostic impact of clinical stroke is well established, but the potential long-term deleterious impact of silent CVEs remains largely unknown, and they may be associated with an increased risk of dementia and an early decline in cognitive function.[27,29]

Bioprosthetic valve thrombosis

Clinical transcatheter heart valve thrombosis is more common than previously considered.[18,30–36] The risk of clinical thrombosis appears highest within the first 3 months after implantation (before endothelialization occurs), is likely to be sustained over a period of years (with an incidence of 0.03–0.07%/year).[18,30,33,37] Jose *et al.*[34] reported an overall rate of 2.8% (4.8% in patients on antiplatelet drugs alone) median time to diagnosis of 181-days (interquartile range: 25–297days) in a large single centre cohort.

Although we currently lack a precise understanding of mechanisms leading to clinical thrombosis, the underlying principles invariably relate to perturbations in blood flow and activation of various haemostatic factors involving mechanisms common to medical device-induced thrombosis.[33] Risk factors include coexisting prothrombotic conditions (e.g. cancer), incomplete expansion and/or apposition to the aortic wall, and native leaflets overhanging the balloon-expandable systems. Thrombosis occurs significantly more often with balloon-expandable valves [odds ratio: 3.45; 95% confidence interval (CI): 1.22–9.81; $P = 0.01$] and valve-in-valve procedures (odds ratio: 5.93; 95% CI 2.01–17.51; $P = 0.005$).[34]

Transcatheter valve thrombosis may consist a spectrum, presenting as imaging abnormalities with normal gradients, increased gradients (and N-terminal pro-brain natriuretic peptide levels) without

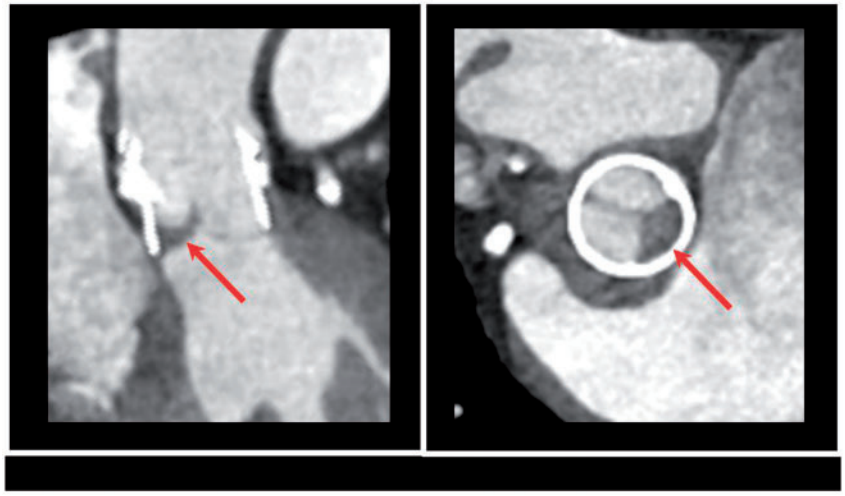

Figure 3 Leaflet thrombosis in a bioprosthetic aortic valve.

symptoms, and elevated gradients with clinical manifestations, including heart failure, thrombo-embolism, or valve failure (*Figure 3*).[34]

Early reduced leaflet motion (RLM) and hypo-attenuated leaflet thickening (HALT) post-TAVI can be detected in up to 10% of patients by advanced CT image processing (three- and four-dimensional volume-rendered CT).[32,35,36,38–40] The course of leaflet restriction appears fundamentally different depending on the presence or absence of anticoagulation, with consistent regression under vitamin-K antagonists [target international normalized ratio (INR) 2.0–3.0], but mostly progression under conventional dual antiplatelet therapy (DAPT) alone.[34,41,42] The observed regression under anticoagulation supports the concept that leaflet thrombosis is the underlying mechanism of early leaflet thickening.[34] Changes in leaflet thickening are associated with changes in transvalvular pressure gradients. Ultimately, this process can result in valve degeneration and failure and exposes patient to the risk of a re-intervention.[33,34] In a recent report from the Mayo Clinic pathology department, bioprosthetic valve thrombosis contributed to 11.3% of cases of bioprosthetic valve dysfunction referred for re-intervention and occurred even several years after surgery.[18] The association between HALT, abnormal valve haemodynamics and stroke is debated.[41,43] Notwithstanding this, it remains to be determined whether HALT and RLM are a clinically meaningful adverse events (i.e. an early marker of thrombosis, CVEs, and valve degeneration) or represents a subclinical imaging phenomenon.[41]

Venous thrombo-embolism

Venous thrombo-embolism (VTE) is a major contributor to the overall disease burden in elderly patients in general involving interactions between acquired or inherited predispositions to thrombosis and various other risk factors.[44,45] Venous thrombo-embolism is a fairly common event, the annual average incidence increases exponentially with age to up to 1% in patients >80 years old.[44,46,47] Strong risk factors for VTE beyond older age include surgery, vascular manipulation, and immobilization. Thrombosis can affect any venous circulation, which includes deep vein thrombosis (DVT) of the leg or pelvis, and its complication, pulmonary embolism. The lack of published data on VTE incidence following TAVI is notable.

Myocardial infarction

Transcatheter aortic valve implantation is systematically associated with some degree of serum creatine kinase-MB (CK-MB) or cardiac troponin release reflecting the occurrence of periprocedural myocardial injury. A higher degree of injury is an independent predictor of 30-day and 1 year all-cause and cardiac mortality.[48,49]

The identification of obstructive coronary stenoses resulting in myocardial ischaemia is not trivial in patients with severe AS.[50] Concurrent coronary artery disease (CAD) is present in 34–75% of patients with severe AS undergoing TAVI and is associated with impaired outcomes.[51,52] Both diseases share a number of risk factors, including male gender, diabetes mellitus, arterial hypertension, chronic kidney disease, and age.[53] The prognostic impact of CAD after TAVI (and revascularization) appears to vary based on the anatomic extent and complexity of the disease as quantified by the (residual) SYNTAX score.[52,54]

Bleeding

Early and late bleeding events after TAVI are observed frequently and have an adverse effect on long-term prognosis.[16,55,56] They may be categorized by severity as minor, major, or in life-threatening according to the Valve Academic Research Consortium (VARC) consensus definitions.[16,24]

In the Placement of Aortic Trancatheter Valve (PARTNER) I trial, 11.3% of patients developed a major bleeding complication (modified

Valve Academic Research Consortium Definitions) within 30 days after the intervention.[55] In-hospital bleeding results in an increased risk of mortality [hazard ratio (HR) 6.1; 95% CI 2.9–12.9] within the first 30 days after the intervention, with no additional hazard arising between 30 days and 12 months.[16] Early, in-hospital, major bleeding complications after TAVI are related to vascular complications or injury to cardiac structures (e.g. pericardial tamponade).[55] Two-thirds of early bleeding events are attributed to the access site and are considered vascular- or access-related complications.

Late bleeding events (≥30 days) after TAVI occurred in approximately 6% of patients in the PARTNER I trial at a median time of 132 days (interquartile range: 71–230 days) after the index procedure. Major bleeding events beyond the peri-procedural period were associated with a fourfold (adjusted HR 3.91; 95% CI 2.67–5.71; $P < 0.001$) increase in mortality after 12 months of follow up.[56] Late events may be attributed to patients' bleeding susceptibility, but post-operative antiplatelet and thrombotic management played a substantial role in this frail and vulnerable patient population. Neurological (15.5%) and gastrointestinal (40.8%) complications were among the most frequent late bleeding complications beyond 30 days of follow-up.[55] Angiodysplastic gastrointestinal bleeding is seen in association with an acquired von Willebrand factor deficiency, a condition known as Heyde's syndrome.[57,58] This abnormal condition is corrected shortly after TAVI but not after balloon valvuloplasty.[59,60]

Antithrombotic therapeutic options

With insufficient evidence regarding appropriate adjunct antithrombic pharmacotherapy during and after TAVI procedures, clinicians have resorted to extrapolating from related surgical and percutaneous procedures and clinical consensus. However, the level of evidence of antithrombotic therapy is rather limited in relation to SAVR, and valve types and patients differ considerably. Due to changing aetiology of complications over time, antiplatelet and anticoagulant therapy after TAVI should be carefully balanced. Extrapolating what we know from coronary or peripheral vascular stenting procedures is equally fraught due to differences in valve prosthetic material, patient populations, and technical considerations.

Pretreatment

A strategy of routine dual antiplatelet pretreatment with clopidogrel in patients undergoing TAVI has been abandoned by most centres because of a perceived increase in bleeding risk without a demonstrated reduction in ischaemic risk.[61] Most patients have high residual platelet reactivity after pretreatment with 300 mg clopidogrel.[62]

Adjunct antithrombotic treatment during transcatheter aortic valve implantation

Unfractionated heparin (UFH) is the most common agent for anticoagulation during TAVI procedures (*Table 2*). In the PARTNER randomized studies, UFH was administered as a parenteral bolus of 5000 IU followed by additional doses to achieve an activated clotting time ≥250 s.[20] A subsequent American College of Cardiology Foundation/American Association for Thoracic Surgery/Society for Cardiovascular Angiography and Interventions/Society of Thoracic Surgeons (ACCF/AATS/SCAI/STS) expert consensus document on TAVI recommended maintenance of an activated clotting time >300 s with reversal of UFH after the procedure using protamine sulphate at a milligram-to-milligram neutralization dose.[63] However, there is no evidence showing the relevance of activated clotting time in this specific setting.

The intraprocedural safety and efficacy of bivalirudin instead of UFH was investigated in the Effect of Bivalirudin on Aortic Valve Intervention Outcomes 2/3 (BRAVO 2/3 pilot trial) trial.[65] There were no significant differences in ischaemic and bleeding events at 48 hours [3.5% vs. 4.8%; relative risk (RR) 0.73, 95% CI 0.37–1.43, $P = 0.35$; 6.9% vs. 9.0%, RR 0.77, 95% CI 0.48–1.23; $P = 0.27$, respectively] or net adverse cardiovascular events at 30 days (14.4% vs. 16.1%, RR 0.89, 95% CI 0.64–1.24; risk difference -1.72, 95% CI -6.70 to 3.25, $P = 0.50$) in patients undergoing TAVI establishing UFH as the default intraprocedural anticoagulant, and also in view of its low cost.[28,65] In addition, there were no differences in magnetic resonance imaging (MRI)-detected cerebral embolization (65.5% vs. 58.1%, $P = 0.55$). Despite the absence of a reversal agent, bivalirudin did not expose any safety signal, and in fact was found to be non-inferior to UFH and can be an alternative anticoagulant in case of allergy or heparin-induced thrombocytopenia or other contraindication to UFH. From the research point of view, this study established that immediate reversal availability is not a mandatory property of anticoagulants used in TAVI patients.

Adjunct antithrombotic treatment after transcatheter aortic valve implantation

Two competing hypotheses surround recommendations regarding long-term antithrombotic therapy after TAVI, namely the antithrombin and antiplatelet hypotheses. Unfortunately, data to indicate whether presumed thrombo-embolic events after TAVI are primarily due to platelet-based or thrombin-based clot formation are lacking.

There are no uniform recommendations regarding antithrombotic therapy after SAVR for patients in sinus rhythm amongst guidelines (*Table 2*): (i) European guidelines support the use of acetylsalicylic acid (IIa recommendation) or a vitamin K antagonist (VKA, IIb recommendation) for a duration of 3 months[65]; (ii) American Heart Association/American College of Cardiology/Society of Thoracic Surgeon (AHA/ACC/STS) guidelines recommend long-term low-dose aspirin (IIa recommendation; level of evidence [LOE] B) whereas VKAs are considered reasonable for the first 3 months (IIb recommendation, LOE C)[63]; (iii) American College of Chest Physicians (ACCP) guidelines support low-dose aspirin over VKA (Grade 2C).[65] Therefore, some but not all guidelines recommend VKAs within the first 3–6 months after SAVR, whereas aspirin may be preferred for long-term treatment. Of note, all guidelines call for life-long anticoagulation in patients with other risk factors such as AF.

Table 2 Current guideline recommendations for anticoagulation in patients after transcatheter aortic valve implantation

	American College of Cardiology (ACC)/American Heart Association (AHA)/Society of Thoracic Surgeons (STS)[63]	European Society of Cardiology (ESC)[64]	American College of Chest Physicians (ACCP)[65]
TAVI			
Procedural	Unfractionated heparin (ACT >300 s)	Unfractionated heparin (ACT >300 s)	Not mentioned
Post-procedural	Aspirin 75–100 mg/day indefinitely	Aspirin or clopidogrel indefinitely	Aspirin 50–100 mg/day, indefinitely (Grade 2C)
	Clopidogrel 75 mg/day, for 6 months	Aspirin and clopidogrel early after TAVI	Clopidogrel 75 mg/day, for 3 months (grade 2C)
	If VKA indicated, no clopidogrel	If VKA indicated, no antiplatelet therapy	
Bioprosthetic valves			
Low risk	Aspirin 75–100 mg/day (Class IIaB[a])	Low-dose aspirin (Class IIaC[b])	Aspirin 50–100 mg/day indefinitely (Grade 2C)
	VKA INR 2.0–3.0 (Class IIbB[b])	VKA INR 2.0–3.0 (Class IIbC[c])	
High risk	Aspirin 75–100 mg/day (Class IIaB[a])	VKA (target INR 2.5) (Class IC[a])	
	VKA INR 2.0–3.0 (Class I[a])		

AHA risk factors: AF, left ventricular dysfunction, previous thrombo-embolism, and hypercoagulable condition; ESC risk factors: AF, venous thrombo-embolism, hypercoagulable state, or with a lesser degree of evidence, severely impaired left ventricular dysfunction (ejection fraction ≤35%).
AF, atrial fibrillation; INR, international normalized ratio; TAVI, transcatheter aortic valve implantation; VKA, vitamin K antagonist.
[a]Class I: conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective.
[b]Class IIa: weight of evidence/opinion is in favour of usefulness/efficacy.
[c]Class IIb: usefulness/efficacy is less well established by evidence/opinion.

The current recommendations pertaining to antithrombotic treatment after TAVI in patients in sinus rhythm are largely based on expert consensus (*Table 2*); namely, the use of DAPT with aspirin (indefinitely) and clopidogrel (3–6 months) to obviate the metallic stent-mediated risk of thrombosis/embolization followed by long-term single antiplatelet therapy with aspirin alone.[68,69] Dual antiplatelet therapy is also indicated for those TAVI patients with concomitant obstructive CAD after stent placement. Nevertheless, the benefits of DAPT after TAVI in patients in sinus rhythm remain controversial. A pooled analysis of individual patient data from four small trials, including in total 672 participants, suggested that the addition of clopidogrel to aspirin did not improve efficacy and safety.[70] However, this study remains inconclusive in view of several limitations, including the relatively low statistical power, inclusion of randomized and non-randomized studies, and short duration of follow-up.

The benefits and risks of long-term oral anticoagulation compared with an antiplatelet-based strategy involving DAPT or single antiplatelet therapy with aspirin, prasugrel, or ticagrelor needs to be addressed carefully. These issues are being investigated in the Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation (POPular-TAVI) trial.[69] POPular-TAVI is a multicentre open-label RCT with an all-comers design to test the safety, net-clinical benefit, and efficacy of omission of clopidogrel compared with a strategy using aspirin (≤100 mg o.d. for at least 1 year, recommended life-long) plus clopidogrel (75 mg o.d. for 3 months) or an oral anticoagulant (OAC, a VKA) in combination with clopidogrel in 1000 patients during 1 year of follow-up. Patients are randomized before the TAVI. In patients receiving a VKA, the procedure will be performed during uninterrupted therapy. The hypothesis is that the omission of clopidogrel in the first 3 months after TAVI may be safer and similarly effective than the addition of clopidogrel to aspirin or an OAC.

For patients with an indication for an OAC undergoing TAVI (e.g. AF, DVT, or mechanical mitral valve prosthesis), the best treatment regimen after TAVI is unknown, but a combination of an OAC and aspirin or $P2Y_{12}$ inhibitor is frequently used.[65,71] However, prescribing antiplatelet therapy for patients with AF after TAVI who are already on long-term anticoagulation may not confer additional benefits and can expose patients to added bleeding risk. In a recent study by Abdul-Jawad Altisent *et al.*[72] adding antiplatelet therapy (vs. warfarin alone) use did not reduce the incidence of stroke, major adverse cardiovascular events, or death in patients undergoing TAVI, while increasing the risk of major or life-threatening bleeding. These data were consistent with the WOEST trial results[73] as well as the PIONEER AF-PCI trial results.[74] Similar findings had been reported previously in studies on antithrombotic therapy involving surgical bioprostheses, which suggested that anticoagulation treatment may be implemented for 3–6 months after implantation of a surgical prosthesis while avoiding combinations with aspirin, which is associated with excess bleeding.[13,18,75,76] For patients with a intracoronary stent, if an OAC must be combined with an antiplatelet treatment, it seems preferable to choose clopidogrel rather than aspirin.

Ongoing and further studies will need to address this and other outstanding issues including the role of clopidogrel monotherapy, the need for a loading dose and the potential role of newer $P2Y_{12}$ antagonists including prasugrel or ticagrelor in analogy to the combined use of anticoagulation and antiplatelet drugs among patients undergoing percutaneous coronary intervention.

Table 3 Ongoing trials with direct oral anticoagulants in patients after transcatheter aortic valve implantation

	POPular-TAVI	ATLANTIS	GALILEO	ENVISAGE-TAVI AF
ClinicalTrials.gov Identifier	NCT02247128	NCT02664649	NCT02556203	NCT02943785
Trial design	Multicentre, prospective, open-label, randomized	Multicentre, phase IIIb, prospective, open-label, randomized	Multicentre, phase IIIb, prospective, open-label, randomized	Multicentre, phase IIIb, prospective, open-label, randomized, safety/efficacy
Test drugs	Cohort A (patients without an indication for an OAC prior to TAVI): clopidogrel 75 mg o.d. AND aspirin ≤100 mg o.d. Cohort B (patients with an indication for an OAC prior to TAVI): clopidogrel 75 mg AND OAC (according to its indication). Recommended to omit other antiplatelet therapy (e.g. aspirin) at least 5 days prior to TAVI procedure	Apixaban 5 mg bid Apixaban 2.5 mg bid if the patient has two or more of the following: age ≥80 years, body weight <60 kg, serum creatinine ≥1.5 mg/dL (133 μmol/L). If severe renal insufficiency (calculated CrCl [Cockcroft–Gault]15–29 mL/min)	Rivaroxaban 10 mg o.d. AND aspirin 75–100 mg o.d., followed by rivaroxaban 10 mg o.d. If new-onset AF occurs: rivaroxaban 20 or 15 mg o.d. AND aspirin 75–100 mg o.d., followed by rivaroxaban 20 or 15 mg o.d.	Edoxaban-based regimen 60 mg and 30 mg film-coated tablet for o.d. oral use (and 15 mg film-coated tablet for transitioning at end of treatment). Dosing must follow the locally approved label Antiplatelet therapy (if prescribed)[a]: aspirin 75–100 mg/day or generic/branded clopidogrel 75 mg/day (chronic therapy after loading dose) as the preferred agents
Treatment duration	Cohort A + B: clopidogrel discontinued 90 days post-randomization. Cohort A: aspirin continued for at least 1 year but recommended lifelong	12 months.	ASA discontinued 90 days post-randomization. Rivaroxaban continued until the predefined number of efficacy endpoints is reached	Edoxaban/VKAs continued until the predefined number of efficacy endpoints is reached or up to 36 months. Minimum follow-up: 6 months ASA or clopidogrel discontinued 90 days post-randomization (except patients with stenting post-TAVI: up to 12 months, DAPT is allowed for 1 month)
Active comparator	Cohort B: aspirin ≤100 mg (recommended to omit other antiplatelet therapy at least 5 days prior to the TAVI procedure) Cohort B: OAC (according to indication). Recommended to continue the OAC therapy periprocedural (INR aimed at 2.0). Recommended to omit antiplatelet therapy (e.g. clopidogrel) at least 5 days prior to the TAVI procedure)	VKA (AF) or Antiplatelet therapy (sinus rhythm)	Clopidogrel 75 mg o.d. AND ASA 75–100 mg o.d. If now-onset AF occurs, VKA with a target INR 2–3 AND ASA 75–100 mg o.d. VKA (target INR 2–3)	VKA of choice (any locally approved), dose adjusted throughout the study for target INR 2.0–3.0 (inclusive) Antiplatelet therapy (if prescribed)[a]: aspirin 75–100 mg/day or generic/branded clopidogrel 75 mg/day (chronic therapy after loading dose) as the preferred agents
Treatment duration	Aspirin at least 1 year, but recommended lifelong	12 months	Clopidogrel must be discontinued at 90 days post-randomization and ASA 75–100 mg o.d. continued until the predefined number of efficacy endpoints reached	VKA continued until the predefined number of efficacy endpoints is reached or up to 36 months. Minimum follow-up in all patients: 6 months ASA or clopidogrel discontinued 90 days post-randomization (except for patients with stenting post-TAVI: up to 12 months, DAPT allowed for 1 month)
Time of randomization	Prior to TAVI	After successful TAVI	1–7 days after successful TAVI	1–5 days after successful TAVI

Continued

Table 3 *Continued*

	POPular-TAVI	ATLANTIS	GALILEO	ENVISAGE-TAVI AF
Patients	Without need for long-term OAC	Patients with clinically successful TAVI procedure irrespective of prior antithrombotic treatment are eligible for randomization	Successful TAVI of a native aortic valve stenosis by ilio-femoral or subclavian access with any approved/marketed device Patients without an ongoing indication for OAC treatment	Successful TAVI of a native aortic valve stenosis by access with any approved/marketed device Patients with AF and ongoing indication to chronic OAC
Primary outcome measures	Freedom from all BARC-defined bleeding complications at 1 year after TAVI. Co-primary outcome: safety endpoint defined as freedom of non-procedure-related bleeding complications at 1 year after TAVI.(time frame: up to 12 months)	Composite of death, MI, stroke, peripheral embolism, intracardiac or bioprosthesis thrombus, any episode of DVT or PE, major bleeding at 1 year follow-up. (time frame: up to 13 months)	Death or first adjudicated thrombo-embolic event defined as composite of all-cause death and adjudicated any stroke, MI, symptomatic valve thrombosis, PE, DVT, or non-CNS SE (time frame: up to 25 months) Primary bleeding event defined as the composite of adjudicated life-threatening, disabling or major bleeding, classified according to the VARC definitions following the BARC classification (time frame: up to 25 months)	Number of participants experiencing NACE: all-cause death, MI, ischaemic stroke, SEE, valve thrombosis, and ISTH major bleeding (time frame: within 36 months) Number of participants experiencing major bleeding (ISTH definition) (time frame: within 36 months)
Secondary outcome measures	Net clinical benefit endpoint (time frame: 1 year) defined as freedom of the non-hierarchical composite of cardiovascular mortality, non-procedure related bleeding, stroke, or MI at 1 year after TAVI (time frame: up to 12 months) Efficacy endpoint: co-secondary outcome is an efficacy endpoint of freedom of the non-hierarchical composite of cardiovascular mortality, ischaemic stroke, or MI at 1 year after TAVI (time frame: up to 12 months)	Presence or not of an indication (other than TAVI) for anticoagulation described in the medical record. (time frame: from screening to randomization) First occurrence of any event of the following composite criteria: (a) death, MI, any stroke through 1 year of randomization, (b) death, any stroke/TIA or peripheral embolism (c) each individual parameter of the primary endpoint (time frame: up to 13 months)	Composite of cardiovascular death, any stroke, MI, symptomatic valve thrombosis, PE, DVT or non-CNS SE (time frame: up to 25 months) Net clinical benefit defined as the composite of all-cause death, any stroke, MI, symptomatic valve thrombosis, PE, DVT, non-CNS SE, life-threatening, disabling and major bleeding events (time frame: up to 25 months) Bleeding complications defined as any of the following: composite of TIMI major or minor bleeding, ISTH major bleeding, composite of BARC 2, 3, or 5 bleeding (time frame: up to 25 months)	Number of participants experiencing the described adverse event composite (all-cause death, MI, ischaemic stroke, SEE, valve thrombosis, and BARC or TIMI major bleeding (time frame: within 36 months) Percentage of participants experiencing BARC or TIMI major bleeding per other than ISTH definition (time frame: within 36 months) Percentage of participants experiencing stroke (ischaemic, haemorrhagic, or undetermined) (time frame: baseline to 36 months) Percentage of participants experiencing SEE (time frame: baseline to 36 months)
Location	Netherlands	France	Global	USA, Canada, and Europe (Austria, Belgium, France, Germany, Italy, the Netherlands, Spain, Switzerland, and UK)

Continued

Table 3 *Continued*

	POPular-TAVI	ATLANTIS	GALILEO	ENVISAGE-TAVI AF
Estimated enrolment	1000	1509	1520	1400

ATLANTIS, Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischaemic and Hemorrhagic Events After Trans-Aortic Valve Implantation for Aortic Stenosis; ENVISAGE, Edoxaban Versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation (TAVI)—in Atrial Fibrillation; GALILEO, Global Multicenter, Open-label, Randomized, Event-driven, Active-controlled Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement (TAVR) to Optimize Clinical Outcomes; POPular-TAVI, Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation; DAPT, dual antiplatelet therapy; NACE, net adverse clinical events; VARC, valve academic research consortium; BARC, bleeding academic research consortium; TIMI, thrombolysis in myocardial infarction; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; MI, Myocardial infarction; PE, pulmonary embolism; DVT, deep vein thrombosis; non-CNS SE, non-central nervous system systemic embolism; SEE, systemic embolic events.

[a]Type and duration of antiplatelet agent must be pre-declared at randomization.

Role of direct oral anticoagulants post-transcatheter aortic valve implantation

The direct oral factor Xa inhibitors apixaban, rivaroxaban, and edoxaban offer new perspectives in the TAVI era when oral anticoagulation is considered.[77,78] The rapid onset of action of the direct oral anticoagulants (DOACs) and their favourable safety and efficacy compared with VKAs in the prevention and treatment of thrombo-embolism render them attractive therapeutic options.[79–85]

The use of DOACs (instead of antiplatelet treatment) not only in patients with AF but also in those in sinus rhythm after TAVI is currently being investigated in three prospective randomized trials (*Table 3*): Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis (ATLANTIS),[86] Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes (GALILEO),[87] and Edoxaban Versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation—in Atrial Fibrillation (ENVISAGE TAVI AF).[88]

For patients on an OAC for AF no adaptations of the regional approved doses for this indication are proposed post-TAVI in ATLANTIS, ENVISAGE TAVI AF, or GALILEO if patients develop new-onset of AF after the TAVI procedure. For patients in sinus rhythm in GALILEO not on an OAC for an established indication, a rivaroxaban 10 mg o.d. dose is selected in combination with low-dose aspirin for 90 days to provide an early, sustained, adequate efficacy in the prevention of thrombotic events and an acceptable safety (bleeding) profile compared with standard of care.[89] The rivaroxaban 2.5 mg b.i.d. dose, tested in secondary prevention after acute coronary syndrome, was anticipated to lack the desired efficacy given the pro-thrombotic pathophysiology of both AS and the post-TAVI period. In ENVISAGE, one daily dose of edoxaban 60mg (or 30 mg according to dose adjustment criteria) will be used. In ATLANTIS, the same dose of apixaban is considered for all patients, with or without AF.

Role of adjunct devices to reduce neurologic events

A considerable proportion of CVEs occur during the TAVI procedure, and the majority have a thrombotic component.[3,5,6,21,23] Prevention of peri-procedural CVEs, will rely on the combination of optimal delivery technique of the valve, the development of less traumatic smaller profile devices, all of which reduce catheter manipulation of the aorta, as well as the combination of targeted anticoagulation. In an all-inclusive meta-analysis, embolic protection devices prevented metrics of cerebral embolization, as assessed by MRI, whereas the impact on clinical stroke events remained inconclusive.[90] The use of embolic protection devices remain optimistic in their safety, and may reduce the volume and number of CVEs.[91] Studies are underway to evaluate the role of these devices in reducing neurologic insult during TAVI procedures.[92–94] The multicentre randomized trial evaluating the role of embolic protection using the Sentinel device during TAVI found that the device was safe although it did not meet the primary efficacy endpoint of reduction in median new lesion volume in protected territories assessed by MRI at 2–7 days.[23] In addition, neurocognitive function was not significantly improved. Importantly, the burden of atherosclerosis and thrombosis at pre-intervention was the stronger predictor of post-TAVI cerebral embolization and neurocognitive score decline.

Role of left atrial appendage closure

In patients with symptomatic severe AS at high bleeding risk with a formal indication for an OAC for AF, the combination of TAVI with a left atrial appendage closure device may provide additional treatment options for patients with AS and concomitant cardiovascular problems.[95,96]

Conclusion

Transcatheter aortic valve implantation is an area where scientific data on the balance of efficacy and safety of different peri-procedural and long-term antithrombotic strategies is limited. Clearly, more studies, including the randomized trials described, will be required to

develop a rational and customized strategic approach to balance the bleeding risks of new drug therapies and their antithrombotic value in preventing important valve-related thrombotic events.

Authors' contributions

P.V. and S.W. drafted the manuscript, all authors made critical revisions, and approved the final manuscript for submission.

Conflict of interest: P.V. reports receiving speaking or consulting fees from Bayer Health Care, Daiichi-Sankyo and AstraZeneca outside the submitted work. S.W. reports receiving has received research grants to the institution from Astra Zeneca and speaking or consulting fees from AstraZeneca outside the submitted work. R.C.W. reports receiving research grants from Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Edwards Lifesciences, Eli Lilly, Jansen, Pfizer and has received speaking or consulting fees from Amgen, Astra Zeneca, Bayer, Bristol Myers Squibb, Jansen, Pfizer. M.V. reports receiving grants from The Medicines Company, grants from Terumo, during the study; grants from AstraZeneca, and personal fees from Terumo, St Jude Vascular, and Abbott Vascular, outside the submitted work. R.M. reports receiving research grants from Abbot Laboratories, AstraZeneca, Bayer, Bristol-Myers Squibb, CSL Behring, the Medicines Company, OrbusNeich and Eli Lilly/Daiichi Sankyo. Mehran also reports serving as a consultant and on advisory boards for Abbott Laboratories, AstraZeneca, Boston Scientific, Cardiovascular Systems Inc, Sanofi USA-LLC, Shangahai BraccoSine Pharmaceuticals, Merck & Company, Janssen Pharmaceuticals, Medscape, the Medicines Company, Osprey Medical and Watermark Research Partners (member Data Safety Monitoring Board), small amount of stock options in Claret Medical, Elixir Medical Corp. G.D. reports grants from Bayer, grants from Daichi-Sankyo, grants from Medicines Company, advisory board fees (spouse) from Janssen/Johnson & Johnson; advisory board fees (spouse) from Claret Medical outside the submitted work; and his spouse has small (<1%) amount of stock options in Claret Medical.

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