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THE PRESENT AND FUTURE

*JACC* REVIEW TOPIC OF THE WEEK

# Thrombotic Versus Bleeding Risk After Transcatheter Aortic Valve Replacement

## *JACC* Review Topic of the Week

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**ABSTRACT**

A large amount of evidence supports the widespread use of transcatheter aortic valve replacement (TAVR) among patients who are at low to intermediate risk for surgery. However, several controversies exist about the optimal antithrombotic regimen to use in these patients. On the one hand, concerns about ischemic stroke, subclinical leaflet thrombosis, valve thrombosis, and long-term durability suggest the need for a stronger antithrombotic regimen to ensure a better patient and valve outcome. On the other hand, the high bleeding risk of this population and the current lack of strong evidence in favor of a more aggressive antithrombotic strategy require caution. This review analyzes the rationale of antithrombotic therapy in TAVR illustrating the present scenario and future perspectives.
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While transcatheter aortic valve replacement (TAVR) is expanding its indication, a gamut of both hemorrhagic and thrombotic complications might occur (1). Despite similarities with percutaneous coronary intervention, TAVR represents a setting in which bleeding and thrombotic risk are enhanced (**Figure 1**) and optimal antithrombotic/anticoagulation management is still debated. In brief, increased early and long-term risk of ischemic stroke and prevalence of atrial fibrillation favor a stronger antithrombotic therapy while inherent comorbidities and peculiar hematologic alterations suggest a nonaggressive strategy. In the present review, we discuss the balance between bleeding and thrombotic risk in TAVR and offer a summary of current recommendations, a perspective on ongoing clinical trials, and possible future developments.

## BIOENGINEERING ASPECTS OF TRANSCATHETER AORTIC VALVE REPLACEMENT

Biological tissues have long been employed for cardiac surgery; they are favored because they do not require anticoagulation when compared with mechanical prosthesis, despite their shorter durability.

Materials employed for biological surgical valves include both human tissue and xenografts of animal origin. Most are stented, meaning that the graft leaflets are sutured to a rigid alloy made of metal, polymers, or carbon; the alloy itself is covered by biological or synthetic materials. Finally, a fabric-made sewing ring is attached to this frame. On the other hand, stentless valves lack the rigid support of the alloy and are entirely made of biological tissue (2).

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## HIGHLIGHTS

- TAVR is associated with bleeding complications and short- and long-term thrombotic risk.
- Clinical and bioengineering aspects of TAVR should be assessed for optimal medical management, but evidence is still scarce and scattered.
- Data about optimal antithrombotic therapy are still uncertain, without clear proof of advantage of stronger antithrombotic regimen to avoid valve degeneration.
- Research should seek to clarify the best strategy for different patient subsets.

The most widely available transcatheter bioprosthetic heart valves (BHVs) all feature a stented design and 3 leaflets made of bovine or porcine pericardium (Figure 2).

**STENTS.** The stent is a frame offering mechanical support for the xenograft tissue sewn over. Differently from their surgical counterparts, transcatheter BHV stents are not covered by a fabric ring and directly exposed to blood flow. Stents employed in aortic transcatheter BHV are made of stainless steel, cobalt-chromium, or nitinol. Stainless steel was used in the earliest TAVR models (3), whereas cobalt-chromium stents were first introduced in the Edwards XT valve allowing for better biophysical properties of the frame (thinner, stronger, more open, and compressible struts). Nitinol is an alloy of nickel and titanium with superelasticity and shape-memory effect (deformability at cooler temperatures and original shape recovery at body temperature) properties. Nitinol frames are used for self-expandable valves and offer the potential for a thinner delivery system allowing repositioning. No study compared the thrombogenicity potential of BHV according to different stent materials, but lessons can be learned from research in coronary stents. In particular, nitinol, when compared with stainless steel, might offer better hemocompatibility and lower thrombogenicity independently of device design, wall thickness, and metallic surface area (4).

## ABBREVIATIONS AND ACRONYMS

**BHV** = bioprosthetic heart valve

**DAPT** = dual antiplatelet therapy

**DOAC** = direct oral anticoagulant

**HALT** = hypoattenuating leaflet thickening

**OAC** = oral anticoagulant

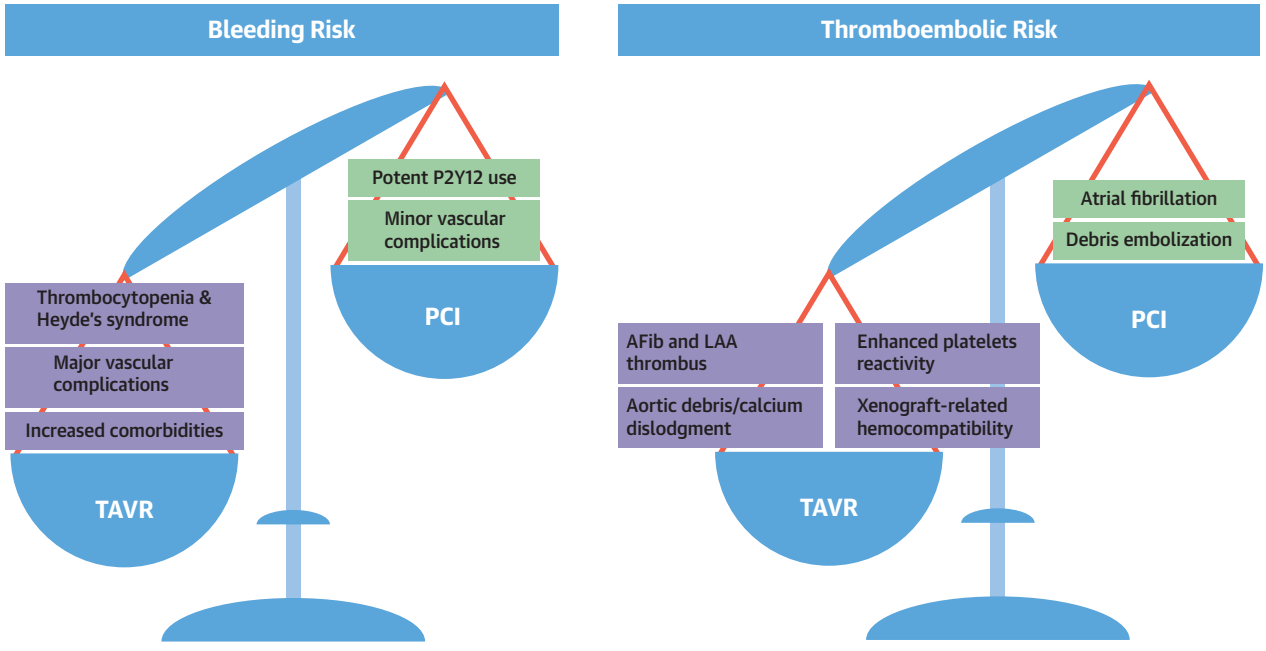
**SAPT** = single antiplatelet therapy

**TAVR** = transcatheter aortic valve replacement

**VKA** = vitamin K antagonist

**vWF** = von Willebrand factor

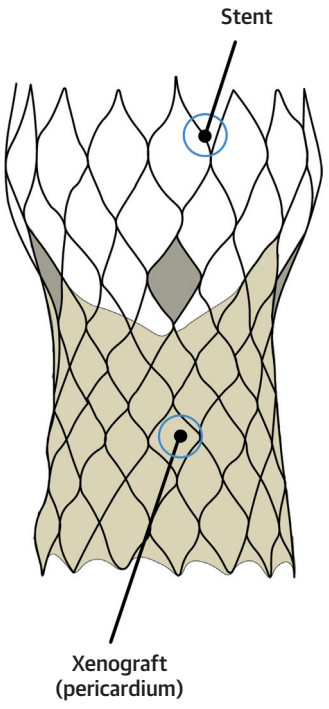
**FIGURE 1 Balance Between Bleeding and Thrombotic Risk Factors in PCI Versus TAVR**




Transcatheter aortic valve replacement (TAVR) and percutaneous coronary intervention (PCI) share common risk factors for bleeding and thromboembolic events. Nonetheless, technical aspects and peculiar hematological alterations inherent to aortic stenosis account for excess risk of both these events in the setting of TAVR. AFib = atrial fibrillation; LAA = left atrial appendage.

**FIGURE 2** **Bioengineering Characteristics of Widely Commercially Available TAVR Prosthesis**

| | Stent Type | Xenograft | Expansion |
|---|---|---|---|
| Cribier-Edwards | Stainless steel | Equine | BE |
| Edwards SAPIEN | Stainless steel | Bovine | BE |
| Edwards SAPIEN XT | Cobalt-Chromium | Bovine | BE |
| Edwards SAPIEN 3 | Cobalt-Chromium | Bovine | BE |
| Edwards Centera | Nitinol | Bovine | SE |
| Medtronic CoreValve | Nitinol | Porcine | SE |
| Medtronic CoreValve Evolut R | Nitinol | Porcine | SE |
| Medtronic CoreValve Evolut PRO | Nitinol | Porcine | SE |
| Boston Scientific Lotus | Nitinol | Bovine | SE |
| Boston Scientific Lotus Edge | Nitinol | Bovine | SE |
| Boston Scientific Acurate Neo | Nitinol | Porcine | SE |
| St. Jude Medical Portico | Nitinol | Bovine | SE |




Many TAVR models exist, with different characteristics in terms of stent material, xenograft used, and expansion mechanism. BE = balloon-expandable; SE = self-expandable; TAVR = transcatheter aortic valve replacement.

**ENDOTHELIZATION.** Little is known about stent endothelization post-TAVR. Postmortem histological findings revealed the valve xenograft to be covered by layers of (from outer to inner): inflammatory cells, fibroblasts and collagen, and then true endocardium (5). Although incomplete, endothelization of stent struts was reported in both Sapien and CoreValve as early as 28 days after TAVR with almost complete endothelization at longer time intervals (5-7). This process was prominent in struts in direct contact with native endocardium and was absent in those protruding in the ascending aorta lumen. These findings are in accordance with the non-drug-eluting nature of stents employed in TAVR design, and as coronary bare-metal stents retain an increased risk of acute stent thrombosis, the potential for early thrombogenicity deserves further attention. A large ongoing registry aims to systematically characterize TAVR prosthesis postmortem with a multimodality approach (8).

**LEAFLET GRAFTS.** Leaflets made of bovine or porcine xenografts (**Figure 2**) are applied to the stent frame. The leaflets are polarized, meaning that the inflow and outflow surfaces are made by the parietal and serous layers of the animal pericardium, respectively (9). Before assembly, the graft tissue undergoes heavy processing, including glutaraldehyde fixation (cross-linking and antigen masking to make bioprosthetic materials immunologically inert), anticalcic treatment to improve valve durability, sterilization, and preservation. Ex vivo studies characterized histological and biophysical behavior of pericardial tissue (9). Decellularization leaves extracellular collagen poorly organized on the inflow surface and smooth and well organized on the outflow surface. Furthermore, platelet uptake (a marker of minor hemocompatibility) is superior on the inflow surface both for bovine and porcine xenografts (9). Finally, despite a large retrospective analysis in surgical valves excluding any difference in survival rates at 10 years (49.0% vs. 50.3%; $p = 0.767$) (10), biophysical properties of bovine and porcine tissues are consistently different with potential implications for crimping performance, hemodynamics, and

subsequent development of leaflet thrombosis. However, neither an in vivo nor an ex vivo comparison of thrombogenicity in porcine versus bovine BHV is available despite both types presenting the potential for hemocompatibility hazard. Therefore, porcine and bovine pericardium should not be considered interchangeable (11).

**CRIMPING.** Crimping consists of applying mechanical external circumferential forces to the intact valve to achieve reduced dimensions fit to enter peripheral small vessels.

Different biophysical profiles might affect crimping-inducing surface tears and breakdown, a potential initial stimulus for thrombosis; ex vivo and animal studies proved substantial modifications after crimping in bovine pericardial leaflets (12). By doing this, the valves' leaflets are exposed to a level of stress that is not exerted on the surgical bioprosthetic valves. These findings suggest that crimping time and force should be as limited as possible.

**HEMODYNAMIC THROUGH THE BHV.** Finally, in an ex vivo model, an axial flow directed toward the BHV opening was observed both in systole and diastole, which was associated with decreased turbulence, flow velocity, and shear rate when compared with the physiological condition (13). These fluidodynamic conditions create a region of relative fluid stagnation between the Valsalva sinus and the native valve leaflets, which might account for increased thrombogenicity after TAVR. As a matter of fact, recent studies have reported a HALT (hypoattenuating leaflet thickening) and concurrent reduced motion at serial computed tomography scans (14). Possible correlation between blood stagnation and HALT development deserve further attention.

## THROMBOTIC VERSUS BLEEDING RISK BALANCE

**BLEEDING RISK.** Patients undergoing TAVR have an adjunctive risk of bleeding, which has been associated with poor outcome whether occurring immediately after the procedure or later on (15). Factors increasing bleeding risk include high prevalence of peripheral vasculopathy, chronic kidney disease, acquired reversible von Willebrand factor (vWF) deficiency, and acquired thrombocytopenia (**Table 1**). In particular, the unfolding of vWF multimers impairs their pivotal role in primary hemostasis and platelet activation due to turbulent flow through the stenotic valve and accounts for gastrointestinal bleeding observed in Heyde's syndrome (16). A significant increase in the vWF multimer ratio was observed immediately after TAVR (17), albeit increased risk of bleeding might be further sustained by other biological factors. Postulated mechanisms include: persistence of vWF deficiency due to shear stress across a regurgitant prosthesis (17), the reversal of shear stress-induced suppression of antithrombotic molecules (18), and transient acquired thrombocytopenia (19). This latter phenomenon is secondary to increased platelet consumption secondary to an immune response (to the bioprosthesis material or to the fixation medium) or to an inflammatory reaction. Thrombocytopenia can also be related to the activation of the coagulation cascade, platelet destruction at the valve site due to shear stress, hemodilution due to multiple blood transfusions, and the effect of drugs, including antiplatelets and heparin (20). Acquired thrombocytopenia after TAVR has been inconstantly associated with increased risk of short-term complications including increased bleeding (21,22).

Periprocedural bleeding occurs early after TAVR and is related to vascular complications at puncture sites or injury to cardiac structures (e.g., pericardial tamponade) and is associated with an increased risk

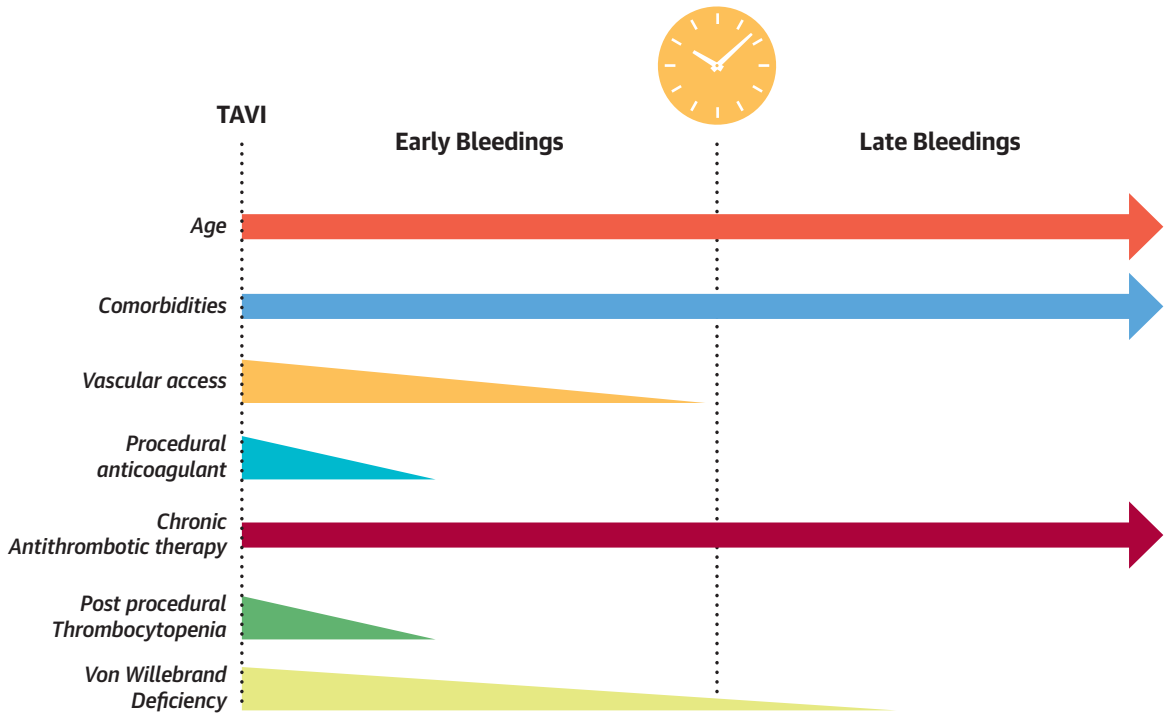
**TABLE 1 Bleeding and Thrombotic Risk Factors: Prevalence and Definition**

| Risk Factor | Prevalence (%) | HR (95% CI) | Ref. # |
|---|---|---|---|
| Bleeding risk | | | |
| Intrinsic | | | |
| Chronic kidney disease | 37.6 | 1.35 (1.27–1.44); 2.13 (1.85–2.44) for ESRD | (52) |
| Peripheral artery disease | 31.1 | 1.18 (1.09–1.27) | (53) |
| Enhanced thrombotic milieu | | | (31) |
| Acquired vWF syndrome | 67–92 | | (54) |
| Acquired thrombocytopenia | 45 | | (20) |
| Procedural | | | |
| Access site (transapical vs. femoral) | | | |
| Access caliber | | | |
| Damage to heart structure | | | |
| Residual aortic regurgitation (and persistent vWF deficiency) | 10–20 | | (18) |
| Long-term | | | |
| Antithrombotic drug regimen (need of OAC and/or DAPT) | | | |
| Thrombotic risk | | | |
| Atrial fibrillation | 35 | | (55) |
| Bilateral carotid stenosis | 1.9 | 4.02 (1.86–8.69) | (56) |
| Peripheral artery disease* | 31.1 | 1.29 (1.03–1.61) | (53) |
| Left atrial appendage thrombus | 11 | | (55) |

Adjusted HR for thromboembolic and bleeding events are reported; if unavailable, odds ratios are reported. Study Definitions: Peripheral artery disease: aortic aneurysm, claudication, positive noninvasive test, prior amputation for arterial vascular insufficiency, and prior vascular reconstruction, peripheral bypass surgery, or percutaneous peripheral vascular intervention. Chronic kidney disease: includes patients with ESRD. Acquired thrombocytopenia: post-procedural platelet nadir $<50 \times 10^9$/l. Coronary artery disease: definition was variable and included at least ≥50% stenosis, >70%, or >90%. Carotid artery stenosis: any carotid lesion exceeding 50% diameter stenosis. *Increased intra-hospital ischemic stroke risk in patients undergoing transfemoral TAVR.

CI = confidence interval; DAPT = dual antiplatelet therapy; ESRD = end-stage renal disease; HR = hazard ratio; OAC = oral anticoagulation; vWF = von Willebrand factor.

**FIGURE 3** Summary of Bleeding Risk Factors and Their Impact on Early and Late Events




Different factors are involved in bleeding events after transcatheter aortic valve replacement (TAVR). Intraprocedural factors use up their effect in the early post-TAVR period, whereas age, comorbidities, and the chronic antithrombotic regimen keep a high bleeding risk also later after the procedure.

of death. Technical advancements, including a dramatic reduction in sheath size, consequent expansion of transfemoral access, and inclusion of lower-risk patients, have led to a progressive reduction in procedural bleeding (3.6% vs. 10.4% vs. 24.2% in PARTNER [Placement of AoRTic TraNscathetER Valve Trial] 3 [23] vs. PARTNER 2 [24] vs. PARTNER 1 [25]). Moreover, late-onset bleeding (occurring >30 days after TAVR) is associated with a 4-fold (adjusted hazard ratio [HR]: 3.91; 95% confidence interval [CI]: 2.67 to 5.71; $p < 0.001$) (26) increase in mortality after a 12-month follow up and is represented mainly by gastrointestinal (40.8%) and neurological bleeding (15.5%). These late hemorrhagic events are secondary to patients' bleeding susceptibility and to long-term antithrombotic and anticoagulant strategy (**Figure 3**).

**THROMBOEMBOLIC RISK.** A high thromboembolic burden, including prevalent atherosclerosis and atrial fibrillation (**Table 1**), enhances the risk of stroke during and after TAVR procedures (major stroke at 1 year: 0.2%, 5.0%, and 7.8% in low-, intermediate-, and high-risk patients, respectively) (23-25). Rapid ventricular pacing during TAVR deployment, inadvertent wire passage through the mitral valve apparatus into the left atrium, or cardioversion during the procedure might lead to left appendage thrombus dislodgment. Furthermore, ischemic stroke might be caused by mechanical dislodgment of debris mobilized during the implantation steps (27). Although risk of stroke peaks within 48 h after TAVR, it remains elevated for up to 3 months. Subacute and late cerebrovascular accidents are mainly thromboembolic in their origin and are caused by atrial fibrillation and dislodgment of small thrombi from the stent of the implanted valves. Furthermore, the risk of systemic embolization via similar mechanisms exists after TAVR, although no data are available regarding its incidence in clinical practice (28). Nonetheless, results from the GALILEO (Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes) (29) and ENVISAGE-TAVI AF (Edoxaban Versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation in Atrial Fibrillation) (30) trials will likely clarify this issue, as systemic embolization has been included as a composite of the primary endpoint.

Finally, an enhanced thrombogenic environment has been suggested in the setting of aortic stenosis, including shear stress-induced endothelial damage and systemic release and activation of prothrombotic factors. These factors might account for increased platelet activation and circulating microemboli formation (31).

**SUBCLINICAL AND CLINICAL VALVE THROMBOSIS.** At present, anticoagulation is needed in patients undergoing TAVR only in the presence of concomitant disease with indication for oral anticoagulants (OACs) (atrial fibrillation, recent venous thromboembolism, or the presence of other mechanical valve prosthesis). However, recent evidence on valve degeneration, HALT, and clinical valve thrombosis highlighted the possible role of anticoagulation to preserve the integrity of the newly deployed valve. Clinical valve thrombosis is rare (<1%), detected within the first 2 years from TAVR (median time to thrombosis: 181 days), and reversed by anticoagulation (32). Proceeding with anticoagulation appears to be safe and feasible in maintaining a prolonged normalization of the gradients (33). However, HALT appears to be common among different types of both surgical (0% to 11.9%) and transcatheter BHVs (0% to 33%) (**Table 2**), but overall more frequent in the latter (4% vs. 13%; $p = 0.001$) (34). Hypoattenuating leaflet thickening was detected at various time intervals from TAVR (mean 159 ± 177 days; range 21 to 596 days); then, it might regress, stabilize, or progress (14). Both vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) were associated with less HALT (35,36) when compared with no, single, or dual antiplatelet therapy (DAPT) (4% vs. 15%, 16%, and 15%, respectively; all $p < 0.0001$) (34), and were predictive of less progression of HALT (14). Moreover, a short course (3 months) of anticoagulation, but not of DAPT, resolved this phenomenon (37), and anticoagulation suspension resulted in a 50% recurrence of HALT (vs. 0% recurrence if anticoagulation was continued; $p = 0.008$) (35).

Whether HALT has an effect on stroke development and whether a more potent anticoagulation/antiplatelet regimen might lower the burden of cerebral ischemic events after TAVR must still be clarified. Hypoattenuating leaflet thickening was associated with increased incidence of neurological events (transient ischemic attacks and strokes; $p < 0.001$) (35), questioning whether proper prevention and treatment should be addressed systematically in TAVR patients. Nonetheless, considering the observational, retrospective, nonrandomized design of these studies, no causation can be proven, and imaging substudies of PARTNER 3 (Placement of AoRTic TraNscathetER Valve Trial 3) (NCT02675114) and Medtronic Evolut Transcatheter Aortic Valve Replacement in Low Risk Patients (NCT02701283) along with clarification of the neurological effect of HALT are being awaited.

**TABLE 2 Hypoattenuating Leaflet Thrombosis in Different Valve Types**

| Valve Type | Study Type | Hypoattenuating Leaflet Thrombosis, % (Total) | Median Follow-Up Duration (Days) | Ref. # |
|---|---|---|---|---|
| Surgical | | | | |
| Edwards Perimount | Registry | 3 (39) | 540 | (34) |
| | Clinical trial | 9.1 (11) | 183 | (36) |
| | Clinical trial | 11.9 (9) | 183 | (36) |
| St. Jude Medical Epic | Registry | 0 (16) | 540 | (34) |
| Medtronic Freestyle | Registry | 0 (2) | 540 | (34) |
| St. Jude Medical Trifecta | Registry | 0 (33) | 540 | (34) |
| St. Jude Medical Trifecta | Clinical Trial | 0 (3) | 183 | (36) |
| LivaNova Mitroflow | Registry | 0 (11) | 540 | (34) |
| | Clinical Trial | 0 (1) | 183 | (36) |
| LivaNova Perceval | Clinical Trial | 0 (2) | 183 | (36) |
| Transcatheter | | | | |
| Edwards Sapien | Registry | 5 (22) | 540 | (34) |
| Edwards Sapien XT | Registry | 10 (122) | 540 | (34) |
| | Registry | 16 (309) | 540 | (34) |
| | Case series | 1.2 (257) | 86 | (37) |
| | Case series | 4 (140) | 71 | (57) |
| | Case series | 8.1 (173)* | 365 | (35) |
| | Case series | 14.3 (70) | 365 | (58) |
| Edwards Sapien 3 | Registry | 20 (10) | 540 | (34) |
| | Case series | 8.5 (461) | 86 | (37) |
| | Case series | 10.3 (156) | 92 | (59) |
| | Case series | 6 (232)* | 365 | (35) |
| Edwards Centera | Registry | 14 (7) | 540 | (34) |
| Medtronic CoreValve | Clinical trial | 0 (4) | 183 | (36) |
| | Registry | 4 (70) | 540 | (34) |
| | Case series | 1.3 (77) | 86 | (37) |
| Medtronic Evolut R | Registry | 8 (75) | 540 | (34) |
| | Case series | 6 (50) | 86 | (37) |
| St. Jude Medical Portico | Registry | 33 (50) | 540 | (34) |
| | Clinical trial | 16 (37) | 183 | (36) |
| | Case series | 12.5 (8) | 86 | (37) |
| Boston Scientific Lotus | Registry | 14 (83) | 540 | (34) |
| | Case series | 16 (25) | 86 | (37) |
| Acurate Symetis Neo | Registry | 13 (8) | 540 | (34) |

*Including 5 cases of obstructive thrombosis; authors did not specify in which type of transcatheter heart valve these happened.

## THERAPEUTIC STRATEGIES DURING AND AFTER TAVR

**ANTIPLATELET THERAPY AFTER TAVR.** The antiplatelet hypothesis derives from the understanding of ischemic events after percutaneous coronary intervention and aims at preventing thromboembolic events through the inhibition of platelet-mediated

**TABLE 3 Summary of Studies Investigating SAPT Versus DAPT After TAVR**

| Study/First Author (Ref. #) | Study Type | N | Treatment Arms | Notes | Outcomes | Time (Months) |
|---|---|---|---|---|---|---|
| Ussia et al. (60) | RCT | 79 | DAPT vs. aspirin alone (100 mg daily) | DAPT: aspirin plus clopidogrel (300 mg LD, 75 mg daily) | No differences in all-cause ($p = 0.49$) and cardiovascular death ($p = 0.51$), major adverse cardiovascular events ($p = 0.49$) and minor, major and life-threatening bleedings (all $p > 0.05$) | 6 |
| SAT-TAVI (61) | RCT | 120 | DAPT vs. aspirin alone (75–160 mg daily) | DAPT: aspirin plus clopidogrel (75 mg daily) or ticlopidine (500 mg bid) | Similar rates of major stroke and the 30-day VARC safety endpoint, and cardiovascular death<br>Lower rate of vascular complications in patients assigned to SAPT ($p = 0.03$) | 6 |
| ARTE (38) | RCT | 222 | DAPT vs. aspirin alone (80–100 mg daily) | DAPT: aspirin plus clopidogrel (300 mg LD, 75 mg daily) | DAPT group experienced a higher rate of major or life-threatening bleeding ($p = 0.038$)<br>DAPT group experienced a higher rate of ischemic events ($p = 0.065$) | 3 |
| Mangieri et al. (62) | Retrospective observational | 439 | DAPT vs. aspirin (75–160 mg daily) | DAPT: aspirin plus clopidogrel (75 mg daily)<br>Only patients with contraindication to DAPT received SAPT | Similar rate of net clinical events ($p = 0.77$), cerebrovascular events ($p = 0.12$), and all-cause ($p = 0.23$) and cardiovascular mortality ($p = 0.44$) | 12 |
| Ahmad et al. (63) | Meta-analysis | 11,781 | DAPT vs. SAPT | Variable pre- and post-TAVR antiplatelet regimens; only 13.3% of centers based their practice on guidelines | Similar rates of stroke ($p = 0.49$), death ($p = 0.72$), and bleeding ($p = 0.91$) | 3 |

If not specified, patients were in chronic aspirin therapy.

DAPT = dual antiplatelet therapy; LD = loading dose; RCT = randomized clinical trial; SAPT = single antiplatelet therapy; TAVR = transcatheter aortic valve replacement; VARC = Valve Academic Research Consortium.

thrombosis on the percutaneous biological valve stent frame until full endothelization is obtained at approximately 3 months. Dual antiplatelet therapy (DAPT) with aspirin (80 to 325 mg/day) and clopidogrel (75 mg/day) has been empirically administered to patients from the beginning of the TAVR era in most centers and studies, even in the absence of clear evidence. Studies comparing a single antiplatelet therapy (SAPT) and DAPT regimen after TAVR have shown no significant differences between the 2 treatments, with only 1 study reporting increased rate of bleeding in the DAPT arm (38) (**Table 3**). Since the duration of DAPT was heterogeneous, ranging from 1 to 6 months, and studies were underpowered, any conclusions should be interpreted as hypothesis-generating only. Furthermore, recent findings suggest that ticagrelor achieves faster and better platelet suppression than clopidogrel, and that the latter was associated with a significant recovery of platelet reactivity over time (39). Whether these promising results are associated with better clinical outcomes is still unknown.

**ANTICOAGULANT THERAPY AFTER TAVR. Anti-vitamin K.** Randomized studies on antithrombotic strategies in TAVR patients with the concomitant need for anticoagulation are scarce, and our knowledge of long-term safety and efficacy of OAC therapy after TAVR is limited. Registries include a variety of treatments and give inconsistent conclusions (40–42) (**Table 4**). A pooled analysis of 656 patients with atrial fibrillation discharged on warfarin reported major/life-threatening bleeding ranging from 5% to 48% with no clear data about the long-term outcome of this population. The use of an antiplatelet agent on top of VKA increased the risk of bleeding without any benefit on hard clinical endpoints (41). Moreover, the France-TAVI registry demonstrated that OAC treatment after TAVR, mainly using VKA, was associated with increased long-term mortality despite adjustment in the presence of atrial fibrillation (43). This finding highlights the possible harm of OAC-related bleeding after TAVR and the need to reduce the risk of bleeding in this frail population.

**Direct oral anticoagulants.** Little evidence supports the use of direct oral anticoagulants (DOACs) after TAVR and concomitant atrial fibrillation. Apixaban (2.5 mg twice daily) versus VKA resulted in a significant reduction in life-threatening bleeding (3.5% vs. 5.3%; $p < 0.01$) and 30-day rate of stroke (2.1% vs. 5.3%; $p = 0.17$) (44). A retrospective analysis found no difference in terms of a composite endpoint of post-procedural death, stroke, embolism, and severe bleeding in patients treated with DOAC versus VKA monotherapy (11% vs. 8.1%; $p = 0.45$) (45).

Interestingly, the randomized, phase 3, GALILEO trial (rivaroxaban plus aspirin vs. aspirin plus clopidogrel), which included patients with no history of

**TABLE 4 Summary of Studies Investigating OAC Alone and/or in Combination With Antiplatelet Therapy After TAVR**

| First Author (Ref. #) | Study Type | N | Treatment Arms | Notes | Outcomes | Time (Months) |
|---|---|---|---|---|---|---|
| OAC as therapy immediately after TAVR | | | | | | |
| Durand et al. (64) | Prospective study, propensity score matched | 292 | DAPT vs. APT + OAC | Group A monoantiplatelet therapy = 164 patients: aspirin or clopidogrel and VKA; Group B = 128 patients: dual antiplatelet therapy | Higher rate of bleeding complications at 30 days in Group B vs. Group A: life-threatening bleeding 3.7% vs. 12.5%; p = 0.005; major bleedings 2.4% vs. 13.3%, p <0.0001 | 1 |
| Holy et al. (65) | Retrospective single-center registry analysis | 514 | APT vs. APT + OAC/DOAC | At 1 yr, valve thrombosis was reported in 8 (2.5%) patients in the DAPT group but not in the OAC group (p = 0.02). | No difference in both efficacy and safety endpoints were observed at 30 days and 6 months with DAPT (315 patients) vs. OAC (199 patients, including 188 warfarin, 7 rivaroxaban, and 4 dabigatran) | 12 |
| Abdul-Jawad Altisent et al. (41) | Prospective multicenter clinical study | 621 | Warfarin vs. warfarin + APT | No difference in mortality and in thromboembolic event | Increased risk of hemorrhage with warfarin + APT vs. warfarin alone: Adjusted HR for VARC-2 major or life-threatening bleeding: 1.85; 95% CI: 1.05–3.28; p = 0.04 | 13 |
| Seeger et al. (44) | Prospective single-center clinical study | 617 | Warfarin vs. DOAC | Lower stroke rate (2.1% vs. 5.3%; p = 0.17) at 30 days and 12 months (1.2% vs. 2.0%; p = 0.73) of follow-up | Significantly lower rate of the early safety endpoint in patients with AF treated with DOAC (apixaban) compared with patients treated with warfarin (13.5% vs. 30.5%; p < 0.01) | 12 |
| OAC in screening studies for hypoattenuating leaflet thrombosis | | | | | | |
| Chakravarty et al. (34) | Observational study | 890 | OAC vs. DAPT OAC vs. SAPT | SLT 13% Time to CT: 1–12 months SLT: mean gradient >20 mm Hg and increase >10 mm Hg | OAC vs. DAPT: 4% vs. 15%; p < 0.001; OAC vs. SAPT: 4% vs. 16%, p < 0.001; DAPT vs. SAPT: 15% vs. 15%, p = 0.83 | 1–12 |
| Hansson et al. (35) | Cohort study | 405 | Warfarin vs. no warfarin | SLT 7% Time to CT: 1–3 months. Significantly higher gradient: 10 mm Hg vs. 8 mm Hg; p = 0.003 | Warfarin vs. no warfarin: 1.8 vs. 10.7% (RR: 6.1; 95% CI: 1.9–19.8) | 3 |
| Pache et al. (59) | Observational study | 156 | OAC vs. SAPT vs. DAPT | SLT 10% Time to CT: 5 days Significantly higher gradient: 15 mm Hg vs. 12 mm Hg; p = 0.026 | No difference between OAC vs. SAPT vs. DAPT | 5 |
| Makkar et al. (36) | Registries | 55 | Warfarin vs. DAPT | SLT 40% Time to CT: 1 month No difference in gradient | Warfarin vs. DAPT: 0% vs. 51% (p = 0.007) | 1 |

DOAC = direct oral anticoagulant; OAC = oral anticoagulation therapy; SLT = subclinical leaflet thrombosis; other abbreviations as in Table 3.

atrial fibrillation, was prematurely halted after a preliminary analysis for increased risk of all-cause death (7% vs. 3%) in the rivaroxaban arm, while similar rates of first thromboembolic events were reported (7.4% vs. 7.3%) (46). These recent findings question the safety of DOAC plus antiplatelet agent in TAVR patients without indication to long-term OAC. Complete results and landmark analysis are awaited.

**Intraprocedural anticoagulation.** Anticoagulation is required during TAVR procedures, and a joint expert consensus document suggests maintaining activated clotting time >300 s (47), although the basis for this target and the modalities to achieve it are not yet well defined. The intraprocedural safety and efficacy of bivalirudin versus unfractionated heparin was investigated (48), with no significant differences in terms of ischemic and bleeding events at 48 h, net adverse cardiovascular events at 30 days, or in terms of cerebral embolization at magnetic resonance imaging (49). Therefore, heparin is preferred over bivalirudin (50), which might be a reasonable alternative in case of allergy, heparin-induced thrombocytopenia, or other contraindication to unfractionated heparin.

## GUIDELINE RECOMMENDATIONS

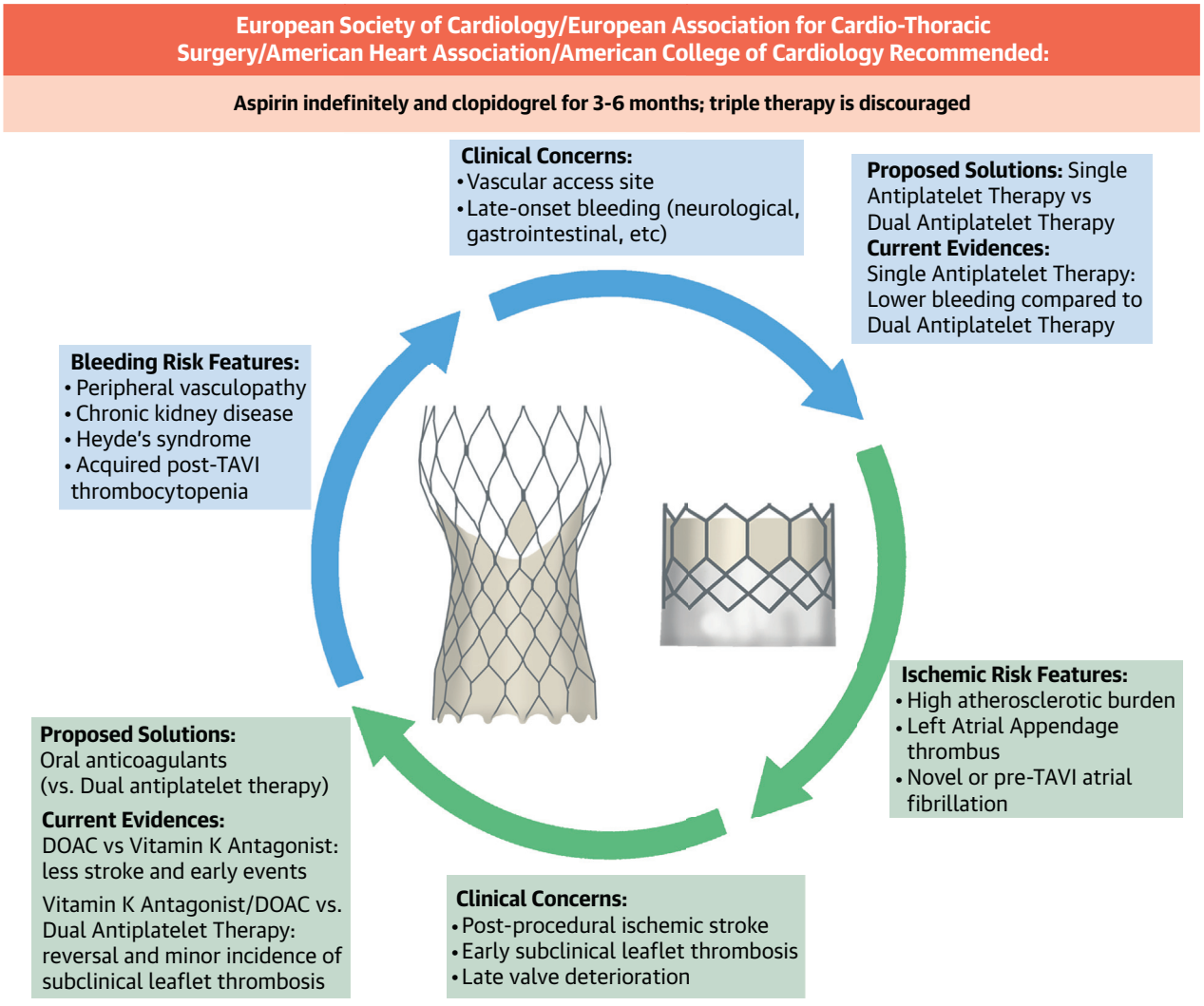
Current recommendations about the antithrombotic regimen after TAVR are largely based on expert consensus (50,51) and are summarized in **Table 5**. In patients in sinus rhythm, the use of DAPT with aspirin (indefinitely) and clopidogrel (3 to 6 months) is encouraged by both the European Society of Cardiology/European Association of Cardio-Thoracic Surgery (ESC/EACTS) and the American Heart Association/American College of Cardiology (AHA/ACC),

**TABLE 5 Summary of Recommendation and Expert Consensus for Antithrombotic Therapy After TAVR**

| | | | Does the Patient Have an Indication for OAC? | | | |
|---|---|---|---|---|---|---|
| | | | No | | Yes | |
| | | | What Is the Patient's Bleeding Risk? | | What Is the Patient's Bleeding Risk? | |
| Society Guidelines | Year | Timing After TAVR | Low | High | Low | High |
| ACC/AHA guidelines | 2017 focus update of the 2014 guidelines | Short-term | VKA to achieve an INR of 2.5 | Clopidogrel 75 mg daily + Aspirin 75–100 mg daily | No clear indication | No clear indication |
| | | Duration | 3 months | 6 months | No clear indication | |
| | | CoR/LoE | IIb/B-NR | IIb/C | No clear indication | |
| | | Long-term | Aspirin 75–100 mg daily | | No clear indication | No clear indication |
| | | Duration | Lifelong | | No clear indication | |
| | | CoR/LoE | IIa/B | | No clear indication | |
| | | BVT | In patients who are hemodynamically stable and have no contraindications to anticoagulation, initial treatment with a VKA is reasonable (CoR IIa, LoE: C-LD) | | | |
| ESC/EACTS guidelines | 2017 | Short-term | Dual antiplatelet therapy | Single antiplatelet therapy | OAC + aspirin or thienopyridine | OAC |
| | | Duration | 3–6 months | Lifelong | 3 months | Lifelong |
| | | CoR/LoE | IIa/C | IIb/C | IIa/C | I/C |
| | | Long-term | Aspirin or thienopyridine alone | | OAC | |
| | | Duration | Lifelong | | Lifelong | |
| | | CoR/LoE | IIb/C | | I/C | |
| | | BVT | No clear indication | | | |
| ACCP clinical practice guidelines | 2012 | Short-term | Aspirin 50–100 mg daily + Clopidogrel 75 mg daily over VKA therapy and over no platelet therapy | | No clear indication | No clear indication |
| | | Duration | 3 months | | No clear indication | |
| | | CoR/LoE | Grade 2C | | No clear indication | |
| | | Long-term | Aspirin 50–100 mg daily | | No clear indication | No clear indication |
| | | Duration | Lifelong | | No clear indication | |
| | | CoR/LoE | Grade 2C | | No clear indication | |
| | | BVT | For patients with right-sided prosthetic valve thrombosis, in the absence of contraindications we suggest administration of fibrinolytic therapy over surgical intervention (Grade 2C). | | | |
| CCS position statement | 2012 | Short-term | Low-dose aspirin + Thienopyridine | | • The need for adjunctive antiplatelet agents is controversial<br>• Triple therapy should be avoided unless definite indications exist | |
| | | Duration | 1–3 months | | No clear indication | |
| | | CoR/LoE | Position statement | | Position statement | |
| | | Long-term | Low-dose aspirin | | (see short-term) | |
| | | Duration | Not specified | | No clear indication | |
| | | CoR/LoE | Position statement | | Position statement | |
| | | BVT | Prophylaxis against valve-related thromboembolic complications is currently empiric. | | | |
| ACCF/AATS/SCAI/STS expert consensus | 2012 | Short-term | Aspirin and clopidogrel (to decrease the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications) | | • Warfarin/direct thrombin inhibitor/Factor Xa inhibitor + low-dose aspirin<br>• Other antiplatelet therapy should be avoided, if possible | |
| | | Duration | 3–6 months | | No clear indication | |
| | | CoR/LoE | Expert consensus | | Expert consensus | |
| | | Long-term | Aspirin 75–100 mg daily | | (see short-term) | |
| | | Duration | Lifelong | | No clear indication | |
| | | CoR/LoE | Expert consensus | | Expert consensus | |
| | | BVT | If any intracardiac thrombus is detected, then early institution of heparin followed by oral anticoagulants is suggested. | | | |

AATS = American Association for Thoracic Surgery; ACC = American College of Cardiology; ACCP = American College of Clinical Pharmacy; BVT = bioprosthetic valve thrombosis; CCS = Canadian Cardiovascular Society; CoR = Class of Recommendation; LoE = Level of Evidence; EACTS = European Association of Cardio-Thoracic Surgery; ESC = European Society of Cardiology; SCAI = Society for Cardiovascular Angiography & Interventions; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; VKA = vitamin K antagonist.

**CENTRAL ILLUSTRATION** **Optimal Antithrombotic Therapy According to Bleeding Versus Thrombotic Balance**




**Mangieri, A. et al. J Am Coll Cardiol. 2019;74(16):2088–101.**

European and American scientific societies only express a recommendation to treat all transcatheter aortic valve replacement patients with dual antiplatelet therapy for at least 6 months, and discourage triple therapy. Furthermore, concerns regarding valve durability and thrombosis have been raised, and anticoagulation was suggested. Clinical considerations might discourage from a potent antithrombotic regimen, and a tailored therapy might be necessary. At present, little evidence supports these concepts; major trials are currently available but are ongoing. DOAC = direct oral anticoagulant.

whereas SAPT with aspirin in high-bleeding risk patients is encouraged by the ESC/EACTS only (**Central Illustration**). Dual antiplatelet therapy is also indicated for TAVR patients in sinus rhythm and concomitant obstructive coronary artery disease after stent placement. ESC/EACTS and AHA/ACC both recommend the extension of OAC therapy in patients with indication for other diseases such as atrial fibrillation (50,51). The guidelines do not provide a more precise recommendation on the triple antithrombotic therapy, and data in this setting are lacking. Therefore, this strategy should be considered only in special situations, including recent coronary stenting and concomitant atrial fibrillation in patients undergoing TAVR. The AHA/ACC guidelines recommend the use of VKA to offset the risk of leaflet

**TABLE 6 Summary of Ongoing Studies About Optimal Antithrombotic Therapy After TAVR**

| | ATLANTIS | GALILEO | GALILEO-4D (Substudy) | AVATAR |
|---|---|---|---|---|
| ClinicalTrials.gov identifier | NCT02664649 | NCT02556203 | NCT02833948 | NCT02436655 |
| Experimental arm | Apixaban 5 mg twice daily | Rivaroxaban 10 mg once daily plus acetylsalicylic acid 75–100 mg (for 90 days only) | Rivaroxaban 10 mg once daily plus acetylsalicylic acid 75–100 mg (for 90 days only) | VKA alone |
| Comparison arm | VKA or antiplatelet therapy or combination | Aspirin and clopidogrel for 3 months only | Aspirin and clopidogrel for 3 months only | VKA plus aspirin |
| Start date | August 26, 2016 | December 16, 2015 | May 2016 | June 1, 2017 |
| Status | Recruiting | Completed; interrupted by data and safety monitoring board | | Recruiting |
| Estimated completion date | May 31, 2020 | November 27, 2018 | March 6, 2019 | April 2020 |
| Sample size | 1,510 | 1,653 | 232 | 170 |
| Design | Randomized, multicenter, open-label | Event-driven, randomized, multicenter, open-label | Event-driven, randomized, multicenter, open-label | Event-driven, randomized, multicenter |
| Trial phase | 3 | 3 | 3 | 4 |
| Nonvalvular atrial fibrillation patients | Included and stratified for | Excluded | Excluded | Included and stratified for |
| Follow-up, months | 13 | 25 | | 12 |
| Primary endpoint (composite of) | Death, MI, stroke, systemic embolism, intracardiac or bioprosthesis thrombus, any episode of deep vein thrombosis or pulmonary embolism, life-threatening or disabling or major bleeding defined according to VARC-2 definitions over 1-yr follow-up | All-cause death, MI, stroke, systemic embolism, MI, symptomatic valve thrombosis, deep vein thrombosis or pulmonary embolism; composite of adjudicated life-threatening, disabling or major bleeding, classified according to the VARC definitions following the BARC classification | Rate of patients with at least 1 prosthetic leaflet with >50% motion reduction as assessed by cardiac 4D CT scan (time frame: 3 months) | Death from any cause, myocardial infarction, stroke all causes, valve thrombosis and hemorrhage ≥2 as defined by the VARC 2 |

4D = 4-dimensional; ATLANTIS = Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis; AVATAR = The Aortic Valve replAcemenT versus conservative treatment in Asymptomatic seveRe aortic stenosis; BARC = Bleeding Academic Research Consortium; CT = computed tomography; GALILEO = Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes; GALILEO 4D = Comparison of a Rivaroxaban-based Strategy With an Antiplatelet-based Strategy Following Successful TAVR for the Prevention of Leaflet Thickening and Reduced Leaflet Motion as Evaluated by Four-dimensional, Volume-rendered Computed Tomography; MI = myocardial infarction; VARC = Valve Academic Research Consortium; other abbreviations as in Table 5.

*Continued on the next page*

thrombosis in patients who are at low bleeding risk and to treat clinically relevant leaflets thrombosis with hemodynamic deterioration. At the moment, HALT is not addressed by current recommendations.

## FUTURE DIRECTIONS: A TAILORED ANTITHROMBOTIC REGIMEN

A number of unresolved issues persist regarding optimal management of oral anticoagulation and antiplatelet therapy after TAVR, with several clinical trials ongoing (Table 6). Due to the great heterogenicity among the TAVR population, a unique optimal antithrombotic therapy for all TAVR patients does not exist, and antithrombotic therapy should be tailored to the patient's individual balance between thromboembolic and bleeding risk and dictated by concomitant comorbidities. Ongoing, large randomized studies will give more answers to the unresolved questions of optimal antithrombotic management of TAVR patients. In the present review, we also highlight topics that deserve more attention in future research, including further characterization of the hemocompatibility profile of valve grafts and stents, vWF, and overall thrombogenicity status including post-procedural thrombocytopenia and the use of potent $P2Y_{12}$ inhibitors.

## CONCLUSIONS

Even if TAVR is gaining momentum due to the procedural improvements observed over the last few years, uncertainty still surrounds its optimal antithrombotic management. At present, few observational studies and small randomized-controlled trials indicate that a more aggressive anticoagulant and antiplatelet therapy gives any benefit in terms of reduction of thromboembolic events, but instead confers an increased risk of bleeding with negative impact on prognosis. However, concerns about HALT might suggest a potential role for OAC to preserve long-term durability of the valve and to prevent

**TABLE 6 Continued**

| ADAPT-TAVR | ENVISAGE TAVI-AF | POPULAR TAVI | AUREA |
|---|---|---|---|
| NCT03284827 | NCT02943785 | NCT02247128 | NCT01642134 |
| Edoxaban (60 mg once daily) for at least 6 months | Edoxaban 60 mg | Cohort A: aspirin plus clopidogrel; Cohort B: VKA plus clopidogrel | Acenocumarol |
| Clopidogrel (75 mg once daily) plus aspirin (75–100 mg once daily) for at least 6 months | VKA | Cohort A: aspirin only; Cohort B: VKA only | Association of aspirin 100 mg and clopidogrel 75 mg |
| March 15, 2018 | March 21, 2017 | January 2014 | April 2013 |
| Recruiting | Recruiting | Recruiting | Recruiting |
| December 2020 | May 2020 (primary completion); November 2020 (study completion) | January 2019 (primary completion); January 2020 (study completion) | October 2018 (primary completion); April 2019 (study completion) |
| 220 | 1,400 | 1,000 | 124 |
| Multicenter, randomized, open-label, active-treatment | Event-driven, randomized, multicenter, open-label | Randomized, multicenter, open-label | Randomized, multicenter |
| 4 | 3 | 4 | 4 |
| Excluded | Included | Included and stratified for | Excluded |
| 6 | 36 | 12 | 3 months |
| An incidence of leaflet thrombosis on 4D, volume-rendered cardiac CT imaging | Death, MI, ischemic stroke, systemic embolic events, valve thrombosis, and major bleeding per definition of the International Society on Thrombosis and Hemostasis | Freedom from all bleeding complications at 1 yr after TAVR (coprimary outcome: freedom of non-procedure related bleeding complications) | Efficacy of antithrombotic evaluated by detection of new areas of cerebral infarction by MRI 3 months after TAVR (Time Frame: 6 months) |

neurological events. In conclusion, a complex balance between residual thrombotic versus bleeding risk exists in patients undergoing TAVR. Results from several large ongoing randomized control trials are awaited to cast light on this obscure topic and to optimize antithrombotic strategy according to the risk profile of each individual patient.

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