

Antithrombotic Therapy Following Transcatheter Aortic Valve Replacement

Subjects: Cardiac & Cardiovascular Systems

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Transcatheter aortic valve replacement (TAVR) is expanding towards a low-risk patient category as a result of technical advances and operators' improved skills. However, the post-TAVR antithrombotic regimen remains challenging. Single antiplatelet therapy appears to be the best compromise when there is no compelling indication for chronic oral anticoagulation. Whether it should be aspirin or clopidogrel is not established. There is no supportive evidence to use oral anticoagulation when there is no established indication for oral anticoagulation other than the TAVR procedure. The gap in evidence as to whether DOACs should be preferred over VKA remains when there is an indication for oral anticoagulation (OAC) use. It seems that DOACs are not the same and randomized trials are awaited. Likewise, whether oral anticoagulant therapy should be continued or interrupted during the procedure remains unclear.

Keywords: TAVR ; antithrombotic therapy ; oral anticoagulation ; DOAC ; VKA ; SAPT

1. Bleeding Events after TAVR

While bleeding risk is less frequent after transcatheter compared to surgical aortic valve replacement ^[1], it remains a major complication during and after transcatheter aortic valve replacement (TAVR). Bleeding events are categorized as early (<30 days post-TAVR) and late (>30 days post-TAVR) complications. The prior Valve Academic Research Consortium 2 (VARC-2) consensus document divided bleeding events into three types, following the Bleeding Academic Research Consortium (BARC) classification: minor bleeding (BARC 2 and 3a depending on severity), major bleeding (BARC 3a) and life-threatening or disabling bleeding (BARC 3b, 3c, 5) ^[2]. Recently, the classification of bleeding events after TAVR has been updated in the VARC-3 consensus document, and is now divided into four types: type 1 (minor: BARC 2 and 3a depending on severity), type 2 (major: BARC 3a), type 3 (life-threatening: BARC 3b, 3c and 4) and type 4 (leading to death: BARC 5) ^[3]. Most of the time, bleeding complications appear within the first 30 days post-procedure ^[4]. In the pivot trials, early life-threatening and disabling bleeding rates (VARC-2 defined) ranged from 9 to 17% in high-surgical-risk patients, but decreased to 10–12% in intermediate-risk patients and 2–11% in low-risk patients. Bleeding risk remains long after TAVR, with a 1-year severe bleeding incidence from 2.4 to 22.3% ^{[5][6][7][8][9][10][11][12]}. Not only related to fewer comorbidities in lower-surgical-risk patients, the decrease in bleeding rates noticed over the years is associated with an increase in the operator's experience, reduction of sheath catheter diameter and the use of trans-femoral access rather than trans-apical access where possible. Data from the PARTNER trial reported major late bleeding events in 6% of patients, mainly from gastrointestinal (40%) and neurological (15%) origin ^[13]. Both early and late bleeding events are associated with poor outcomes and higher 30-day and 1-year post-TAVR mortality rates ^{[14][15][16]}.

2. Periprocedural Antithrombotic Therapy

Bleeding events have a dreadful impact on TAVR patients and mostly occur within the 30 days post-intervention with great risk during the procedure, as well as ischemic stroke and TIA. Optimal periprocedural antithrombotic strategy is the first key step. The BRAVO-3 trial showed no reduction of major thromboembolic events (4.1% vs. 4.1%, $p = 0.97$), but a higher rate of major vascular complications (11.9% vs. 7.1%, $p = 0.02$) with pre-loading clopidogrel on top of aspirin prior to TAVR ^[17]. Low-dose aspirin alone is the treatment of choice, usually started pre-TAVR, in patients with no indication of OAC ^[18].

Parenteral anticoagulation therapy with unfractionated heparin (UFH) is routinely given to prevent periprocedural thromboembolism, particularly stroke. In the BRAVO-3 trial, bivalirudin did not reduce major bleeding or adverse cardiovascular events at 48 h when compared with UFH ^[19]. In 2012, an expert consensus document recommended heparin administration to maintain an activated clotting time (ACT) >300 s ^[20]. More recently, the consensus document of the ESC and the European Association of Percutaneous Cardiovascular Intervention (EAPCI) recommend the use of UFH

with an ACT between 250 and 300 s to prevent catheter thrombosis and thromboembolism, with bivalirudin an option if there is prior evidence of heparin-induced thrombocytopenia [24]. Baseline ACT-guided heparin administration has been shown to reduce major bleeding during transfemoral TAVR [22]. Expert consensus documents also suggest that protamine sulfate can be used to reverse anticoagulation before closure to reduce vascular access-site complications and bleeding. Indeed, a significant decrease of major and life-threatening bleeding is obtained with protamine sulfate after TAVR, without a rise in the occurrence of stroke and MI [23].

3. Antithrombotic Therapy after TAVR

3.1. Antiplatelet Therapy after TAVR: Updated Guidelines in 2021

Since 2020, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend a single antiplatelet therapy of aspirin (75–100mg daily) after TAVR in the absence of other indications for oral anticoagulants (class of recommendation: 2a, level of evidence: B-R), while dual antiplatelet therapy (aspirin 75–100 mg plus clopidogrel 75 mg daily) for 3 to 6 months has been retroceded to class of recommendation 2b [24] (Table 1). Indeed, after years of debate, recent RCTs showed no advantage of DAPT when compared to SAPT in patients undergoing TAVR with no indication of OAC and no prior coronary stenting. Two small-scale RCTs did not report difference between SAPT and DAPT after TAVR on ischemic outcomes in this population [25][26]. Consistently, the ARTE (Aspirin Versus Aspirin plus Clopidogrel as Antithrombotic Treatment Following TAVI) trial reported no difference between SAPT and DAPT in the occurrence of death, stroke or TIA at 3 months post TAVR, whereas DAPT was associated with a higher rate of major or life-threatening bleeding events (10.8% vs. 3.6% in the SAPT group, $p = 0.038$) [27]. These results were corroborated by the recent Cohort A of the POPular TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation) trial, in which 665 patients with no indication for OAC were randomized to receive either aspirin alone or aspirin plus clopidogrel for 3 months after TAVR. Bleeding events and the composite end point of bleeding or thromboembolic events at one year were significantly less frequent with aspirin alone than with DAPT (15.1% vs 26.6%, respectively, relative risk (RR) 0.57; 95% CI: 0.42-0.77; $p = 0.001$ for bleeding; 23.0% vs 31.1% $p < 0.001$ for noninferiority; RR = 0.74 $p = 0.04$ for superiority, for composite of bleeding or thromboembolic events) [28]. In addition, 2 recent meta-analyses reported lower bleeding events with aspirin alone when compared to DAPT after TAVR without significant differences in mortality, myocardial infarction or stroke [29][30]. Thus, these studies demonstrate no difference between SAPT and DAPT in preventing thromboembolic outcomes after TAVR in patients with no indication of OAC, but a consistent and significant increase in major bleeding events with DAPT. Taking these results into consideration, guidelines from the ESC and the European Association for Cardio-Thoracic Surgery (EACTS) on valvular heart disease were updated in 2021, and from this point, a lifelong single antiplatelet therapy with aspirin (75–100 mg daily) or clopidogrel (75 mg daily) is recommended after TAVR in patients with no baseline indications for OAC (class of recommendation: I, level of evidence: A). DAPT with low dose aspirin (75–100 mg daily) plus clopidogrel (75 mg daily) is recommended after TAVR only in case of recent coronary stenting (< 3 months), with duration according to bleeding risk (between 1 and 6 months), followed by a lifelong SAPT [18] (Table 1, Figure 1).

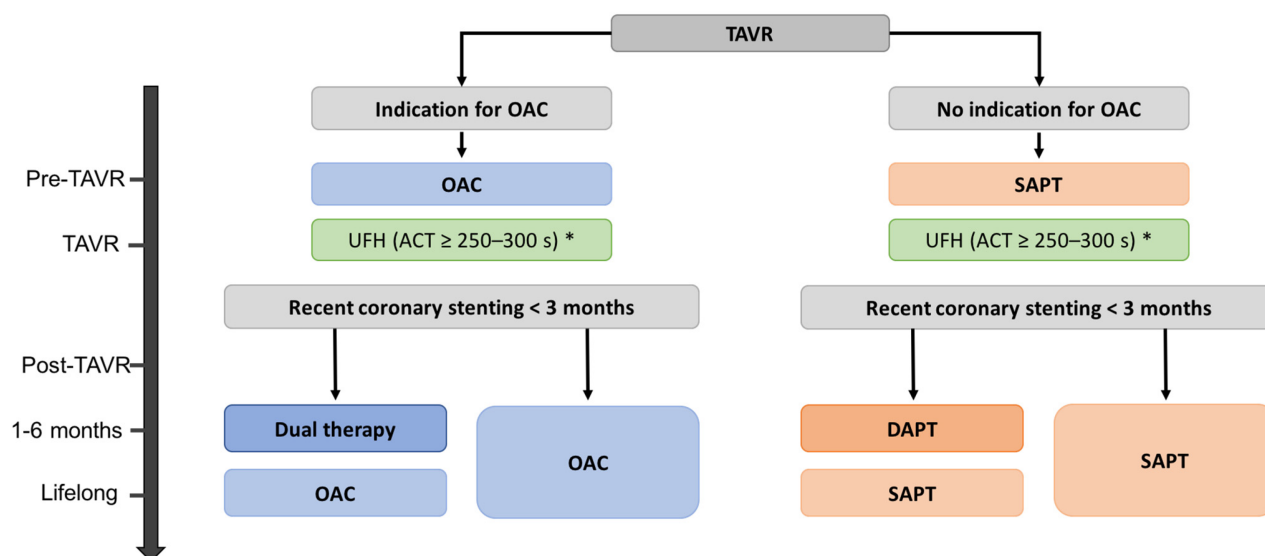


Figure 6. ESC/EACTS recommendations for antithrombotic strategy during and after transcatheter aortic valve replacement. Dual therapy: OAC plus aspirin or clopidogrel. SAPT: Low-dose aspirin or clopidogrel. DAPT: Low-dose aspirin and clopidogrel. OAC: VKA or DOAC. * Bivalirudin if heparin induced thrombocytopenia. ACT: activated clotting time; DAPT: dual antiplatelet therapy; DOAC: non-vitamin K antagonist oral anticoagulant; OAC: oral anticoagulation;

SAPT: single antiplatelet therapy; TAVR: transcatheter aortic valve replacement; UFH: unfractionated heparin; VKA: vitamin K antagonist.

Table 1. Current Recommendations on Antithrombotic Therapy after TAVR.

Guidelines and Expert Consensus	Recommendations	Class of Recommendation	Level of Evidence
ESC/EACTS 2021 Guidelines ^[18]			
	Patients without underlying indication for chronic OAC		
	Lifelong single antiplatelet therapy (aspirin 75–100 mg daily or clopidogrel 75mg daily) is recommended after TAVR in patients with no baseline indication for OAC	I	A
	Routine use OAC is not recommended in patients with no baseline indication for OAC	III	B
	Patients with underlying indication for chronic OAC		
	OAC is recommended lifelong for TAVR patients who have other indications for OAC	I	B
AHA/ACC 2020 Guidelines ^[24]			
	Patients without underlying indication for chronic OAC		
	For patients with a bioprosthetic TAVR, aspirin 75–100 mg daily is reasonable in the absence of other indications for oral anticoagulants.	IIa	B-R
	For patients with a bioprosthetic TAVR who are at low risk of bleeding, dual antiplatelet therapy with aspirin 75–100 mg and clopidogrel 75 mg may be reasonable for 3–6 months after valve implantation.	IIb	B-NR
	For patients with a bioprosthetic TAVR who are at low risk of bleeding, anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for at least 3 months after valve implantation.	IIb	B-NR
	For patients with a bioprosthetic TAVR, treatment with low-dose rivaroxaban (10 mg daily) plus aspirin (75-100 mg) is contraindicated in absence of other indications for oral anticoagulants.	III	B-R
	Patients with underlying indication for chronic OAC		
	No specific recommendation		
CCS 2019 Position Statement ^[31]			
	Patients without underlying indication for chronic OAC		
	Lifelong aspirin 75–100 mg daily	Expert consensus	
	In patients with a recent PCI, dual antiplatelet therapy (aspirin 75–100 mg/d plus clopidogrel 75 mg/d) may be continued as per the treating physician	Expert consensus	
	Patients with underlying indication for chronic OAC		
	DOAC for patients with atrial fibrillation unless contra-indicated* in addition to aspirin for TAVR patients	Expert consensus	
	Oral anticoagulation for other indications as per standard guidelines	Expert consensus	
	It is prudent to avoid triple therapy in patients at increased risk of bleeding.	Expert consensus	
ACCF/AATS/SCAI/STS 2012 Expert Consensus ^[20]			
	Patients without underlying indication for chronic OAC		

Guidelines and Expert Consensus	Recommendations	Class of Recommendation	Level of Evidence
ESC/EACTS 2021 Guidelines ^[18]			
	Antiplatelet therapy for at least 3–6 months after TAVR is recommended to decrease the risk of thrombotic or thromboembolic complications	Expert consensus	
	Patients with underlying indication for chronic OAC		
	In patients treated with warfarin, a direct thrombin inhibitor, or factor Xa inhibitor, it is reasonable to continue low-dose aspirin, but other antiplatelet therapy should be avoided, if possible	Expert consensus	
	ACCP-2012 Clinical practice guidelines ^[32]		
	Patients without underlying indication for chronic OAC		
	Aspirin (50–100 mg/d) plus clopidogrel (75 mg/d) over VKA therapy and over no platelet therapy in the first 3 months	2	C
	Patients with underlying indication for chronic OAC		
	No specific recommendation		

* Warfarin would be preferable for patients with contraindication to DOAC in the setting of mitral valve stenosis or mechanical valve replacement. AATS, American Association for Thoracic Surgery; ACC, American College of Cardiology; ACCF, ACC Foundation; ACCP, American College of Chest Physicians; AHA, American Heart Association; CCS, Canadian Cardiovascular Society; DOAC, direct oral anticoagulation; EACTS, European Association for Cardio-Thoracic Surgery; ESC, European Society of Cardiology; INR, international normalized ratio; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; SCAI, Society for Cardiovascular Angiography and Interventions; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; VKA, vitamin K antagonist.

3.2. In Antiplatelet Monotherapy, Use of Aspirin or Anti-P2Y12?

Minimal data are available on the optimal SAPT following TAVR. While clopidogrel is also an option in the guidelines, aspirin is commonly used when SAPT is indicated after TAVR. However, whether aspirin or an oral P2Y12 inhibitor should be used remains unknown. Only one observational study compared clopidogrel to aspirin after TAVR. The OCEAN-TAVI Japanese registry reported lower 2-year cardiovascular mortality in patients treated with clopidogrel versus aspirin, with (2.7% vs. 8.5%, respectively) and without (5.2% vs. 18%, respectively) anticoagulation. Neither difference was noticed on all-cause deaths, nor stroke, life-threatening or major bleeding at 2 years ^[33]. Additional data are needed to evaluate the optimal choice between clopidogrel or aspirin in patients undergoing TAVR with no indication of OAC. However, many studies have highlighted the issue of inhomogeneity in platelet response to clopidogrel in patients undergoing PCI, which has been reported in 20 to 40% of patients. Of note, high platelet reactivity (HPR) has been associated with a higher risk of ischemic events ^[34]. Limited data are available on the frequency and clinical impact of variable platelet response to antiplatelet therapy in patients undergoing TAVR. While well established in patients experiencing acute coronary syndrome, the safety and efficacy of the oral P2Y12 inhibitor ticagrelor in patients undergoing TAVR needs further investigation. The REAC TAVI (Assessment of Platelet Reactivity after Transcatheter Aortic Valve Implantation) randomized trial compared the efficacy of aspirin plus clopidogrel to aspirin plus ticagrelor after TAVR in patients identified with prior HPR. Among 68 patients, 70% were identified with HPR. Ticagrelor achieved suppression of HPR in all patients, while only 21% of patients treated with clopidogrel had a platelet reactivity reduction ^[35]. Thus, ticagrelor provides a better and persistent reduction of HPR among patients with aortic stenosis undergoing TAVR. Consistently, the PTOLEMANIOS trial (a trial to assess the safety and efficacy of Prophylactic Ticagrelor With Acetylsalicylic Acid vs. Clopidogrel With Acetylsalicylic Acid in the Development of Cerebrovascular Embolic Events During TAVI) reported better platelet inhibition with ticagrelor (90 mg bd) plus aspirin when compared to clopidogrel plus aspirin, which resulted in fewer suspicious signals of cerebrovascular microembolic events on periprocedural transcranial Doppler ^[36]. The effect of a lower dose of ticagrelor is currently being investigated in the REACTIC-TAVI (Platelet Reactivity According to Ticagrelor Dose After Transcatheter Aortic Valve Implantation; NCT04331145) trial. This single-arm trial aims to determine the pharmacodynamic effects of 3 months of low-dose ticagrelor (60 mg bd) monotherapy in patients with HPR. Patients with inadequate response to clopidogrel (75 mg qd) are switched to low-dose ticagrelor after TAVR until completing 3 months of treatment, with the efficacy of ticagrelor in suppressing HPR evaluated at different timelines after TAVR.

3.3. Patients with Life-Long Indication for Anticoagulation

In patients requiring long-term OAC, previous observational studies have compared outcomes between OAC alone vs. OAC plus antiplatelet therapy. Rates of stroke and mortality were similar between the two antithrombotic regimens, while there was an increased risk of bleeding complications with OAC plus APT [37][38][39]. Conversely, the analysis of the PARTNER 2 cohort by Kosmidou et al. questioned the efficacy of OAC alone in the prevention of stroke after TAVR, showing that the 2-year stroke incidence was not reduced with OAC alone, while antiplatelet with or without anticoagulant therapy reduced the risk of stroke at 2 years. However, OAC alone was associated with a reduced risk of combined death and stroke [40]. More recently, cohort B of the POPular-TAVI trial randomized 313 patients to receive OAC (direct oral anticoagulant (DOAC) or VKA) alone or OAC plus clopidogrel for 3 months. The 1-year incidence of bleeding post-TAVI was significantly higher with OAC plus clopidogrel than with OAC alone (34.6% vs. 21.7%, respectively; $p = 0.01$), while the composite endpoint of death from cardiovascular cause and thromboembolic complications (MI and stroke) appeared non-inferior between the two groups [41]. Thus, an association of OAC plus antiplatelet therapy leads to a higher rate of bleeding complications with no advantage in long-term thromboembolic complications. Based on these results, OAC alone is recommended by the ESC/EACTS guidelines after TAVR for patients with a lifelong indication of OAC (class of recommendation: I, level of evidence: B), if no concomitant or recent PCI. In the case of coronary stenting in the past 3 months or concomitant to the valve intervention, dual therapy consisting of OAC plus aspirin (or clopidogrel) is recommended for 1 to 6 months according to the bleeding risk, then switched to life-long anticoagulation [18] (Figure 6). No specific recommendations are provided in the ACC/AHA Guidelines for patients undergoing TAVR and requiring long-term OAC.

3.4. In Patients Requiring OAC, Which Anticoagulant to Choose?

Whether DOAC can be used instead of VKA in patients undergoing TAVR and requiring OAC is a matter of debate. The use of DOACs has been widely approved in patients with nonvalvular AF, with proven noninferiority versus VKA in the prevention of thromboembolic events for dabigatran, rivaroxaban and edoxaban [42][43][44], and superiority for apixaban, with lower rate of bleeding events [45]. In comparison with warfarin, DOACs reduce the risk of stroke, systemic embolism and intracranial hemorrhage in AF patients with valvular heart disease (VHD) (with the exception of severe mitral stenosis or mechanical heart valve) [46]. Furthermore, the North American Consensus Statements have recently been updated and DOAC is the treatment of choice in AF patients undergoing PCI [47].

AF is frequent in TAVR patients and associated with poorer outcomes. Furthermore, OAC is correlated to mortality independently of AF in this population [48]. Observational studies comparing DOACs with VKA provided inconsistent findings [49][50][51][52]. In the combined France-TAVI and France-2 registries, 8962 patients were treated with OAC after TAVR (24% on DOACs, 77% on VKAs). After 3 years of follow-up, after propensity matching, there was a significant increase of 37% in mortality rates (VKA vs. DOAC: 35.6% vs. 31.2%; $p < 0.005$) and 64% in major bleeding (12.3% vs. 8.4%; $p < 0.005$) with VKAs compared to DOACs. No between-group difference on ischemic stroke and acute coronary syndrome was reported [53]. Consistently, the STS/ACC registry, the largest to date with 21,131 patients undergoing TAVR with pre-existing or incident AF discharged on OAC, demonstrated a significantly lower incidence of death in patients on DOACs versus VKAs (15.8% vs. 18.2%, respectively; adjusted hazard ratio (HR) 0.92; 95% confidence interval (CI), 0.85–1.00; $p = 0.043$). In addition, DOACs were also associated with a 19% decrease in bleeding rates compared to VKAs (11.9% vs. 15.0%, respectively; adjusted HR 0.81; 95% CI, 0.33–0.87; $p < 0.001$). The 1-year incidence of ischemic stroke was similar between the two groups [54]. Moreover, in a recent meta-analysis of 12 studies, including patients with an indication for OAC, DOACs were associated with lower all-cause mortality compared to VKAs after more than 1 year of follow-up (RR = 0.64; 95% CI 0.42–0.96; $p = 0.03$), while no between-group difference was shown in stroke and valve thrombosis rates [55]. Conversely, in one nonrandomized study, the composite outcome of any cerebrovascular events, myocardial infarction and all-cause mortality was 44% higher in the DOAC group vs. VKA (21.2% vs. 15.0%, respectively; HR 1.44; $p = 0.05$). Nevertheless, the 1-year incidence of all-cause mortality was comparable between the two groups (16.5% vs. 12.2% for DOAC and VKA, respectively; HR: 1.36; 95% CI: 0.90–2.06; $p = 0.136$). Bleeding rates were also similar between the two groups [56]. Of note, the increase of ischemic events was of borderline statistical significance. These findings could be the result of heterogeneity in baseline and procedural characteristics, considering the absence of randomization, and the higher prevalence of renal impairment and peripheral vascular among patients treated with NOAC. Furthermore, previously described observational studies and large registries did not correlate with these findings. Thus, in observational and large registries, DOACs seem to provide similar efficacy to VKA in the prevention of stroke, but improvement in the rates of mortality and bleeding, which could favor the use of DOACs after TAVR in patients with an underlying indication of OAC. However, these data from non-randomized studies should be carefully interpreted.

3.5. Patients without Underlying Indication for Anticoagulation

Considering the high risk of thromboembolic complications following TAVR and the potential development of subclinical obstructive valve thrombosis, post-TAVR OAC has been tested in the absence of other indications for anticoagulation. The GALILEO trial compared 3 months administration of low dose rivaroxaban (10 mg daily) plus aspirin followed by rivaroxaban alone with 3 months of aspirin plus clopidogrel followed by aspirin alone. The trial was terminated prematurely, with treatment with rivaroxaban being associated with a significantly higher risk of all-cause death (increase of 69%), of thromboembolic complications and of VARC-2 major, disabling or life-threatening bleeding (increase of 50%), compared to antiplatelet therapy [57]. Consistently, in the Stratum 2 of the ATLANTIS trial, treatment with apixaban resulted in higher all-cause and non-cardiovascular mortality compared with SAPT or DAPT among patients without an indication of OAC [58]. Similar results were reported in An et al. meta-analysis [54]. In the ESC/EACTS guidelines, OAC is contraindicated after TAVR in patients with no indications of OAC (class of recommendation: III, level of evidence: B) [18].

3.6. Ongoing Trials Evaluating Antithrombotic Therapy after TAVR

The main ongoing trials evaluating the antithrombotic regimen in TAVR patients are summarized in **Figure 2**. The AVATAR (Anticoagulation Alone Versus Anticoagulation and Aspirin Following Transcatheter Aortic Valve Interventions) open-label randomized controlled trial ($n = 170$) will evaluate the safety and efficacy of anticoagulant therapy alone (VKA or DOAC) versus anticoagulant plus aspirin (NCT02735902) in patients requiring OAC who underwent successful TAVR, after a 12-month follow-up. This trial is expected to end in April 2023. The POPular PAUSE TAVI randomized trial previously cited will provide information on the optimal anticoagulant strategy to adopt during the TAVR procedure, with a comparison of the effect of peri-operative discontinuation versus continuation of OAC on VARC-2 ischemic and bleeding outcomes in patients undergoing TAVR with prior OAC therapy (NCT04437303). Finally, in low-risk patients undergoing TAVR with no indication for OAC, the ongoing LRT (Strategies to Prevent Transcatheter Heart Valve Dysfunction in Low Risk Transcatheter Aortic Valve Replacement) trial is currently exploring the effect of VKA in addition to aspirin, compared to aspirin only, on clinical outcomes and valvular heart deterioration (NCT03557242, with the estimation completion date in July 2023).

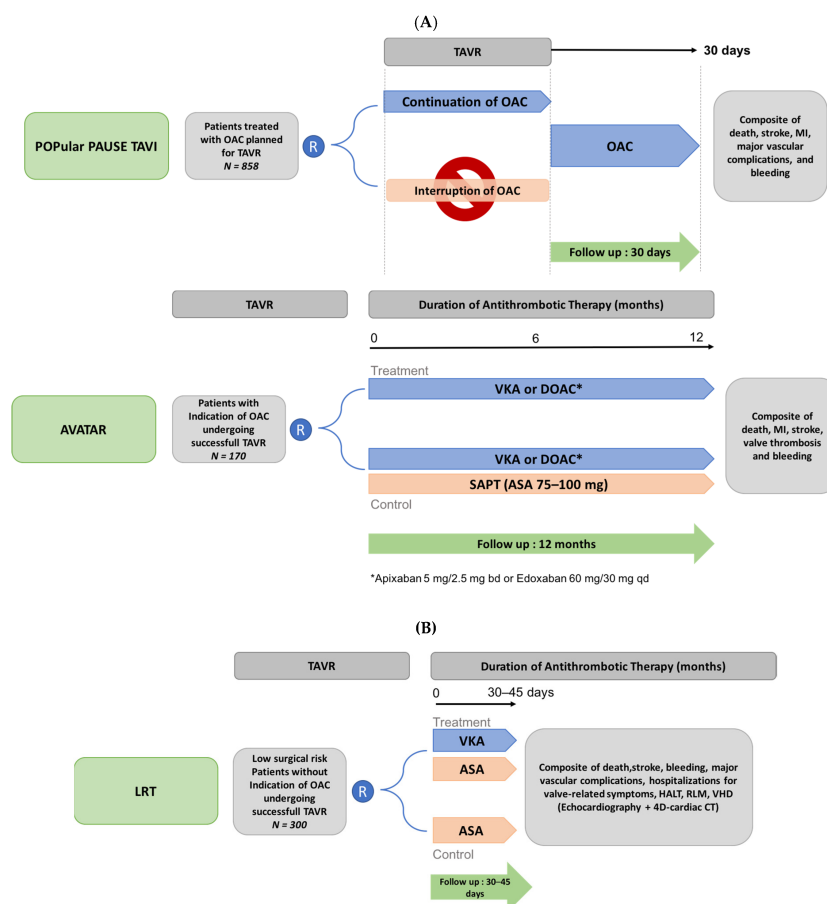


Figure 2. Design of ongoing trials of antithrombotic strategies in patients undergoing transcatheter aortic valve replacement with (A) and without (B) an indication for oral anticoagulation. 4D-CT: 4-dimensional computed tomography; ASA: aspirin; DOAC: direct oral anticoagulation; HALT: hypoattenuated leaflet thickening; MI: myocardial infarction; RLM: reduced leaflet motion; TAVR: transcatheter aortic valve replacement; VHD: valvular hemodynamic deterioration; VKA:

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