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Review Article,

The Use of Antiplatelet and Anticoagulation After TAVR: A Brief Review of Important Literature

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Abstract:

Aortic stenosis is the most common valvular heart disease in the elderly patient population. Surgical aortic valve replacement (SAVR) has been the standard of practice for treating aortic stenosis for years. But recently in the past decade, the minimally invasive procedure Transcatheter aortic valve replacement/implantation (TAVR/TAVI) has been a revolutionary treatment modality for aortic stenosis patients, particularly those who are at high risk of surgery. The patients who undergo TAVR are at high risk for bleeding and thromboembolic events afterward. The use of antiplatelet and anticoagulation after TAVR is to decrease the risk of thromboembolic complications such as stroke, but it comes with the risk of bleeding associated with antiplatelet and antithrombotic. Current guidelines recommend the use of dual antiplatelet (DAPT) for 3 to 6-month after TAVR in the absence of an indication for oral anticoagulation followed by lifelong single antiplatelet therapy (SAPT). However, the use of dual antiplatelet is associated with an increased risk of bleeding without significant ischemic benefits. Lifelong oral anticoagulation is recommended for patients who have other indications for anticoagulation. These treatment guidelines are driven by expert opinion, given the lack of large randomized control trials (RCT). In this review, we aim to discuss the need for antithrombotic and antiplatelets after TAVR and review important literature about current practice and expert recommendations about antiplatelet and anticoagulation after TAVR.

Keywords: Antiplatelet after transcatheter aortic valve replacement, antithrombotics after transcatheter aortic valve replacement, transcatheter aortic valve replacement complications, SAPT VS DAPT after transcatheter aortic valve replacement

Introduction:

Transcatheter aortic valve replacement (TAVR) has become the preferred strategy for treating severe aortic stenosis. However, no single antithrombotic regimen is recommended in the guidelines. Treatment approaches vary significantly. Multiple ongoing Studies are comparing various combinations of antithrombotic therapy. Many of these studies are testing less aggressive antithrombotic regimens aimed at reducing the risk of post-procedure Bleeding. Others are studying the use of direct oral anticoagulant therapy (DOACs), especially in patients with atrial fibrillation undergoing TAVR. Bleeding after TAVR indicates an adverse

prognosis. Nearly 80% of all bleeding events occur within the first 30 days following TAVR [1-2]. This article aims to discuss the current practice and expert recommendations about antiplatelet and anticoagulation after TAVR and the need for a large randomized control trial (RCT) to develop concrete treatment guidelines.

The Need for Antithrombotics after TAVR:

The patients who undergo TAVR are at increased risk of thromboembolic complications such as cerebrovascular accident (CVA), prosthetic valve thrombosis, myocardial infarction (MI), and bleeding episodes. The risk of stroke after TAVR is 3 to 7% and most of the cases are seen within the first 24 after the procedure. CVA can result from the embolization of debris from a calcified aortic valve during the procedure and some patients had new onset of atrial fibrillation (a-fib) after the procedure which can also increase the risk of thromboembolic CVA [1]. The incidence of per procedural MI is 1.1% and 1.9% for transapical and transarterial approaches respectively. MI can result from hypotension, trauma to the ventricular apex in the transapical approach, micro embolism to the coronary arteries, and direct compression of the myocardium due to expansion of the prosthetic wall [1]. The incidence of MI is around 2% within 1 year of the procedure [2]. The third major complication is bleeding and most of the bleeding episodes occurred within the first 30 days of the procedure [2]. 50% of the bleeding episodes are related to the excess site. The GI bleed is the most common non-access site bleeding reported [3]. Considering that TAVR is associated with a high risk of thrombotic and bleeding complications, it underscores the importance of the need for antithrombotic after TAVR.

Single antiplatelet therapy (SAPT) vs dual antiplatelet therapy (DAPT) after TAVR:

Transcatheter aortic valve replacement/implantation (TAVR/TAVI) continues to be a radical paradigm for treating symptomatic and/or severe aortic stenosis and is an efficacious therapeutic substitute for SAVR candidates of intermediate- or high- surgical risk [3]. Recent reports in *the Journal of the American College of Cardiology* state that the number of TAVI procedures have overshadowed surgical aortic valve replacement (SAVR). TAVR still carries the risk of hemorrhage [4]. Post-procedure patients remain at high risk for both thromboembolic and bleeding crises, major adverse cardiac/cerebral-vascular events (MACE) including mortality of all-cause, major MI, and CVA, thus making it paramount to optimize antiplatelet and anticoagulant approach after TAVI [4].

Primary TAVR access is via the femoral artery, while other access sites include the apex, aorta, subclavian, carotid, and iliac arteries [3]. Originally, TAVR was the standard of care for intermediate- and high-risk patients with symptomatic aortic stenosis when transfemoral access was possible [5]. With TAVR's current progress, advancement in technology, and fine-tuning implantation methods, TAVR has now expanded to low-risk patients as it has ameliorated outcomes and improved TAVR procedure since it was done first in 2002 [5]. With further trials in low-risk patients, TAVR indications will continue to expand with the completion of more trials [5].

Causes of acute peri-procedural (i.e. Within <24 hours of procedure) thromboembolic/ischemic events such as stroke are likely due to a) newly diagnosed or new-onset afib, b) device associated thrombi, atheroma, calcium, or connective tissue debris embolus arising from mechanical manipulation/from the interaction between calcified valves and device c) hemodynamic instability and hypoperfusion during rapid ventricular pacing in TAVR and d) difference in anatomical and bioprosthetic valve structure causing incongruity and related turbulent flow [4]. A stroke occurs in up to 7% of candidates within one year since TAVR, similar to patients who had surgical aortic valve replacement (SAVR) [5].

Patients can have cerebral emboli visible on neuroimaging without correlating clinical diagnosis/ episode of stroke [5]. Subacute stroke (in <30 days) after TAVR could be due to new-onset afib found in approximately 10% of patients during hospitalization for TAVR procedure [5].Risk factors of late stroke (30 days to 1 year) are pre-existing afib seen in 1/3rd of patients having TAVR and atherosclerotic arterial disease. There are situations where pre-existing afib doesn't contribute to post-TAVR stroke risk, likely due to the influence of anticoagulation used to prevent bioprosthetic valve thrombosis [5].

American College of Cardiology and American Heart Association (ACC-AHA) 2020 guidelines advocated for DAPT (with Aspirin and Clopidogrel) for initial 3-6 months after TAVI in patients with low risk of bleeding [4]; current

guidelines recommend the above (Class IIb) or monotherapy (Class IIa) using low-dose aspirin (ACC). Guidelines for the initial elaborate antiplatelet strategy with DAPT are thought to lower thrombo-embolic risk arbitrated by prosthetic valves prior to completion of endothelialization [4]. While DAPT reduces the risk of thrombo-embolic events, it increases the probability of bleeding remarkably compared to a single antiplatelet therapy (SAPT) and is not better than SAPT with regard to MACE or ischemic events such as MI/CVA prevention [4].

Guidelines recommending DAPT are largely rooted in an expert consensus view [6]. Without RCT data, proposing DAPT over SAPT is based on data extrapolation recommending DAPT post-PTCA with drug-eluting stent placement (6,7]. But the thrombotic propensity is different for TAVI valves vs. coronary artery stents, thus stymieing such extrapolation in scenarios will disparate risk [6]. Principal differences are due to the bigger size and bioprosthetic nature of TAVR valves compared to smaller metallic stents in PTCA, and sample characteristics wherein TAVI patients are of advanced age, debilitated, and have many comorbidities that increase their bleeding risk [6,7]. SAPT with Aspirin is sufficient in such populations [6].

The meta-analysis, RCT comparison and pooled data didn't show a reduction in MI/CVA with initial DAPT therapy or significant variability in all-cause and CV mortality in either DAPT/SAPT groups at one month or past three months, 30-day major/minor stroke event, 30-day spontaneous MI; but there was an observable benefit in SAPT over DAPT in terms of lower risk of major/life-threatening bleed in studies/trials including in the ARTE (Aspirin Versus Aspirin + Clopidogrel following TAVI) trial [4-10]. Studies researched in the meta-analysis used DAPT for 3-6 months, while some studies incorporated other antiplatelet strategies such as DAPT for 1 month, SAPT with permanent low-dose ASA therapy, SAPT with ASA for 6 months, or use of thienopyridine, e.g. ticlopidine [3]. Post-TAVI ischemic events generally evaded antiplatelet activity due to thienopyridines [11]. Per the ARTE trial, SAPT with aspirin has a lower 3-month bleeding incidence than DAPT with aspirin [8]. SAPT vs DAPT given for 3 months reduced risk of all and non-procedural bleeding at 1 year [8]. The risk of procedural bleeding (BARC Type 4 counting severe hemorrhage but excluding puncture site bleed) was low but only seen in the DAPT population [8].

Meta-analysis showed no improved benefit of using DAPT beyond 1 month for major bleed, stroke rate, or overall mortality; and that post-TAVR DAPT/adding P2Y12 inhibitors didn't decrease ischemic event risk but increased patients' susceptibility and risk for life-threatening/major bleeding [9,12]. In the POPular TAVI trial Cohort B (Antiplatelet Therapy for Patients Undergoing TAVI), adding clopidogrel to oral anticoagulants was associated with increased bleeding with no reduction in the incidence of ischemic events compared to using anticoagulation alone [8]. Clopidogrel used alone had a lower occurrence of all-cause mortality, CV mortality, and 1-month GI bleeding incidence than Aspirin alone in a 2-year follow-up study in patients undergoing TAVR. Aspirin monotherapy has reduced the risk of life-threatening/major bleeding and comparable risk of MI, CVA, and all-cause mortality in TAVI patients who don't have an indication for long-term anticoagulation [12]. In Cohort A of the trial, SAPT and DAPT for 3 months after TAVI were compared in TAVI patients with no indication for long-term oral anticoagulation [8]. The short duration of DAPT still raised concerns about the risk of bleeding events as most of them occurred within 30 days post-procedure, mostly secondary to periprocedural antithrombotic use and bleeding in access sites [12]. While many studies encourage SAPT over DAPT, another study showed no notable difference in the safety profile/ periprocedural bleeding complications and associated 90-day mortality of DAPT vs. SAPT samples (Seoudy et al., 2021). The study concluded based on multivariable analyses that DAPT can be safely used in transfemoral-TAVR patients' samples [11].

Bias and limitations in study data cannot be excluded due to 1) retrospective nature of study, 2) baseline differences in assignment of DAPT/SAPT by clinicians in patients based on their ischemic or hemorrhagic medical history i.e. using DAPT in patients with higher ischemic risk and SAPT in those with higher hemorrhagic risk, 3) presence of other comorbidities, malignancies and chronic diseases in patients unrelated to antiplatelet therapy 4) small randomized sample size of RTCs with a short follow-up length, small sample due to lower available published studies with less data on outcomes beyond one month that

reduces statistical power, unavailability of detailed data that would've been useful for sub-group investigation to assess for variability, adverse events, acute/subacute/chronic outcomes, population heterogeneity that would make it difficult to extrapolate the data to the general population without accounting for the above 5) most bleeds happened in 1st month after TAVI thus prompting disproportionate 1-year hazards requiring the study to use relative risk instead of hazard ratios [3,4,7,8,13].

In conclusion, periprocedural stroke risk in post-TAVI patients is routinely managed with antiplatelet therapy. Per the general consensus, SAPT/monotherapy can achieve comparable antithrombotic effects with a lower risk of bleeding than DAPT. There is no concrete evidence for the choice of mainstream therapy agents pointing toward the benefit of DAPT over SAPT or vice versa and for the duration of antithrombotic therapy given there is minimal available data reflected by the uncertainty in published guidelines [6]. Most current guidelines recommend lifelong aspirin therapy and clopidogrel temporarily [13]. Bigger RCTs with longer follow-ups are necessary to evaluate for any plausible differences in mortality or ischemic consequences [7]. An analysis of the most current systematic review and meta-analysis of RCTs including the Brouwer et al. trial [8] (with relatively longest follow-up) comparing post-TAVR antiplatelet therapies concluded SAPT to be the preferred antithrombotic regimen [7]. Choosing the right antiplatelet strategy is complicated due to most patients with aortic stenosis often being older, and having many co-morbid conditions including but not limited to atrial fibrillation and coronary artery disease [3]. Warfarin and non-vitamin K oral anticoagulation are now researched more to address complexities due to newly diagnosed or pre-existing afib and to diminish subclinical leaflet thrombosis [5].

Anticoagulants use following TAVR:

Afib is a common post-procedural complication happening in 15-50% of the patients undergoing TAVI for symptomatic Aortic stenosis. The same cohort of patients due to an advanced age are also prone to thromboembolic as well as bleeding events [14,15]. D'ascenzo et al found the pooled incidence of leaflet thrombosis to be 0.43%/month (5.16%/Year, 95% CI=0.22-0.72), where the presence of diabetes, afib, and higher society of thoracic surgery (STS) score were significantly associated with increased risk of thrombosis (p=0.01) [16]. They also found that presence of leaflet thrombosis increases the risk of stroke 4 times (OR=4.21, 95% CI 1.27-13.98).Vitamin K antagonists have been a time tested remedy with proven clinical efficacy for afib and are most commonly used treatment in clinical practice. Though they require strict patient compliance, and because of multiple food and drug interactions, require frequent follow-up with regular monitoring, especially for the under-study group of the population being on multiple medications likely to have interaction with the VKAs [17]. These limitations are easily overcome by the use of Novel Oral Anticoagulants (NOACs) [18]. Though they are costlier medications, they have proven to reduce 1-year mortality, and risk of acute coronary syndrome (ACS). Additionally, they have a reduced risk of bleeding complications than VKAs [19]. However, there have been reports of subclinical TAVR leaflet thrombosis among patients using NOACs [20]. Jockheim et al conducted a multicentric registry-based observational comparison [21] Analysis showed comparable results regarding 30 days mortality, bleeding complications, and life-threatening bleeding events. However, the use of NOACs was associated with a significantly elevated risk of non-debilitating stroke (NOACS=1.2%, VKA= 0%, p<0.0001). 1 year follow up revealed increased all-cause mortality (20.9% vs 14.4% HR=1.47, 95% CI= 1.06-2.04, p=0.018) and non-debilitating stroke (1.6% vs 0.3%, HR=5.0, 95%CI= 0.97-25.81, p=0.054) in NOACs users as compared to VKAs use. Comparable findings were also found by Seeger et al [15]. This was contrary to the findings of Kalogeras et al and Ueyama et al, who found no significant difference between the two groups at any level [22-23]. They also found that a significant number of patients treated with VKAs receive DAPT (46.7% vs 17.2%, p=0.001) as compared to those who get NOACs. Patients receiving DAPT with VKAs had a moderately increased incidence of paravalvular leaks than those with NOACs. (12.2% vs 3.5%, p=0.001). However, with adjustment of DAPT status, multivariate analysis shows similar bleeding risk between both subgroups. (OR 1.6, 95%CI= 0.40-6.33, p=0.503). Zilberszac et al found that presence of peripheral artery disease was associated with increased chance to face post-procedural vascular complication during in-patient

(25.2 vs 16.7%, OR=1.68. 95% CI 1.06-2.66, p=0.027) and 30 days Follow up (29.4% vs 17.3%, OR=1.99, 95% CI=1.28-3.10, p=0.002). For such patients with PAD, the use of unfractionated heparin as compared to Bivalirudin during the procedure was significantly helpful in decreasing the vascular complication, both in-patient (3.4 vs 23.3%, p =0.001) and at 30 days Follow up (5.1 vs 28.3%, p=0.001) [24].

Conclusion:

TAVR is associated with a high risk of thromboembolic and bleeding complications that challenge the antithrombotic treatment. Currently, most experts recommend using DAPT for 3 to 6-month followed by lifelong aspirin for those patients who do not have an indication for oral anticoagulation. The current practice guidelines are mainly based on expert opinion based on the data and experience from peripheral arterial disease and coronary artery disease. The patient population who undergoes TAVR is different in terms of comorbidities compared to those who have coronary artery disease and peripheral artery disease, so what is recommended for patients with coronary artery disease and peripheral artery disease may not be applicable to those who underwent TAVR. Furthermore, there is evidence that the use of DAPT is associated with a higher risk of bleeding complications compared to SAPT. The data for optimal antithrombotic therapy given in patients undergoing TAVR is also limited. The large RCT is warranted to develop the concrete guideline for antithrombotic therapy in patients undergoing TAVR, in the meanwhile the decision for antithrombotic therapy can be made on a case-by-case basis.

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