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EDITORIAL COMMENT

Antithrombotic Therapy for Prevention of Cerebral Thromboembolic Events After Transcatheter Aortic Valve Replacement

Evolving Paradigms and Ongoing Directions*

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Transcatheter aortic valve replacement (TAVR) carries a sizeable risk of cerebrovascular ischemic events, which in contemporary trials of patients at intermediate surgical risk has been reported in 5% to 6% at 30 days, 8% to 10% at 1 year, and 10% to 13% at 2 years (1,2). There is no definitive understanding at present of the mechanism for thrombus formation leading to such ischemic sequelae, which has important therapeutic implications. In fact, if the process was mediated primarily by platelets, then it would be logical to prefer antiplatelet drugs for stroke or transient ischemic attack prevention; if the process was primarily mediated by thrombin, then it would be logical to prefer anticoagulants; if the process was mediated both by platelets and thrombin, then combination therapy would be the most rational choice. The issue of how to effectively prevent cerebrovascular accidents in TAVR patients is further complicated by individual coexisting indications for antiplatelet therapy (i.e., coronary artery disease with or without stenting) or oral anticoagulation (OAC) therapy (i.e., atrial fibrillation). Importantly, the prevalence of these medical conditions increases with age, which raises questions surrounding not only the antithrombotic treatment regimen associated with greatest efficacy, but also with the most favorable safety profile to mitigate bleeding complications in the elderly (3). Indeed, the variety of ongoing studies of adjunctive pharmacotherapy after TAVR reflects current uncertainties in the field (**Figure 1**) (4).

In this issue of *JACC: Cardiovascular Interventions*, Rodés-Cabau et al. (5) report on the result of the ARTE (Aspirin Versus Aspirin + ClopidogRel as Antithrombotic Treatment Following Transcatheter Aortic Valve Implantation With the Edwards Sapien XT Valve: A Randomized Pilot Study), an open-label, multicenter randomized study of dual antiplatelet therapy (DAPT) with clopidogrel and aspirin for 3 months versus aspirin alone in patients mostly treated with the balloon-expandable Edwards Sapien XT bioprosthesis (Edwards Lifesciences, Irvine, California) who were not receiving concurrent OAC (5). The study was interrupted prematurely after inclusion of 222 patients due to slow recruitment and lack of financial support. However, the study already lacked a formal sample size assumption and originally targeted only 300 patients for exploratory purposes. This is important to keep in mind when interpreting the results, because ARTE was not adequately powered for any endpoint and therefore its results should be considered merely hypothesis generating. At 3 months, the primary endpoint combining death, myocardial infarction, transient ischemic

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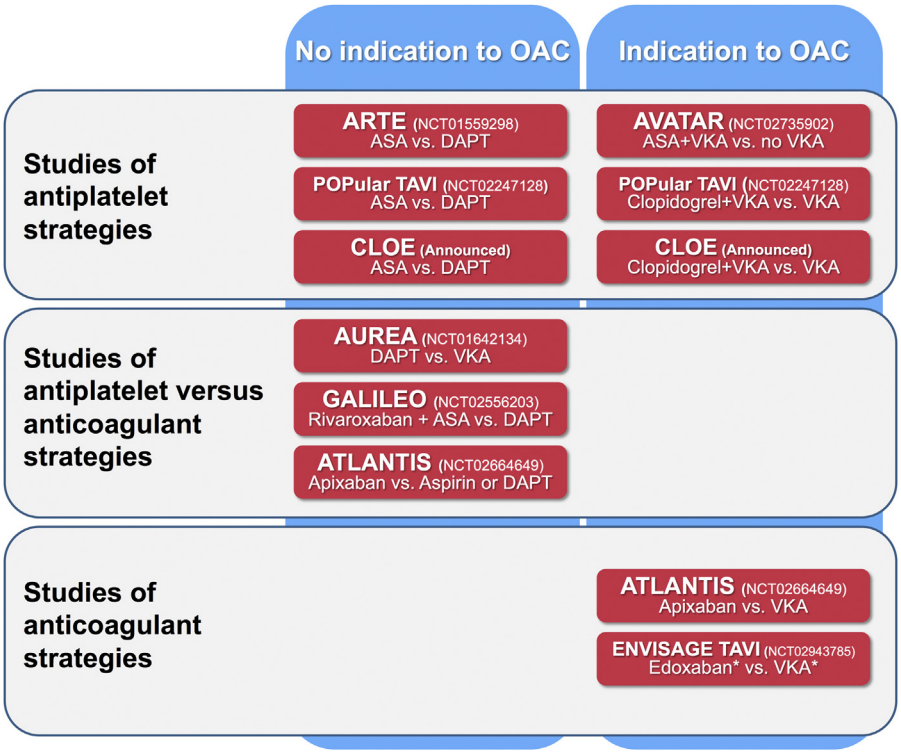
FIGURE 1 Studies of Different Antithrombotic Strategies After TAVR in Patients With or Without OAC Therapy

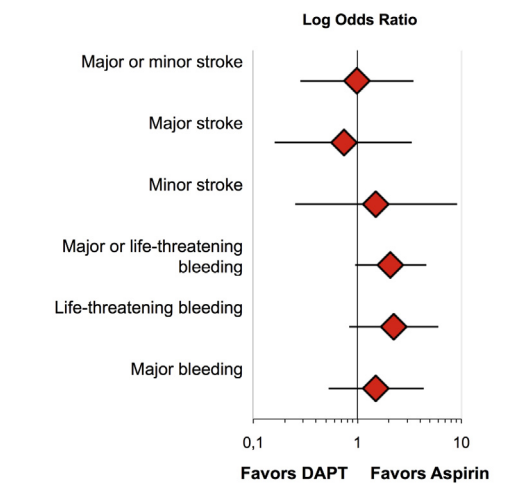


Studies of different antithrombotic strategies after transcatheter aortic valve replacement (TAVR) in patients with or without indication to oral anticoagulation (OAC) therapy. *With or without antiplatelet therapy. ARTE = Aspirin Versus Aspirin + ClopidogRel as Antithrombotic Treatment Following Transcatheter Aortic Valve Implantation With the Edwards Sapien XT Valve: A Randomized Pilot Study; ASA = aspirin; ATLANTIS = Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis; AUREA = Dual Antiplatelet Therapy Versus Oral Anticoagulation for a Short Time to Prevent Cerebral Embolism After TAVI; AVATAR = Anticoagulation Alone Versus Anticoagulation and Aspirin Following Transcatheter Aortic Valve Interventions; DAPT = dual antiplatelet therapy; ENVISAGE TAVI = Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation; GALILEO = Global Study Comparing a rivaroxaban-based Antithrombotic Strategy to an antiplatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes; POPular-TAVI = Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation; VKA = vitamin K antagonist.

attack/ischemic stroke, or major/life-threatening bleeding was more than doubled in patients on DAPT compared with patients on aspirin alone, albeit a formal statistical significance for this difference was not attained (15.3% vs. 7.2%; p = 0.065). This finding was driven by a statistically significant increase in major or life-threatening bleeding events in the DAPT group (10.8% vs. 3.6%; p = 0.038), all occurring during the first 30 days after TAVR and mostly attributable but not limited to vascular or access site complications. No significant differences were noted in all-cause mortality, myocardial infarction, and transient ischemic attack/ischemic stroke, although the odds ratios for these outcomes pointed toward a relative increase with DAPT (1.78, 4.13, and 3.11, respectively). In terms of generalizability, these findings apply to a population of elderly patients (mean age 79 years) with an estimated 30-day surgical mortality of 6%, which resembles the risk profile of intermediate-risk subjects randomized in the PARTNER (Placement of AoRTic TraNscathetER Valves) 2A trial, a study also using the Sapien XT bioprosthesis (1). Conversely, they are not applicable to patients with atrial fibrillation requiring OAC, for whom other investigations of disparate antithrombotic strategies are currently ongoing (**Figure 1**).

ARTE follows 2 previous trials of DAPT versus aspirin after TAVR in non-OAC patients, which were also limited by their even smaller sample size (6,7). The pooled results of the 3 trials now cumulatively suggest no benefit of DAPT in reducing 30-day stroke and a trend toward an increase in major or life-threatening bleeding over a total of 421 randomized patients (**Figure 2**). Thus, the limited evidence

FIGURE 2 30-Day Outcomes in Patients From 3 Randomized Trials of DAPT Versus Aspirin After TAVR



Fixed-effect meta-analysis of 30-day outcomes in 421 patients from 3 randomized trials (5–7) of DAPT versus aspirin after TAVR. Log odds ratio with 95% confidence intervals are displayed. Abbreviations as in Figure 1.

collected so far is consistent with the hypothesis that adding clopidogrel to aspirin is more harmful than beneficial after TAVR. This is at variance with the current recommendation from the U.S. guidelines for valvular heart disease that in patients with no concurrent indication to OAC it may be reasonable to prescribe clopidogrel 75 mg daily after TAVR for the first 6 months in addition to life-long aspirin (Class IIb, Level of Evidence: C) (8). Because life-threatening or disabling bleeding remains a substantial cause of morbidity in elderly patients who are currently offered TAVR (1,2), further investigations of strategies that positively affect the efficacy-safety trade-off of antithrombotic therapy are needed in this fragile population. The safety of monotherapy with aspirin or OAC versus additional clopidogrel following TAVR is the objective of 2 trials (POPular TAVI and CLOE [announced]) with randomization stratified by indication to OAT, which will cumulatively enroll about 5,000 patients.

The risk of stroke after TAVR mostly clusters during the initial 24 h after the procedure, likely as the consequence of manipulation of the delivery system inside the aorta, which may lead to debris embolization (9). Therefore, safeguarding the supra-aortic trunks with embolic protection devices might represent a better strategy than using only antiplatelet drugs, but this hypothesis is currently unproven (10). Subacute stroke events occurring after 24 h might be more related to new onset atrial fibrillation, whose effective prevention requires OAC rather than aspirin, clopidogrel, or the combination of both antiplatelet agents (9). Concerns over bioprosthetic valve thrombosis have recently emerged, which could represent a source of late embolization on top of increased transprosthetic gradients and bioprosthetic valve failure. TAVR thrombosis has been characterized by multidetector computerized tomography as reduced leaflet motion and hypoattenuating opacities, and it has been reported in 7% to ~40% of patients depending on the study or OAC status (8). In 890 patients with aortic bioprostheses and interpretable multidetector computerized tomography scans from a pooled analysis of the RESOLVE (Assessment of TRanscathetEr and Surgical Aortic BiOprosthetic Valve Thrombosis and Its TrEatment With Anticoagulation) and SAVORY (Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed With 4D CT) registries, subclinical leaflet thrombosis was detected more frequently in transcatheter than surgical valves (13% vs. 4%), and OAC with a vitamin K antagonist (VKA) or a non-VKA OAC was suggested to be more effective than DAPT for the purposes of prevention or treatment (11). The U.S. guidelines now incorporate a recommendation that using a VKA to achieve an international normalized ratio of 2.5 may be reasonable for at least 3 months after TAVR in patients at low risk of bleeding (Class IIb, Level of Evidence: B) (8).

With the valvular disease guidelines endorsing blockade of either platelets or the coagulation cascade to prevent thrombus formation, physicians are now puzzled with the challenge of choosing between antiplatelets and anticoagulant agents for secondary prevention of cerebrovascular events after TAVR (12). This dilemma resembles the early days of percutaneous coronary intervention, when historical trials comparing anticoagulant and antiplatelet drugs contributed to defining current adjunctive pharmacotherapy strategies to prevent stent thrombosis. Future trials will hopefully address the issue within the TAVR landscape. The AURA (Dual Antiplatelet Therapy Versus Oral Anticoagulation for a Short Time to Prevent Cerebral Embolism After TAVI; NCT01642134) trial is testing the efficacy of DAPT versus OAC with VKA in preventing cerebral thromboembolism assessed with magnetic resonance imaging at 3 months in patients with no indication for OAC. Two larger studies powered for clinical endpoints have been initiated to test non-VKA OAC:

GALILEO (Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes; NCT02556203) will randomize approximately 1,500 non-OAC patients to rivaroxaban 10 mg once daily plus aspirin (followed by rivaroxaban 10 mg once daily alone) or DAPT (followed by aspirin alone); ATLANTIS (Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis; NCT02664649) will randomize approximately 1,500 patients to apixaban 5 mg twice daily versus DAPT (or a single antiplatelet agent) in case of no baseline indication for OAC, and to VKA if OAC is indicated. Due to its pre-specified imaging substudies, GALILEO is particularly well equipped to address current uncertainties surrounding antithrombotic strategies to prevent the occurrence of cerebral thromboembolism and bioprosthetic leaflet thickening.

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