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Antithrombotic Therapy in Transcatheter Aortic Valve Replacement Patients without an Indication for Oral Anticoagulation: Insights from the GALILEO and ATLANTIS Trials

Ranbir Singh[1,2], Johny Nicolas[2] and George Dangas[2]*

[1]*Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA*
[2]*The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai Hospital, One Gustave L. Levy Place, New York City, NY 10029-6574, USA*

Abstract

Transcatheter aortic valve replacement (TAVR) is a plausible therapeutic approach in patients with symptomatic aortic stenosis. Antithrombotic therapy after TAVR is of utmost importance to prevent thrombo-embolic complications. Few randomized trials investigating antithrombotic therapy in TAVR patients without an indication for chronic oral anticoagulation have been reported. GALILEO compared an intermediate-dose (10mg daily) rivaroxaban to a clopidogrel-based strategy after successful TAVR; ATLANTIS recently reported results with full-dose apixaban anticoagulation versus a similar control group. In the former trial, there was increased major bleeding with anticoagulation versus control, whereas this was not apparent in the latter. In both trials, the anticoagulation-based treatment strategy was associated with a higher risk of mortality, including non-cardiovascular death, when compared to an antiplatelet based strategy. Both trials showed decreased risk of bio prosthetic valve leaflet thrombosis with anticoagulation versus control, as assessed with 4-dimensional computerized tomographic angiography. Further studies are needed to elucidate the clinical significance of subclinical leaflet thrombosis, its relation to valve durability, and enhance our understanding of the risk-benefit tradeoff in post-TAVR antithrombotic therapy.

Over the past years, Transcatheter aortic valve replacement (TAVR) has emerged as an alternative to surgical aortic valve replacement (SAVR) in the management of symptomatic aortic stenosis [1]. Thromboembolic complications after TAVR (as well as SAVR) remain significant with a direct impact on short and long-term prognosis [2]. Only a few randomized trials investigating oral anticoagulation (OAC) after TAVR (in patients with otherwise no indication for this type of treatment) have been published over the past few years.

The GALILEO (Global Study comparing a rivaroxaban-based Antithrombotic Strategy to an antiplatelet-based Strategy After Transcatheter aortic valve replacement to Optimize Clinical Outcomes) trial is a randomized, open-label, multicenter study that investigated intermediate-dose rivaroxaban (10mg daily, rather than the 20mg prescribed for complete anticoagulation in atrial fibrillation) versus an antiplatelet-based strategy after successful TAVR in patients without an established indication for OAC [3]. A total of 1,644 patients were randomized, 1 to 7 days after successful TAVR to either rivaroxaban (plus aspirin) or clopidogrel (plus aspirin) for 3 months followed by rivaroxaban or aspirin monotherapy, respectively. The primary efficacy outcome (a composite of death or thromboembolic events including any stroke, myocardial infarction, symptomatic valve thrombosis, non-central nervous system systemic embolism, deep vein thrombosis, or pulmonary embolism) occurred in 12.7% in the rivaroxaban group versus 9.5% in the clopidogrel group (HR: 1.35; 95% CI: 1.01-1.81, P=0.04), at a median of 17-month follow-up. This was mostly driven by all-cause mortality in the rivaroxaban arm in comparison to the antiplatelet arm (5.8 versus 3.4 per 100 person-years, HR: 1.69; 95% CI: 1.13–2.53). Interestingly, landmark analysis indicated a significant difference in 90-day mortality (during the combination treatment period), but a dedicated secondary analysis found that most of the mortality difference occurred several months after stopping the study drug. The primary safety outcome (composite of major, disabling, or life-threatening bleeding) tended to be higher in the rivaroxaban arm compared to control arm (5.6% versus 3.8%, HR: 1.50; 95% CI 0.95-2.37, P=0.08). To note, the rate of symptomatic valve thrombosis was very low, occurring in only 3 patients assigned to the rivaroxaban arm and 7 of those assigned to the control arm. The rate of new-onset atrial fibrillation in the trial population was roughly 11%, resulting in a change in the anticoagulation treatment strategy 60-80% of the time. Interestingly, the four-dimensional computed tomography (CT) sub study of the GALILEO trial (GALILEO-4D, n=231 patients) revealed a significantly lower incidence of bio prosthetic valve leaflet thrombosis with rivaroxaban versus control (8.8% less grade ≥3 reduction in at least one prosthetic valve leaflet; 95% CI: −16.5 to −1.9, P=0.01 and 20% less thickening of at least one leaflet; 95% CI: −30.9 to −8.5) [4]. This was the first randomized CT-imaging study of this sort indicating that lower than full-dose anticoagulation was sufficient to prevent this type of thrombus formation on valve leaflets. Based on the results of the GALILEO trial, a recent consensus document from the European Society of Cardiology (ESC) recommends against the use of rivaroxaban plus aspirin after TAVR in patients without an indication for OAC [5].

The ATLANTIS (Anti-Thrombotic Strategy after Trans-Aortic Valve Implantation for Aortic Stenosis) trial is another study assessing the safety and efficacy of a factor Xa inhibitor-based strategy after TAVR [6, 7]. Within this trial, a full-dose apixaban (after a successful TAVR)

***Corresponding author:** Dangas G, The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai Hospital, One Gustave L. Levy Place, New York City, NY 10029-6574, USA, Tel: +1 (212) 659-9649, Fax: +1 (212) 241-0273; E-mail: George.dangas@mountsinai.org

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was compared to standard of care (15% single antiplatelet therapy and 57% dual antiplatelet therapy) in 1,049 patients without an OAC indication (stratum 2) [8]. To note, the study included another cohort of patients with an indication for OAC in which full-dose apixaban was compared to a vitamin K antagonist (stratum 1), however it is not within the scope of this paper. Within stratum 2, the primary composite endpoint of death, stroke, myocardial infarction, intra cardiac or valve thrombosis, pulmonary embolism, deep vein thrombosis, or major bleeding occurred in 16.9% in the apixaban group versus 19.3% in the control group (HR: 0.88; 95% CI: 0.66-1.17). After excluding valve thrombosis, the major cardiac and cerebrovascular event rates were 16.9% versus 13.9%, respectively (HR: 1.16; 95% CI: 0.85-1.60). The primary safety endpoint of life threatening, disabling, or major bleeding occurred in 7.8% within the apixaban group in comparison to 7.3% within the antiplatelet group (HR: 1.09; 95% CI: 0.69-1.69). Overall, there was a higher risk of mortality within the apixaban group compared to the antiplatelet group (5.9% versus 3.4%, HR 1.86; 95% CI: 1.04-3.34). There tended to be higher cardiovascular death within the apixaban group (3.2% versus 2.5%, HR: 1.42; 95% CI 0.69-2.94). In addition, there was a higher non-cardiovascular mortality in the apixaban group (2.66% versus 0.96%, HR: 2.99; 95% CI: 1.07-8.35). A subset of 762 patients underwent 4D CT scans, and there was significantly less grade 3/4 reduced leaflet motion or grade 3/4 hypo attenuated leaflet thrombosis in at least one prosthetic valve leaflet at 90 days in the apixaban group in comparison to the antiplatelet group (8.7% versus 15.9%; P=0.011).

The GALILEO trial was the first randomized study to assess the safety and efficacy of OAC with a factor Xa-inhibitor in TAVR patients without an indication for OAC. Routine OAC in TAVR patients cannot be recommended at the present time in the absence of another clear indication for OAC. Indeed, the rationale of using an OAC-based regimen stemmed from early observational studies suggesting that thrombo-embolic events after TAVR could be partially linked with subclinical bi prosthetic valve thrombosis, which can be prevented or reversed by OAC [9, 10]. Although rivaroxaban use decreased the risk of valve leaflet thickening and motion abnormalities as observed in the GALILEO-4D sub study, this finding did not translate into improved clinical outcomes [11]. The discrepancy between imaging and clinical findings raises questions regarding the overall efficacy of this treatment strategy, especially given that the utilized dosage of rivaroxaban (10 mg) is lower than the standard of care for the prevention of cardio embolic events in atrial fibrillation patients (15-20mg daily) [12]. Possible effects of a very low dose rivaroxaban or apixaban (e.g. 2.5mg twice daily) has not been investigated in any way.

- Similar to the findings of the GALILEO trial, the results of ATLANTIS further corroborate the futility of a routine post-TAVR OAC strategy (in patients without an indication for OAC) despite an associated decrease in leaflet thrombosis. The discrepancy between leaflet thrombosis benefits and unfavorable outcomes again questions the clinical relevance of preventing valve leaflet thrombosis particularly since its relationship with valve durability remains unproven (not yet investigated in any appropriate way). Moreover, the duration of the use of OAC post-TAVR may also have an impact on safety, valve leaflet thrombosis and durability. For example, could an abbreviated, low-dose OAC monotherapy regimen allow prevention of leaflet thrombosis (and possibly enhance valve durability) without adversely affecting clinical outcomes? Further prospective trials are required to solve these enigmas and enhance our understanding regarding the optimal treatment after a successful TAVR in patients without any other indication for chronic OAC.

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