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EDITORIAL COMMENT

Oral Anticoagulation for Atrial Fibrillation After TAVR

Is Vitamin K Antagonist Still the Primary Option?*

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Over the last years, several randomized studies have established transcatheter aortic valve replacement (TAVR) as the primary treatment option in symptomatic patients with aortic stenosis.[1,2] Atrial fibrillation (AF) is present in 30% to 40%[3] of those patients, and while it is associated with a higher risk of death and stroke during follow-up,[4] the ideal oral anticoagulation (OAC) management remains to be defined.

POPULAR TAVI[5] (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation) has shown that adding antiplatelet agents to patients requiring OAC, mainly for AF, is not associated with a reduction of the ischemic risk while increasing the risk of bleeding, and such association is no longer recommended.[6,7]

In patients with AF from a nonvalvular cause, it has been shown that new oral anticoagulants (NOACs), including edoxaban, rivaroxaban, apixaban, and dabigatran, are noninferior to vitamin K antagonists (VKAs) to prevent the risk of stroke while being associated with a lower risk of major bleeding including intracranial hemorrhage.[8]

While, based on these findings, it would be very attractive to recommend NOAC in patients with AF after TAVR, only a few hundred of patients included in those studies had a bioprosthetic heart valve.[8] Furthermore, an observational report including 962 patients with AF undergoing TAVR suggested that the use of NOAC (rivaroxaban, apixaban, dabigatran) as compared to VKA was associated with a 40% increase in the composite risk of all-cause mortality, myocardial infarction, or any cerebrovascular event.[9] Therefore, the last American Heart Association and European Society of Cardiology guidelines for the management of valvular heart disease acknowledged the paucity of data to support the use of NOAC for AF within 3 months after implantation of a surgical or transcatheter bioprosthetic heart valve.[6,7]

Two recent studies have specifically investigated the use of NOAC in the context of patients with AF after TAVR.[10,11] The ENVISAGE-TAVI AF (Edoxaban Versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation [TAVI]-in Atrial Fibrillation) investigated the effect of edoxaban vs warfarin in 1,426 patients and reported that edoxaban was noninferior to VKA for the primary composite endpoint of net adverse clinical outcomes (death from any cause, myocardial infarction ischemic stroke, systematic thromboembolic event, valve thrombosis, or major bleeding). However, the primary safety endpoint of major bleeding occurred 40% (95% CI: 3%-91%) more frequently among patients receiving edoxaban than among those receiving VKA. This was exclusively related to a 2-fold increase in gastrointestinal (GI) major bleeding (edoxaban, n = 56, vs VKA, n = 27) without any increase in non-GI major bleeding (edoxaban, n = 42, vs VKA, n = 41).

Several hypotheses have been proposed to explain the better safety profile of VKA in that study: 1) the TAVR population is 10 years older and had more comorbidities than the population included in previous nonvalvular AF studies; 2) VKA was often

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"subtherapeutic," with only 65% of international normalized ratio values within the therapeutic range; 3) VKA was more frequently discontinued than NOAC (40.5% vs 30.2%); and 4) concomitant use of oral antiplatelet therapy, which was frequent (50% of the study population), was associated with a 60% increase of major bleeding in the NOAC group but not in the VKA group. Importantly, the observation that the increase in major bleeding was exclusively related to an increase in GI bleedings could also suggest a specific role of acquired von Willebrand disease and angiodysplasia in patients with aortic stenosis undergoing TAVR.[12-14]

The "stratum 1" of the ATLANTIS (Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events After Trans-Aortic Valve Implantation for Aortic Stenosis) study randomized 451 patients with AF undergoing TAVR between apixaban and VKA.[11] Although that "stratum" of the ATLANTIS study did not have the statistical power to demonstrate the "noninferiority" of NOAC on the primary endpoint nor the "superiority" of NOAC on major bleedings, the study did not report any "signal" that the use of apixaban would be beneficial over VKA in that population. The rate of the composite of death, myocardial infarction, any stroke, and/or transient ischemic attack was not different between the 2 groups (NOAC = 13.0% vs VKA = 11.8%, HR: 1.13 [95% CI: 0.67-1.91]), nor was the rate of life-threatening, disabling, or major bleeding (NOAC = 10.3% vs VKA = 11.4%, HR: 0.91 [95% CI: 0.52-1.60]).

An important ancillary study of ATLANTIS investigated the effect of apixaban vs VKA on subclinical valve thrombosis by performing 4-dimensional computed tomography within 90 days of the procedure in 204 patients of the stratum 1.[15] Subclinical valve thrombosis defined by hypoattenuated leaflet thickening with or without reduced leaflet motion has been reported as one of the first stage of valve degeneration, and some studies have suggested a link with cerebrovascular events.[15] Interestingly, in the ATLANTIS 4-dimensional computed tomography analysis, VKA was associated with 50% less valve thrombosis (13.7% vs 26.3%, $P = 0.02$) and 50% less hypoattenuated leaflet thickening 3-4/reduced leaflet motion 3-4 (5.5% vs 10.5%, $P = 0.18$) than apixaban.

In this issue of *JACC: Advances*, Mehran et al[16] are reporting a new ancillary analysis of ENVISAGE-TAVR AF focusing on gender. Such an analysis is potentially important because the risk of vascular complication and bleeding and survival after TAVR may differ in men and women.[3] It is also important because, in nonvalvular AF patients, the magnitude of the benefit of edoxaban vs VKA on bleeding complication is more important in women.[17]

Their main observation is that most of the benefits of VKA vs edoxaban regarding the risk of major bleeding reported in the ENVISAGE-TAVR-AF study were related to a massive and statistically significant 45% reduction of major bleeding in men (5.4% vs 9.8%) and similarly in women (8.3% vs 9.1%). At first, this could be interpreted as an argument to use edoxaban as a primary OAC in women with AF undergoing TAVR. Unfortunately, in women, cardiovascular mortality was also 2.5-fold higher with edoxaban than with VKA (4.4% vs 1.9%). Therefore, based on this analysis, it is not possible to identify a gender in which edoxaban could be proposed as the primary treatment option among patients with AF after TAVR.

Based on the information provided by the authors, it is difficult to completely interpret the differential benefit of VKA vs edoxaban on major bleeding according to gender. Women were more likely to receive an adjusted (lower) dose of apixaban and to discontinue their treatment (46.7% vs 40.2%, $P = 0.001$), and this could have played a role in the observed difference. However, 2 important pieces of information are missing. While the combination of OAC and antiplatelet has been reported to be more deleterious on major bleeding in patients receiving edoxaban than in those receiving VKA in the main publication,[10] this information is not provided according to gender in the present report. Similarly, the rates of major GI bleedings according to gender and treatment allocation are not reported.

Overall, despite the several hypotheses discussed above, it is not totally clear why the safety advantage of NOAC vs VKA on bleedings previously reported in nonvalvular AF has not been translated in patients with AF after TAVR. Another recent study conducted in patients with valvular heart disease, the INVICTUS (INVestIgation of rheumatiC AF Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies) study, which failed to demonstrate the noninferiority of rivaroxaban vs VKA in patients with AF and rheumatic valve disease,[18] may also provide some clues. It was proposed that in such severe cases, the more frequent patient-physician interaction required to adapt international normalized ratio of patients receiving VKA could provide additional unmeasured clinical benefits. This interesting hypothesis could also apply to the elderly and comorbid population of patients undergoing TAVR.

Overall, based on the available evidences, in TAVR patients with AF, VKA remains the primary OAC option.

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