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Editorial Comment

Is DOAC the preferred oral anticoagulation therapy after TAVI?

¿Son los anticoagulantes de acción directa la primera elección en pacientes sometidos a TAVI?

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Transcatheter aortic valve implantation (TAVI) is becoming the standard treatment for symptomatic severe aortic stenosis in patients older than 65 years. Despite the increasing procedural safety, thromboembolic events after TAVI (stroke, valve thrombosis, and myocardial infarction) have remained mostly unchanged over time.[1] Moreover, the risk of periprocedural and long-term bleeding events is still relatively frequent. Periprocedural bleeding is mainly related to access-site and nonaccess-site complications. However, long-term bleeding depends mostly on patient comorbidities and antithrombotic therapy. Not surprisingly, antithrombotic treatment remains controversial in TAVI patients.

Several observational and randomized clinical studies have addressed this issue.[2–8] Accordingly, current guidelines recommend antiplatelet monotherapy in patients with no indication for oral anticoagulation (OAC) or dual antiplatelet therapy (DAPT), such as those without atrial fibrillation (AF) or recent coronary stenting, respectively. OAC alone is recommended for patients with a clinical indication for anticoagulation.[1] Currently, up to 40% of patients undergoing TAVI require OAC, mainly due to preexisting AF and new onset AF (∼10%). However, the use of direct oral anticoagulants (DOAC) or vitamin K antagonists (VKA) for OAC remains a topic of debate.

Alperi et al.[9] recently published in *Revista Española de Cardiología* a single-center, observational study including 297 patients undergoing TAVI with an indication for OAC. A total of 206 (69.4%) received VKA and 91 (30.6%) were treated with DOAC. The primary outcome was any clinically significant bleeding. Interestingly, patients under DOAC showed an increased risk of bleeding compared with VKA after a median of 2.8 years of follow-up (9.7 vs 4.2 events per 100 patient-years; hazard ratio, 2.27; 95% confidence interval, 1.21-4.26). No significant differences were found in the distribution of bleeding severity between the groups. Moreover, there were no significant differences in the rate of stroke, hospitalization due to heart failure, and all-cause mortality. Importantly, this was an elderly cohort at high surgical risk (mean age older than 83 years and EuroSCORE II risk higher than 8%). Both groups (DOAC and VKA) were balanced in terms of baseline characteristics, including bleeding and thromboembolic risk. The median HAS-BLED and CHA2DS2-VASc scores were 2 [interquartile range, 1-2] and 4 [interquartile range, 4-5], respectively, in both groups. More than 70% in the VKA group had pre-existing AF, compared with 67% in the DOAC group ($P = .57$). New onset AF was observed in 10% and 9% ($P = .71$) in the VKA and DOAC groups, respectively. Unfortunately, data on the switch between VKA and DOAC at discharge was not reported.

Initially, these results may seem unexpected, especially considering the pivotal clinical trials of DOAC, which demonstrated a lower risk of major bleeding with DOAC compared with VKA in patients with AF.[10] However, elderly patients with high bleeding risk and/or multimorbidity were underrepresented in these trials. On the other hand, some studies have suggested an increased risk of bleeding in frail/elderly populations, as well as in TAVI populations, with DOAC compared with VKA.[5,11]

Data from the ENVISAGE-TAVI AF randomized clinical trial, comparing edoxaban vs VKA after TAVI in patients with AF, also showed a higher incidence of major bleeding in the edoxaban group compared with VKA (hazard ratio, 1.40; 95% confidence interval, 1.03-1.91), especially due to a higher incidence of gastrointestinal bleeding.[5] Moreover, in frail and elderly patients (≥75 years old) with AF, switching to DOAC was associated with an increased risk of major or clinically relevant nonmajor bleeding compared with continuation of VKA.[11] Conversely, in the ATLANTIS trial, stratum 1, a total of 451 patients with an indication for OAC were randomized to apixaban vs VKA after TAVI, showing no statistically significant differences in life-threatening or major bleeding between apixaban and VKA.[4]

Observational data from 2 multicenter studies (four European centers and the Danish national registry) showed similar rates of hemorrhagic events with DOAC and VKA during long-term follow-up after TAVI.[6,7] However, data from the France-TAVI and FRANCE-2 registries observed a higher risk of major bleeding and hemorrhagic stroke with VKA vs DOAC at 3 years of follow-up.[8] Moreover, a recent meta-analysis of 8 studies (with nearly 26 000 patients) reported no difference in major/life-threatening bleeding, but an increased risk of any bleeding for VKA.[12] In

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contrast, the efficacy of DOAC and VKA for the prevention of thromboembolic events (ischemic stroke, myocardial infarction, systemic embolism, or valve thrombosis), and all-cause mortality seems to be similar based on the 2 available randomized clinical trials and this meta-analysis in patients with an OAC indication after TAVI.[4,5,12]

Therefore, the increased risk of bleeding with DOAC vs. VKA remains controversial. Different definitions of hemorrhagic complications may explain part of the discrepancy between the study results. Intracranial and major bleeding rates did not differ in most studies between DOAC and VKA after TAVI. However, clinically relevant non-major bleeding was variable across different cohorts. Patient characteristics and OAC regimens may also contribute to explaining these controversial results and guide our clinical practice. Aging, multimorbidity, polypharmacy, and low weight are associated with patient frailty and frequently observed in patients undergoing TAVI. These factors are likely related to drug availability and may penalize DOAC with fixed dosing (or adjusted dosing by very limited factors). In contrast, regular VKA monitoring can help not only in dose adjustment but also in closer surveillance of these frail patients. Additionally, long-standing OAC with VKA may act as a selection bias for patients with well tolerance and improved outcomes for VKA. Moreover, less than 70% of time in therapeutic range is observed in clinical practice among patients with VKA, which may also contribute to a lower risk of bleeding due to a sub-therapeutic range.

Regarding concomitant antiplatelet therapy, several trials have consistently shown an increase in bleeding with schemes combining DOAC and antiplatelet therapy.[3,5] In this study, a quarter of patients in the DOAC group were under antiplatelet therapy,[9] mainly due to recent coronary stenting. Although a short term of combined antithrombotic therapy was preferred in most patients, this may also contribute to the observed high rate of hemorrhagic events. Furthermore, not all DOACs perform equally. Apixaban seems to have the most favorable profile in terms of bleeding complications compared with other DOACs.[13] In the study by Alperi et al.,[9] almost 40% of patients from the DOAC group were under therapy with apixaban, 28% with rivaroxaban, and 25% with edoxaban. Only 8% received dabigatran. This wide distribution makes it more difficult to draw conclusions for a specific treatment.

Based on current data, the use of DOAC after TAVI might be more appropriate in nonfrail OAC-naïve patients, without concomitant antiplatelet therapy, in those previously treated with well-tolerated DOAC, and preferring the use of apixaban over other DOACs. However, in elderly, frail, high-risk patients with stable INR-guided VKA management, maintaining VKA appears to be a reasonable option after TAVI.

In conclusion, antithrombotic therapy and the type of OAC in patients with TAVI remain controversial. The favorable results of DOAC over VKA in patients with AF do not seem to fully translate to TAVI patients, probably due to the differences in age, frailty, and comorbidities. DOAC appear to be associated with similar efficacy in preventing thromboembolic events but with an increased risk of bleeding in this population. More studies are needed to identify patients who benefit from each strategy. However, it does not appear to be the end of VKA in patients with transcatheter bioprostheses.

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