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Continuation of oral anticoagulation during transcatheter aortic valve implantation: time to change practice?

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Despite considerable technical advances in performing transcatheter aortic valve implantation (TAVI) over the years, both stroke and bleeding remain frequent complications, most often occurring during the periprocedural phase[1]. TAVI patients with concomitant atrial fibrillation (AF) are more prone to these complications than patients in sinus rhythm. Thromboembolic complications are more frequent in AF patients because they are older and more frequently have coexisting atherosclerotic disease. Bleeding is also related to age and frailty but is of course also due to the need for oral anticoagulation (OAC). Current guidelines advise the discontinuation of OAC in patients undergoing interventions who have a high risk of bleeding[2]. However, preliminary observational data suggest that the periprocedural continuation of OAC may decrease the risk of stroke, while it does not seem to significantly increase the risk of bleeding compared to the interruption of OAC[3,4].

Due to the lack of high-quality evidence on this topic, and hence a paucity of guideline recommendations, current practice regarding perioperative OAC management varies considerably between TAVI centres, from the interruption of OAC more than 1 week prior to TAVI to continuation of OAC. Also, of the centres which interrupt OAC, some use low-molecular-weight heparin or antiplatelet therapy for "bridging", whereas others do not. The policies also seem to differ depending on the use of vitamin K antagonists (VKA; more often continuation) or non-vitamin K antagonist oral anticoagulants (NOAC; more often interruption). The rapid and predictable mechanism of action makes the interruption of NOAC relatively easy compared to VKA.

The pioneering research published in the present issue of EuroIntervention by Mangner et al regarding the continuation of both NOAC and VKA during TAVI is therefore of great interest[5]. The same group of researchers, from five high-volume TAVI centres in Europe, have already reported on the safety and efficacy of continued as compared to interrupted OAC[3,4]. In this issue, they report on the results of a subsequent analysis comparing continued NOAC with continued VKA during TAVI[6]. Out of 1,317 OAC patients, 584 patients were treated under continued OAC: 294 (50.3%) with VKA and 290 (49.7%) with NOAC. Age and sex were well balanced between groups, but there were higher rates of previous myocardial infarction and cardiac surgery and higher creatinine values in patients treated with VKA. Small differences were also noted in vascular closure device usage between groups, while the application of cerebral embolic protection was similarly low in both groups (<5%). Rivaroxaban (63.4%) and apixaban (24.1%) were the most frequently used NOAC. The median international normalised ratio (INR) was 2.3 (interquartile range [IQR] 2.1-2.7) in VKA-treated patients.

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After adjustment for potential confounders (age, sex, Society of Thoracic Surgeons Predicted Risk of Mortality, treatment date/period, antiplatelet therapy at baseline and the interaction OAC*antiplatelet therapy at baseline), the composite of major or

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life-threatening bleeding, stroke and all-cause mortality at 30 days after TAVI was similar between both groups (odds ratio [OR] 0.68, 95% confidence interval [CI]: 0.43-1.07; p=0.092). Major or life-threatening bleeding occurred rather frequently and similarly between groups (31 [10.7%] patients with continued NOAC vs 35 [11.9%] patients with continued VKA), and importantly there was no difference in vascular access-site complications. Stroke was lower than anticipated, occurring only in 5 (1.7%) patients in each group. Although mortality was significantly lower at 30 days in patients treated under continued NOAC (2 [0.7%] vs 15 [5.1%], OR 0.13, 95% CI: 0.03-0.58; p=0.043), mortality, potentially related to bleeding, was similar between groups (2 patients in both groups).

When interpreting these results, a number of considerations need to be taken into account. First and foremost is the inherent major limitation of the observational design and retrospective character of this analysis, already addressed in detail by the authors. True differences between VKA and NOAC patients exist. Although appropriate methods to adjust for confounding were applied, a high risk of residual confounding remains, due to factors which were either unknown, unregistered or not taken into account. Also, the results were neither adjusted nor stratified per treating centre, whilst factors like patient selection, preprocedural planning, methods used for vascular access and closure, and periprocedural OAC management may have differed between sites, potentially introducing various forms of bias.

Second, there was a considerable cross-over after TAVI between NOAC and VKA treatment. Contrary to expectation, 21% of patients in the NOAC group were discharged on VKA, whilst 7% of patients in the VKA group were discharged on NOAC. Since OAC was continued throughout TAVI, it remains elusive why switching took place in this substantial number of patients. Perhaps this occurred due to the lack of evidence supporting NOAC use after TAVI at the time the study was running.

Third, the mortality benefit in favour of the NOAC group raises eyebrows. This has seldom been demonstrated in NOAC trials. More specifically, in stratum 1 of the ATLANTIS trial, no difference between apixaban and VKA for any endpoint was observed[6]. In the ENVISAGE-TAVI AF trial, mortality and thromboembolic events were similar, but the incidence of major bleeding was higher with edoxaban than with VKA[7]. However, these studies were dedicated to post-procedural instead of periprocedural OAC treatment.

Finally, the low incidence of stroke in both groups, while patients were at high risk for thromboembolic events with a median CHA_2DS_2-VASc score of 5 (IQR 4-6), is remarkable. We cannot exclude that underreporting played a role in this unmonitored registry data. Yet, since we learned from PROTECTED TAVR[8] that cerebral embolic protection may not provide the final answer for stroke prevention during TAVI, this underlines the importance of further evaluation of peri- and post-TAVI antithrombotic therapy to mitigate thromboembolism. A histopathologic study on debris acquired during TAVI found that it included thrombus, besides other types of tissue, in 90% of the patients[9]. Thus, thrombus formation could indeed be a target for periprocedural OAC treatment. The same applies to the occurrence of events related to early valve thrombosis. However, previous TAVI trials remind us we should not overlook the risk of bleeding in these patients[10]. Therefore, in the ongoing POPular PAUSE TAVI trial (ClinicalTrials.gov: NCT04437303) patients are randomised to interruption versus continuation of OAC and stratified according to NOAC or VKA use. So, we advise not changing practice yet, based on the current studies, but to wait for randomised controlled data.

Conflict of interest statement

J.M. ten Berg has received institutional grants from ZonMw; he is the principal investigator of the POPular TAVI and POPular PAUSE TAVI trials. D-J. van Ginkel has no conflicts of interest to declare.

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