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Oral anticoagulation following bioprosthetic SAVR in patients with atrial fibrillation: what's the current status of NOACs?

Milan Milojevic [a,*], Aleksandar Nikolic[b], Slobodan Micovic[a] and Anders Jeppsson [c,d]

[a] Department of Cardiac Surgery and Cardiovascular Research, Dedinje Cardiovascular Institute, Belgrade, Serbia
[b] Department of Cardiac Surgery, Acibadem-Sistina Hospital, Skopje, North Macedonia
[c] Department of Molecular and Clinical Medicine, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden
[d] Department of Cardiothoracic Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden

* Corresponding author. Department of Cardiac Surgery and Cardiovascular Research, Dedinje Cardiovascular Institute, Milana Tepica 1, 11000 Belgrade, Serbia. Tel: +381113601700; e-mail: mln.milojevic@gmail.com (M. Milojevic).

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The burden of non-rheumatic valvular heart disease has increased rapidly due to the worldwide ageing population [1]. More than 24 million people suffer from degenerative mitral valve disease, while calcific aortic disease steadily rises, reaching 9 million cases before the pandemic [1, 2]. Repair or replacement of the diseased valve by either mechanical or biological prosthesis remains the only definitive treatment for patients with valvular heart disease. Over 200 000 heart valve replacement surgeries are performed annually worldwide, with a predicted increment to 850 000 per year by 2050 [3]. Over the last 2 decades, a massive shift from mechanical to bioprosthetic heart valve (BHV) replacements has been noticed [4], despite unresolved durability issues. The change to a BHV strategy could be partially explained by the preference of younger individuals to avoid lifelong treatment with a vitamin K antagonist (VKA), which mechanical heart valves warrant, and more elderly patients at higher bleeding risk being treated.

Surgical replacement of a diseased valve aims to improve symptoms and prolong life but exposes the patient to potential prosthesis-related complications. Although less thrombogenic than mechanical heart valves, tissue valves are also prone to cause thromboembolic complications, and the risk is exceptionally high during the first 3 months after the operation [5]. Despite the frequency of BHV usage, the optimal postoperative anticoagulation strategy remains unclear. This is especially true for decision-making in cardiac surgery patients with incremental risk of thromboembolic complications, such as prolonged immobility, stroke, malignancy, prior and de novo atrial fibrillation (AF), congestive heart failure, history of major venous and pulmonary thromboembolism and hypercoagulable conditions. Focused research on these clinical scenarios was considered less important, and the academic community has concentrated chiefly on assessing structural failure. Consequently, post-surgical antithrombotic management is based not on valuable research findings but rather on local habits. Recently, however, surgical and transcatheter BHV thrombosis and the prevention of thromboembolic complications have attracted significant attention due to better imaging surveillance [3].

The lack of robust data on the efficacy and safety of different anticoagulation regimens is reflected by seeing lower levels of evidence (LOEs) behind the recommendations in the recently released European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) Guidelines for the management of valvular heart disease [6]. For patients with no baseline indication for oral anticoagulation (OAC), the ESC/EACTS guidelines recommend either low-dose aspirin (75–100 mg/day) or a VKA for the first 3 months after surgical implantation of an aortic BHV [class of recommendation (COR) IIa, LOE B]. For those who received a BVH in the mitral or tricuspid position, a VKA should be considered as the anticoagulation strategy (COR IIa, LOE B). For patients undergoing surgical implantation of a BHV with other anticoagulation indications, the guidelines recommend treatment with OAC (COR I, LOE C). However, the choice between a VKA and a non-vitamin K antagonist (NOAC) remains uncertain. The guidelines recommend that an NOAC be considered over a VKA 3 months after surgical implantation of a BHV in the aortic position in patients with AF (COR IIa, LOE B). In addition, an NOAC over a VKA may be considered after 3 months following surgical implantation of a BHV in the mitral position in patients with AF, but this is a weak recommendation based on low-quality evidence (COR IIb, LOE C).

In this issue of the journal, Magro and Sousa-Uva [7] report the results of a systematic literature search and critical appraisal of available evidence to answer an essential clinical question of whether the efficacy and safety of NOACs are similar to VKAs within 3 months of surgical implantation of a BHV in those patients with AF. The noteworthy findings of the research by Magro and Sousa-Uva [7] can be summarized as follows:

i. out of 324 studies identified in the initial search, only 6 articles were estimated to be of sufficient value to answer this essential clinical question;
ii. among the 6 included studies, 2 unadjusted observational studies suggest no difference between NOACs and VKAs in terms of major bleeding and thromboembolic complications, but the studies use either a 30-day outcome or a 6-month outcome only, and patients with prior AF are excluded [8];
iii. two subgroup analyses of randomized controlled trials (RCTs) have compared NOACs with VKAs in patients with bioprosthetic valves or native valve repair, but they collectively involved 346 patients and their results were inconclusive, mainly due to the unknown timing of anticoagulation initiation;
iv. one pilot RCT has compared the NOAC edoxaban (n = 109) with warfarin (n = 109) in patients with surgical implantation of a BHV in the aortic (49%) or mitral position (21%) or mitral valve repair (39%). The study is vastly underpowered and the results inconclusive given the fact that only 8 patients had experienced major adverse events in total during the study period; the results of primary composite efficacy outcome (0 vs 4, respectively) and primary (major bleeding) safety outcome (3 vs 1, respectively) [9], and;
v. one large-scale RCT has compared the NOAC rivaroxaban with warfarin in 1005 patients with a mitral BHV in the presence of AF or atrial flutter within at least 48 h following surgery. The primary outcome analysis showed similar results for the NOAC rivaroxaban versus warfarin to prevent mortality and thromboembolic and major bleeding events at 12 months. However, only 19% of patients were enrolled in the trial before the third postoperative month [10], which raises a note of caution and calls for confirmation in more extensive investigations before comprehensive practice-changing.

Would NOACs be the future standard of care for specific patients with surgical BHV replacement and baseline indication for OAC? The critical appraisal by Magro and Sousa-Uva [7] showed no significant differences in safety and efficacy outcomes across subgroups, including those treated with NOACs in the early and later stages. Studies included in the present review were not designed among patients with specific types of AF; therefore, it is unknown whether the effects of NOACs differ among patients with longstanding persistent, paroxysmal, and new-onset postoperative AF. Also, no data are available on the use of NOACs in patients with BHVs having indications for concomitant antiplatelet therapy (i.e. presence of stent or bypass graft). Finally, the timing of initiation of an NOAC after cardiac surgery was not uniformly reported, and subclinical leaflet thrombosis was not evaluated in the assessed studies. Despite the data suggesting similar bleeding and thrombotic complications with NOACs, routine use, particularly in the early postoperative period, could not be recommended because the data are insufficient. Questions remain open about the risk of valve thrombosis, embolization, and significant bleeding, knowing that cardiac surgery patients have major physiological derangements associated with cardiopulmonary bypass.

In summary, Magro and Sousa-Uva [7] have confirmed information from current guidelines, calling for more confirmatory evidence regarding the use of NOACs in the early postoperative period in patients receiving a BHV. Unfortunately, the observed data quality requires further multicentre RCTs to better understand the safety and efficacy of different NOACs as an anticoagulation strategy in the immediate postoperative period.

Conflict of interest: Dr Anders Jeppsson has received fees for consultancy or lectures from Werfen, Boehringer Ingelheim and Portola. The remaining authors have no relevant conflicts of interest to declare for this publication.

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