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IM - COMMENTARY

Direct oral anticoagulants in patients with bioprosthetic heart valves

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Non-vitamin K oral anticoagulants, also known as direct oral anticoagulants (DOACs), due to their direct inhibition of thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, and edoxaban) are safe and efficacious alternatives to vitamin K antagonists (VKAs) for the prevention of thromboembolism in atrial fibrillation (AF) and they are recommended in preference to VKAs in AF patients eligible to oral anticoagulants (excluding those with moderate-to-severe mitral stenosis or mechanical heart valves) [1].

AF and valvular heart disease (VHD) frequently coexist, but the thromboembolic risk is not equivalent for all forms of VHD in patients with AF. With the notable exception of mitral stenosis, conferring a high risk of thromboembolism probably related to the low-flow patterns occurring in the left atrium, all forms of VHD accompanying AF do not appear to increase the risk of thromboembolism beyond the level entailed by AF alone. Regarding prosthetic heart valves, mechanical valves lead to a high risk of thromboembolism due to contact with the artificial surface, acting as additional risk factors in patients with AF. Otherwise, biological valves are less thrombogenic than mechanical valves, and the incidence of thromboembolism is not significantly dissimilar from that of an average AF population with risk factors, probably entailing a higher risk in the first three postoperative months before superficial healing of the sewing ring is complete.

Due to their high risk of thromboembolism, patients with AF and moderate-to-severe mitral stenosis or with a mechanical prosthetic heart valve have been consistently excluded from the phase III trials comparing DOACs with VKAs [2–5]. Furthermore, one phase II trial testing dabigatran in patients with mechanical prosthetic valves was prematurely interrupted because of excess stroke in the dabigatran arm at doses also associated with excess bleeding [6]; and in a more recent trial in patients with AF and rheumatic heart disease, VKAs led to a lower rate of a composite of cardiovascular events or death than rivaroxaban, without a higher rate of bleeding [7]. For these reasons, VKAs remain the only recommended oral anticoagulants for the prevention of stroke and systemic embolism in these patients [1].

However, phase III clinical trials of DOACs included variable proportions of VHD patients, other than mitral stenosis and mechanical valves, and individually provided no evidence of a differential effect of DOACs over warfarin in patients with and without VHD [8–11]. Aggregate evaluations of these data confirmed that the coexistence of VHD does not affect the overall relative efficacy or safety of DOACs in terms of prevention of stroke and major bleeding [12].

Of particular interest are patients with AF and biological heart valves (BHVs) because the implantation (surgical or transcatheter) of bioprosthesis is a common, increasingly utilized treatment for valvular heart disease, particularly left-sided.

In a recent issue of Internal and Emergency Medicine, Galliazzo et al. [13] reported on an interesting meta-analysis aimed at comparing the efficacy and safety of DOACs versus VKAs in patients with previously and newly surgically implanted BHV with or without AF. They included two subgroup analyses from ARISTOTLE and ENGAGE AF-TIMI 48 trials, four observational studies, and four randomized controlled trials, for a total of 5808 patients, 1893 on DOACs, and 3915 on VKAs; about 98% of patients had AF.

The ENGAGE AF-TIMI 48 [3] and the ARISTOTLE [4] trials, which compared, respectively, edoxaban and apixaban to warfarin in patients with AF, did not exclude patients

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with BHVs (191 patients in the ENGAGE AF-TIMI 48, and 104 patients in the ARISTOTLE), providing the opportunity to analyze this group of patients. Overall, there were no significant differences between these both factor Xa inhibitors and warfarin for efficacy or safety outcomes in this population [14, 15]. Furthermore, patients with BHVs treated with edoxaban 60 mg had a lower rate of a primary net clinical outcome including stroke, SEE, major bleeding, and death [14]. Notably, patients who had undergone recent (< 3 months) BHV implantation were excluded from both the ARISTOTLE and ENGAGE AF-TIMI 48 trials. Results from observational studies have been consistent with the findings from these trials. Particularly, in a retrospective cohort study on 2672 patients with BHVs and AF treated with warfarin, dabigatran, rivaroxaban, or apixaban between 2011 and 2020, DOACs were as effective as warfarin in preventing ischemic events, while associated with less intracranial bleeding [16], supporting the use of DOACs for AF in patients with BHVs.

Few randomized clinical trials were conducted in this setting and included patients recently implanted. The DAWA pilot phase II study evaluated the use of dabigatran in patients with BHVs in mitral and/or aortic position and AF, indicating that dabigatran 110 mg twice daily was comparable to warfarin in preventing the formation of intracardiac thrombus [17]. The RIVER trial was specifically designed to assess the effects of rivaroxaban in 1005 patients with AF and a BHV in mitral position implanted at any time at least 48 h after mitral-valve surgery [15]. Here, rivaroxaban 20 mg once daily was shown non-inferior to warfarin concerning mean time free from death, major cardiovascular events, or major bleeding. A little randomized trial in 50 patients with AF during the first three months after aortic BHV implantation showed that apixaban 5 mg twice daily was non-inferior to warfarin for thromboembolic events and have a better safety profile than warfarin for the incidence of death or major bleeding [18].

Beyond the limitation of a pooled data analysis including RCTs, sub-analysis of RCTs, and observational studies, the results of the meta-analysis of Galliazzo et al. [13] confirm and strengthen the evidence of the effectiveness and safety of DOACs in previously implanted BHV patients with AF. Regarding the early 3-month period after surgery, the risk–benefit profile of DOACs appeared similar to VKAs, prevalently in patients with AF, although this analysis was underpowered due to the low number of patients enrolled in the two randomized trials aimed at this population.

Galliazzo et al. [13] also included in their meta-analysis the recent ENAVLE trial showing that edoxaban 60 mg once daily is non-inferior to warfarin for preventing thromboembolism and is potentially comparable for risk of major bleeding during the first three months after surgical bioprosthetic valve implantation or valve repair, regardless of the presence of AF [19]. This study tried to address an unmet need in patients with no baseline indications for oral anticoagulants for the first three months after a BHV implantation, although the little number of patients does not allow to ascertain a potential difference in treatment effect between edoxaban and warfarin.

In the absence of AF, the thrombogenicity of the prosthetic heart valve should guide the indication for the optimal antithrombotic strategy. Patients with mechanical heart valves require lifelong treatment with VKAs, targeting INR according to prosthesis thrombogenicity and patient-related risk factors [20]; DOACs currently have no role in these patients. Otherwise, antithrombotic therapy following surgical implantation of a BHV remains controversial. It aims at preventing thromboembolic events and thrombosis of the valve related to the lack of endothelialization during the early postoperative period. While patients with a mitral prosthesis seem to have higher rates of thromboembolism than those with an aortic prosthesis and take advantage of anticoagulant treatment [21], the benefit of an anticoagulant strategy remains debated early after surgical implantation of an aortic BHV. Here, observational studies supported the use of VKAs to reduce the risk of thromboembolism [22, 23], but a small, randomized trial found that VKAs for three months significantly increased major bleeding compared with aspirin, without reducing the rate of deaths or thromboembolic events [24]. Along with the ENAVLE trial, further studies are needed to clarify the efficacy/safety profile of DOACs early after the implantation of BHVs in patients with sinus rhythm.

Authors excluded from their meta-analysis patients undergoing transcatheter aortic valve implantation (TAVI), representing another setting of BHVs. The use of anticoagulants appears not applicable to TAVI in the absence of other indications to anticoagulant therapy, and lifelong single antiplatelet therapy is recommended based on recent trials [25]. On the other hand, in patients with prevalent or incident AF as the indication for oral anticoagulation after TAVI, the ENVISAGE-TAVI AF trial showed that edoxaban 60 mg was non-inferior to VKAs for a composite primary outcome of adverse clinical events including death from any cause, myocardial infarction, ischemic stroke, systemic thromboembolic event, valve thrombosis, or major bleeding; however, edoxaban was associated with a higher risk of major bleeding than VKAs [26].

According to the available evidence, in patients with AF, 2020 ACC/AHA guidelines for the management of valvular heart disease indicate DOACs as an effective alternative to VKAs in patients who received a BHV > 3 months ago (Class I, LoE A), but they consider only the use of VKAs in patients with new-onset AF < 3 months after surgical or transcatheter BHV replacement (Class IIa, LoE B) [27]. Forged further ahead, 2021 ESC/EACTS guidelines indicate that

DOACs should be considered over VKAs after 3 months following surgical implantation of a BHV (Class IIa, LoE B) and may be considered over VKA within 3 months following surgical implantation of a BHV in mitral position (Class IIb, LoE C) [20].

On the other hand, in the absence of baseline indication for oral anticoagulant therapy, 2020 ACC/AHA guidelines recommend VKAs for 3–6 months in patients at low bleeding risk, regardless of the position of the bioprosthesis (Class IIa, LoE B), and low-dose aspirin for all patients lifelong (Class IIa, LoE B) [27]. Differently, 2021 ESC/EACTS guidelines recommend the use of low-dose aspirin and, alternatively VKAs for three months after surgical implantation of an aortic BHV (Class IIa, LoE B), while VKAs should be considered for the first three months after surgical implantation of a bioprosthesis in the mitral or tricuspid position (Class IIa, LoE B) [20].

Finding an optimal oral anticoagulant therapy among patients undergoing BHVs with and without AF is still challenging. Increasing evidence suggests that DOACs should be preferred to VKAs in patients with AF after three months from intervention while further data are needed to reinforce the evidence in the early postoperative period. In patients without AF after surgical implantation of a BHV, data on DOACs are encouraging but still scarce. DOACs are not recommended after TAVI in the absence of other indications for anticoagulation.

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Informed consent For this type of study, formal consent is not required.

References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C et al (2021) 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 42(5):373–498
2. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A et al (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 361(12):1139–1151
3. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL et al (2013) Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 369(22):2093–2104
4. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M et al (2011) Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 365(11):981–992
5. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W et al (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 365(10):883–891
6. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ et al (2013) Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 369(13):1206–1214
7. Connolly SJ, Karthikeyan G, Ntsekhe M, Haileamlak A, El Sayed A, El Ghamrawy A et al (2022) Rivaroxaban in rheumatic heart disease-associated atrial fibrillation. N Engl J Med 387(11):978–988
8. Avezum A, Lopes RD, Schulte PJ, Lanas F, Gersh BJ, Hanna M et al (2015) Apixaban in comparison with warfarin in patients with atrial fibrillation and Valvular heart disease: findings from the Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) Trial. Circulation 132(8):624–632
9. Breithardt G, Baumgartner H, Berkowitz SD, Hellkamp AS, Piccini JP, Stevens SR et al (2014) Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with nonvalvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. Eur Heart J 35(47):3377–3385
10. De Caterina R, Renda G, Carnicelli AP, Nordio F, Trevisan M, Mercuri MF et al (2017) Valvular heart disease patients on edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. J Am Coll Cardiol 69(11):1372–1382
11. Ezekowitz MD, Nagarakanti R, Noack H, Brueckmann M, Litherland C, Jacobs M et al (2016) Comparison of dabigatran and warfarin in patients with atrial fibrillation and valvular heart disease: the RE-LY trial (randomized evaluation of long-term anticoagulant therapy). Circulation 134(8):589–598
12. Renda G, Ricci F, Giugliano RP, De Caterina R (2017) Non-vitamin k antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. J Am Coll Cardiol 69(11):1363–1371
13. Galliazzo S, Pelitti V, Campiotti L et al (2023) Direct oral anticoagulants in patients with a left-sided bioprosthetic heart valve: a systematic review and meta-analysis. Intern Emerg Med 18:535–547. https://doi.org/10.1007/s11739-023-03208-9
14. Carnicelli AP, De Caterina R, Halperin JL, Renda G, Ruff CT, Trevisan M et al (2017) Edoxaban for the prevention of thromboembolism in patients with atrial fibrillation and bioprosthetic valves. Circulation 135(13):1273–1275
15. Guimaraes HP, Lopes RD, de Barros ESPGM, Liporace IL, Sampaio RO, Tarasoutchi F et al (2020) Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. N Engl J Med 383(22):2117–2126
16. Duan L, Doctor JN, Adams JL, Romley JA, Nguyen LA, An J et al (2021) Comparison of direct oral anticoagulants versus warfarin in patients with atrial fibrillation and bioprosthetic heart valves. Am J Cardiol 146:22–28
17. Duraes AR, de Souza RP, de Almeida NB, Albuquerque FP, de Bulhoes FV, de Souza Fernandes AM et al (2016) Dabigatran versus warfarin after bioprosthesis valve replacement for the

management of atrial fibrillation postoperatively: DAWA pilot study. Drugs R D 16(2):149–154
18. Piepiorka-Broniecka M, Michalski TA, Figatowski T, Wojtowicz A, Jurowiecki J, Stanska A et al (2022) NOAC versus warfarin in the treatment of atrial fibrillation during the first three months after bioprosthetic aortic valve replacement. Cardiol J 29(2):355–357
19. Shim CY, Seo J, Kim YJ, Lee SH, De Caterina R, Lee S et al (2023) Efficacy and safety of edoxaban in patients early after surgical bioprosthetic valve implantation or valve repair: a randomized clinical trial. J Thorac Cardiovasc Surg 165(1):58-67.e4
20. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J et al (2022) 2021 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 43(7):561–632
21. Heras M, Chesebro JH, Fuster V, Penny WJ, Grill DE, Bailey KR et al (1995) High risk of thromboemboli early after bioprosthetic cardiac valve replacement. J Am Coll Cardiol 25(5):1111–1119
22. Brennan JM, Edwards FH, Zhao Y, O'Brien S, Booth ME, Dokholyan RS et al (2012) Early anticoagulation of bioprosthetic aortic valves in older patients: results from the society of thoracic surgeons adult cardiac surgery national database. J Am Coll Cardiol 60(11):971–977
23. Merie C, Kober L, Skov Olsen P, Andersson C, Gislason G, Skov Jensen J et al (2012) Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. JAMA 308(20):2118–2125
24. Rafiq S, Steinbruchel DA, Lilleor NB, Moller CH, Lund JT, Thiis JJ et al (2017) Antithrombotic therapy after bioprosthetic aortic valve implantation: Warfarin versus aspirin, a randomized controlled trial. Thromb Res 150:104–110
25. Calabro P, Gragnano F, Niccoli G, Marcucci R, Zimarino M, Spaccarotella C et al (2021) Antithrombotic therapy in patients undergoing transcatheter interventions for structural heart disease. Circulation 144(16):1323–1343
26. Van Mieghem NM, Unverdorben M, Hengstenberg C, Mollmann H, Mehran R, Lopez-Otero D et al (2021) Edoxaban versus vitamin K antagonist for atrial fibrillation after TAVR. N Engl J Med 385(23):2150–2160
27. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F et al (2021) 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. Circulation 143(5):e72–e227