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EDITORIAL COMMENT

Direct oral anticoagulants and surgical bioprosthetic valves: State of the art

DOACs e biopróteses cirúrgicas: estado da arte

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An estimated 300 000 prosthetic heart valves are implanted each year worldwide, a figure that is tending to grow as Western populations age.[1] For the individual patient, implantation of a prosthetic valve is more than a simple surgical procedure, as it entails a lifelong added risk of bleeding (2–9% per year) and thromboembolic events (1–4% per year) compared with the general population.[2] Atrial fibrillation (AF) is a common comorbidity as well as a frequent complication in patients undergoing valvular surgery. The SWEDEHEART registry[3] showed that in a real-world population of more than 7000 patients undergoing surgical valve intervention with a biological prosthesis or valvuloplasty, 29% had a history of AF prior to surgery and 15% would go on to develop new-onset AF. Appropriate management of anticoagulation therapy is therefore a must in the follow-up of these patients. Direct oral anticoagulants (DOACs) were at least as effective as vitamin K antagonists in trials that included more than 70 000 patients with AF, and were associated with less serious bleeding, particularly less intracranial bleeding. In addition, DOACs have fewer drug interactions, and eliminating coagulation monitoring simplifies anticoagulation therapy. Warfarin is associated with many drug and food interactions and it is difficult to keep the international normalized ratio within therapeutic levels and to maintain constant adequate anticoagulation levels (time on target); in addition, warfarin is the top reason (33%) for emergency hospitalizations for drug events in older Americans.[4]

However, results from the phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN) trial showed a greater number of thromboembolic events in patients with mechanical valves treated with dabigatran compared with warfarin, leading to the premature termination of the trial. In light of these findings DOACs are contraindicated in patients with mechanical valves.

The ideal antithrombotic strategy in patients with bioprosthetic valves, however, remains the subject of debate. There has been a reversal in the proportions of mechanical and bioprosthetic valves implanted in the last 20 years, with the percentage of mechanical valves rapidly decreasing and increasing use of bioprosthetic valves, which currently account for more than 70% of valve implantations.[5]

Adding further uncertainty to the already established gap in evidence in these patients is the multitude of possible clinical scenarios and variables contributing to thromboembolic risk, such as valve endothelization, valve position, and baseline indication for anticoagulation, including patients' baseline rhythm. Further contributing to the difficulty in

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selecting the best antithrombotic strategy is the patient's background bleeding risk.

Table 1 summarizes the recommendations of the recent American College of Cardiology/American Heart Association (ACC/AHA)[6] and European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS)[7] guidelines for patients with bioprosthetic valves according to the four most common clinical scenarios.

After three months

Neither the European nor the American guidelines specifically recommend oral anticoagulation three months after surgery in patients in sinus rhythm (SR).

Both guidelines recommend DOAC three months after index valvular surgery in patients with bioprosthetic valves in aortic or mitral position and AF. These recommendations are regardless of CHA_2DS_2-VASc score.

The recommendations in the guidelines are supported by cumulative evidence from post-hoc analysis of the ARISTOTLE[8] and ENGAGE AF-TIMI 48[9] trials, the small DAWA randomized controlled trial (RCT)[5] and pooled analysis of these low-evidence studies in two metanalyses, by Malik et al.[10] and Caldeira et al.[11]

Pooled analysis showed no statistically significant difference in stroke or systemic embolization (Malik et al.: hazard ratio [HR] 0.59; 95% confidence interval [CI] 0.13–2.69; p=0.49; I^2=24%; Caldeira et al.: HR 0.65; 95% CI 0.20–2.08; p=0.46; I^2=6%); major bleeding (Malik et al.: HR 0.67; 95% CI 0.27–1.63; p=0.38; I^2=0%; Caldeira et al.: HR 0.94; 95% CI 0.28–3.18; p=0.93; I^2=0%); or death (Malik et al.: HR 0.82; 95% CI 0.24–2.81; p=0.76; I^2=0%).[10,11] This evidence, however, is based on a small group of patients and events and presents wide CIs suggestive of low statistical power.

More recently, the RIVER trial,[12] a multicenter, open-label, noninferiority trial, randomized 1005 patients with mitral bioprosthetic valves and AF (excluding post-operative transient AF) to receive either rivaroxaban (n=500) or warfarin (n=505). In this trial rivaroxaban achieved non-inferiority for the primary endpoint of mean time free from a composite of death, major cardiovascular events, or major bleeding at 12 months (rivaroxaban, 347.5 days; warfarin, 340.1 days; difference, 7.4 days; 95% CI −1.4 to 16.3; p<0.001 for noninferiority, p=0.10 for superiority). Additionally, stroke rates at 12 months were statistically different, favoring rivaroxaban (rivaroxaban, 0.6%; warfarin, 2.4%; HR 0.25; 95% CI 0.07–0.88). Other secondary endpoints were similar between the two groups including major bleeding, valve thrombosis and death.

First three months

Patients less than three to six months after the index valvular surgery present a particular challenge, as this is viewed as the most thrombogenic period.

The ACC/AHA guidelines recommend anticoagulation with a vitamin K antagonist (VKA) in the first three months after index valvular surgery, regardless of rhythm, valve type or position. This recommendation is based on observational studies, some of which have conflicting results.[13–16]

The ESC/EACTS guidelines also recommend VKAs in the first three months for valves in mitral position and for all patients in AF independently of valve position. In the ESC/EACTS guidelines the use of DOAC should be considered for patients with AF and bioprosthetic valves in mitral position (class of recommendation IIb). For patients with an aortic bioprosthetic valve in SR, the ESC/EACTS guidelines recommend either aspirin or a VKA with a IIa class recommendation. The latter recommendation is based on observational studies[16,17] and a small RCT.[18]

Although still controversial, a growing body of evidence seems to indicate a potential role for DOAC use in the first three months after index surgery.

In the above-mentioned RIVER trial,[12] 18.8% of the randomized patients received either rivaroxaban or warfarin in the first three months after valve surgery. The authors found that the statistical difference between treatments (favoring rivaroxaban) regarding the primary endpoint was especially marked in this subgroup of patients (rivaroxaban, 6.4%; warfarin, 18.9%; HR 0.31; 95% CI 0.12–0.79). However, the authors did not report p-values for interaction in this subgroup (patients randomized in the first three months after surgery).

ENAVLE[19] was a non-inferiority RCT which randomized patients to receive either edoxaban (n=109) or warfarin (n=109) for the first three months after bioprosthesis implantation regardless of rhythm and valve position. Edoxaban was non-inferior to warfarin regarding the primary efficacy endpoint of a composite of death, clinical thromboembolic events or asymptomatic intracardiac thrombosis (edoxaban 0%, warfarin 3.7%; risk difference [RD], −0.0367; 95% CI −0.0720 to −0.0014; p<0.001 for noninferiority), as well as for major bleeding events (edoxaban 2.8%, warfarin 0.9%; RD 0.0183; 95% CI −0.0172 to 0.0539; p=0.013). ENAVLE was also a small RCT with a small number of events, and the results should be interpreted accordingly.

One of the drawbacks of DOACs is the lack of rapidly available tests to measure their effect. Although general tests of coagulation such as activated partial thromboplastin time and prothrombin time can be useful to assess the effects of anticoagulation, the sensitivity of these tests is variable and a normal test does not exclude the presence of the drug. In cases of acute bleeding or need for emergent surgery, discontinuation of DOACs and general measures may be sufficient, due to their relatively short half-life, but DOAC-specific anti-Xa tests and ecarin chromogenic assays need to be readily available in order to identify patients who need reversal agents and to monitor reversal efficacy.

The authors of this editorial recently published a review of the best available evidence regarding DOAC use in the first three months following valve surgery.[20] The above-mentioned results of the RIVER and ENAVLE trials are exciting and hypothesis-generating. However, the low number of events reported overall and wide confidence intervals warrant caution when interpreting these results. Lower evidence data derived from retrospective analyses are consistent with the results of these trials. DOACs appear to be as safe and as effective as VKAs regarding thromboembolic prophylaxis and bleeding event rates in patients with surgical bioprosthetic valves and AF within three months of implantation. However, stronger confirmatory evidence is needed to extend current recommendations.

Table 1 Summary of anticoagulation recommendations in patients with bioprosthetic valves according to the latest ACC/AHA and ESC/EACTS guidelines.

Clinical scenario	2020 ACC/AHA		2021 ESC/EACTS	
	<3 months	>3 months	<3 months	>3 months
Aortic in SR	VKA (2a B-NR)	Aspirin (2a B-NR)	Aspirin or VKA (IIa B)	–
Aortic in AF	VKA (2a B-NR)	DOAC (1 A)	VKA	DOAC (IIa B)
Mitral in SR	VKA (2a B-NR)	Aspirin (2a B-NR)	VKA (IIa B)	–
Mitral in AF	VKA (2a B-NR)	DOAC (1 A)	VKA; may consider DOAC (IIb C)	DOAC (IIa B)

The class of recommendation and level of evidence are presented according to the corresponding guideline definitions.
ACC/AHA: American College of Cardiology/American Heart Association; AF: atrial fibrillation; DOAC: direct oral anticoagulant; ESC/EACTS: European Society of Cardiology/European Association for Cardio-Thoracic Surgery; SR: sinus rhythm; VKA: vitamin K antagonist.

Nevertheless, current recommendations are mainly based on observational and largely outdated data.[13–18] Although not without its flaws, the most recent data from the above-mentioned RCTs appear to indicate a promising future for the expansion of DOAC use to the immediate postoperative period in patients with mitral valve prostheses and patients with AF.

Conflicts of interest

The authors have no conflicts of interest to declare.

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References

1. Sun JC, Davidson MJ, Lamy A, et al. Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends. Lancet. 2009;374:565–76.
2. Durães AR, de Souza Roriz P, de Almeida Nunes B, et al. Dabigatran versus warfarin after bioprosthesis valve replacement for the management of atrial fibrillation postoperatively: DAWA Pilot Study. Drugs R D. 2016;16:149–54.
3. Christersson C, Held C, Modica A, et al. Oral anticoagulant treatment after bioprosthetic valvular intervention or valvuloplasty in patients with atrial fibrillation – a SWEDEHEART study. PLOS ONE. 2022;17:e0262580.
4. Budnitz DS, Lovegrove MC, Shehab N, et al. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med. 2011;365:2002–12.
5. Brown JM, O'Brien SM, Wu C, et al. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. J Thorac Cardiovasc Surg. 2009;137:82–90.
6. Otto CM, Nishimura RA, Bonow RO, et al. 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. 2021;143:e72–227.
7. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2022;43:561–632.
8. Guimarães PO, Pokorney SD, Lopes RD, et al. Efficacy and safety of apixaban vs warfarin in patients with atrial fibrillation and prior bioprosthetic valve replacement or valve repair: insights from the ARISTOTLE trial. Clin Cardiol. 2019;42:568–71.
9. Carnicelli AP, De Caterina R, Halperin JL, et al. Edoxaban for the prevention of thromboembolism in patients with atrial fibrillation and bioprosthetic valves. Circulation. 2017;135:1273–5.
10. Malik AH, Yandrapalli S, Aronow WS, et al. Oral anticoagulants in atrial fibrillation with valvular heart disease and bioprosthetic heart valves. Heart. 2019;105:1432–6.
11. Caldeira D, David C, Costa J, et al. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease: systematic review and meta-analysis. Eur Heart J Cardiovasc Pharmacother. 2018;4:111–8.
12. Guimarães HP, Lopes RD, de Barros e Silva PGM, et al. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. N Engl J Med. 2020;383:2117–26.
13. ElBardissi AW, DiBardino DJ, Chen FY, et al. Is early antithrombotic therapy necessary in patients with bioprosthetic aortic valves in normal sinus rhythm? J Thorac Cardiovasc Surg. 2010;139:1137–45.
14. Sundt TM, Zehr KJ, Dearani JA, et al. Is early anticoagulation with warfarin necessary after bioprosthetic aortic valve replacement? J Thorac Cardiovasc Surg. 2005;129:1024–31.
15. Heras M, Chesebro JH, Fuster V, et al. High risk of thromboemboli early after bioprosthetic cardiac valve replacement. J Am Coll Cardiol. 1995;25:1111–9.
16. Mérie C, Køber L, Skov Olsen P, et al. Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. JAMA. 2012;308:2118–25.
17. Brennan JM, Edwards FH, Zhao Y, et al. 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. 2012;60:971–7.
18. Rafiq S, Steinbrüchel DA, Lilleør NB, et al. Antithrombotic therapy after bioprosthetic aortic valve implantation: warfarin versus aspirin, a randomized controlled trial. Thromb Res. 2017;150:104–10.
19. Shim CY, Seo J, Kim YJ, et al. Efficacy and safety of edoxaban in patients early after surgical bioprosthetic valve implantation or valve repair: a randomized clinical trial. J Thorac Cardiovasc Surg. 2021, http://dx.doi.org/10.1016/j.jtcvs.2021.01.127.
20. Magro PL, Sousa-Uva M. Are NOACs as safe and efficient as VKA regarding thromboembolic prophylaxis and major bleeding in patients with surgical bioprosthesis and atrial fibrillation within 3 months of surgery? Interact Cardiovasc Thorac Surg. 2022:ivab363.