REVIEW

Optimal anticoagulation in patients with atrial fibrillation and bioprosthetic heart valves

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ABSTRACT

The antithrombotic management of patients after surgical or transcatheter bioprosthetic heart valves (BHVs) replacement is still challenging. Our review aims to describe the current evidence on the best antithrombotic strategy among patients undergoing BHVs replacement (surgical or transcatheter) and/or valve repair, with particular attention to those with atrial fibrillation.

Key words: anticoagulation, antithrombotic therapy, bioprosthetic valves, atrial fibrillation

INTRODUCTION

The general increase in life expectancy leads to a more frequent association between atrial fibrillation (AF) and valvular heart disease (VHD) in clinical practice [1]. It is well established that non-vitamin K antagonist oral anticoagulants (NOACs) represent the first-line therapy for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) [2, 3], whereas vitamin K antagonists (VKAs) are the only treatment option in patients with mechanical heart valves (MHVs) [4, 5]. Moreover, NOACs show a better net clinical benefit vs. VKAs among the elderly with AF in a real-world setting [6–10].

The antithrombotic management of patients after bioprosthetic heart valves (BHVs), both surgical and transcatheter, is still challenging. Among patients in need of long-term oral anticoagulation therapy (OAC), such as those with AF, there is little evidence from randomized control trials (RCTs) about the best treatment between NOACs or VKAs in those with BHVs [11–13] or transcatheter aortic valve implantation (TAVI) [14, 15]. Currently, both the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines apply few class-I recommendations or level of evidence A to OAC therapy among patients with BHVs [4, 5]. This review aims to present the current evidence on the best antithrombotic strategy among patients who underwent BHVs replacement (surgical or transcatheter) and/or valve repair, with particular attention to those with AF.

OPTIMAL ANTITHROMBOTIC MANAGEMENT AFTER BHV REPLACEMENT IN THE GENERAL POPULATION

Surgical mitral and tricuspid BHVs replacement

Following surgical BHVs replacement, antithrombotic therapy is needed to avoid thromboembolic events, thrombosis of the valve, and subclinical organized valve thrombus complications, which are presumably related to suture material and a sewing ring that is not yet covered with biofilm and endothelialized [16, 17]. Furthermore, it has been shown that the risk of valve thrombosis and cerebral ischemia is higher in the 180 days after mitral surgery [16, 18, 19]. According to the most re-

Table 1. Characteristics of the studies exploring the best antithrombotic management after aortic bioprosthetic valve replacement in the general population

Author/ /reference	Study design	Enrolled patients, n	Outcomes measured	FU	OAC therapy, n (%)	Antiplatelet therapy, n (%)
Sundt et al. [23]	Retrospective, VKA vs. no-VKA	1151	Stroke, bleeding	90 days	Warfarin 624 (54.2)	OAC group 336 (53.9) no-OAC group 304 (57.7)
Moinuddeen et al. [24]	Retrospective, VKA vs. no-VKA	185	Stroke, bleeding, RO, HS, SR	>3 months	Warfarin 109 (58.9)	N/A
Brennan et al. [25]	Retrospective, VKA vs. ASA and retrospective, VKA + ASA vs. ASA	25656	Death, TE[a], bleeding[b]	3 months	Warfarin 2999 (11.7)	ASA 12457 (48.6) Warfarin + ASA 5972 (23.3)
Rafiq et al. [26]	Prospective, RCT — BHV-only subgroup VKA vs. ASA and BHV + CABG subgroup VKA + ASA vs. ASA	370	TE[c], bleeding, death	3 months	BHV subgroup Warfarin 105 (50.2) BHV + CABG subgroup Warfarin 63 (52.9)	BHV aubgroup ASA 104 (49.8) BHV + CABG subgroup ASA 56 (47.1)
Mérie et al. [27]	Retrospective, VKA vs. no-VKA	4075	Stroke, TE, CVM, bleeding[d]	Time periods (days) 30–89 90–179 365–729 >730	Warfarin[e]	N/A

[a]Cerebrovascular accident, transient ischemic attack, and noncerebral arterial thromboembolism; ASA, acetylsalicylic acid; [b]Hemorrhagic stroke, gastrointestinal bleeding, other bleeding; [c]Myocardial infarction, stroke, transitory cerebral ischemia, pulmonary embolism, deep vein thrombosis, peripheral arterial embolism, intra-cardiac thrombus formation; [d]Gastrointestinal, intracranial, urinary tract, and airway bleeding; [e]Number of patients on warfarin varies for each time period
Abbreviations: BHV, bioprosthetic heart valve; CABG, coronary artery by-pass graft; CVM, cardiovascular mortality; FU, follow-up; HS, hospital stay; n, number; N/A, not available; OAC, oral anticoagulants; RO, repeat operation; SR, survival rate; TE, thromboembolic events; VKA, vitamin-K antagonist

cent guidelines, when there are no other indications for OAC (e.g AF), VKAs therapy is recommended for 3 up to 6 months after mitral and tricuspid BHV surgical replacement [4, 5].

Surgical aortic BHVs replacement

The optimal antithrombotic strategy after surgical aortic BHV replacement is still uncertain [20, 21] – because of the low incidence of thromboembolic events following aortic surgery most studies are underpowered to highlight differences between treatment groups [22–24].

While the association therapy with warfarin and aspirin is clearly associated with an increased risk of bleeding [21, 22], comparing OAC monotherapy with single antiplatelet therapy (SAPT) has yielded controversial results.

In an observational study including 25 656 patients ≥65 years receiving aortic BHV, Brennan et al. [25] showed that warfarin-only therapy seems to have a similar risk of death, embolic events, and bleeding in the 3 months after surgery compared to aspirin-only treatment. On the other hand, in a recent prospective single-center RCT, aspirin was found to be as effective as warfarin in preventing thromboembolic events after BHVs replacement, but with less major bleeding [26].

In a retrospective observational study from the Danish National Patient Registry, including 4075 patients with aortic BHVs replacement discharged on VKA, the discontinuation of warfarin treatment within 6 months after BHVs surgery was associated with increased cardiovascular death and with differences in stroke and bleeding events [27]. This result supports the hypothesis of good effectiveness of prolonged (till 6 months) OAC therapy among aortic BHV patients. Tables 1 and 2 summarize the characteristics and results of the above-mentioned studies.

Considering the currently available literature, the 2021 ESC/EACTS guidelines recommend OAC with VKA or aspirin alone for 3 months after the procedure (class IIa B) [4]. In addition, ACC/AHA guidelines suggest lifelong therapy with aspirin in such patients (class IIa B) even if they were treated with VKA for the first 3 to 6 months after surgery (suggested specifically for low bleeding risk patients, class IIa B) [5].

Transcatheter mitral or aortic BHVs replacement

Mitral valve

Little is still known about the optimal antithrombotic strategy among patients undergoing transcatheter mitral BHV replacement, and no RCTs including these patients are available. Some retrospective observational studies suggest that dual antiplatelet therapy with aspirin plus clopidogrel (DAPT) might be insufficient to avoid post-procedural thrombotic complications [28, 29].

Table 2. Results of the studies analyzing the optimal antithrombotic management after aortic bioprosthetic valve replacement in the general population

Author/reference	Results		
Sundt et al. [23]	Stroke, n (%)	VKA vs. no-VKA	16 (2.5) vs. 9 (1.9) P = N/A (NSD)
	Bleeding, n (%)	VKA vs. no-VKA	Mediastinal 32 (5.0) vs. 42 (7.4) Other bleeding 7 (1.1) vs. 4 (0.8) P = N/A (NSD)
Moinuddeen [24]	Stroke, n (%)	VKA vs. no-VKA Time points <24 hours; 24 hours — 3 m ;> 3 m	5 (4.6), 3 (2.8), and 12 (11) vs. 5 (4.6), 3 (2.8) and 12 (11) P = N/A (NSD)
	Bleeding, n (%)	VKA vs. no-VKA	10 (9.2) vs. 7 (9.2) P = N/A (NSD)
	Repeat operation, n (%)	VKA vs. no-VKA	6 (5.5) vs. 7 (9.2) P = N/A (NSD)
	Hospital staying (mean)	VKA vs. no-VKA	12 months both groups P = N/A (NSD)
	Survival rates (mean%)	VKA vs. no-VKA Time points 1, 5, and 7 years	93%, 84%, and 62% vs. 87%, 74%, and 67% *P* = 0.60
Brennan [25]	Death ARR (95% CI)	Warfarin vs. ASA	1.01 (0.80–1.27)
		Warfarin + ASA vs. ASA	0.80 (0.66–0.96)
	TE ARR (95% CI)	Warfarin only vs. ASA only	0.95 (0.61–1.47)
		Warfarin + ASA vs. ASA-only	0.52 (0.35–0.76)
	Bleeding ARR (95% CI)	Warfarin vs. ASA	1.23 (0.85–1.79)
		Warfarin + ASA vs. ASA	2.80 (2.18–3.60)
Rafiq et al. [26]	TE BHV subgroup	Warfarin vs. ASA	4 (3.8%) vs. 3 (2.9%) *P* = 0.721
	TE BHV + CABG subgroup	Warfarin + ASA vs. ASA	7 (11.1%) vs. 9 (16.1%) *P* = 0.592
	Bleeding BHV subgroup	Warfarin vs. ASA	3 (2.9%) vs. 2 (2.9%) *P* = 0.683
	BHV + CABG subgroup	Warfarin + ASA vs. ASA	6 (9.5%) vs. 1 (1.8%) *P* = 0.117
	Death BHV subgroup	Warfarin vs. ASA	4 (3.8%) vs. 3 (2.9%) *P* = 0.721
	Death BHV + CABG subgroup	Warfarin + ASA vs. ASA	4 (6.3%) 3 (5.4%) *P* = 0.800

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Table 2 (cont.). Results of the studies analyzing the optimal antithrombotic management after aortic bioprosthetic valve replacement in the general population

Author/reference	Results		
Mérie et al. [27]	Stroke Event rate (95% CI)	No-VKA vs. VKA Time period (days) 30-89	7 (4.07–12.06) vs. 2.69 (1.49–4.87) AIRR (95% CI) 2.46 (1.09–5.55) *P* = 0.03
	TE events Event rate (95% CI)	No-VKA vs. VKA Time period (days) 30–89	13.07 (8.76–19.50) vs. 3.97 (2.43–6.48) AIRR (95% CI) 2.93 (1.54–5.55) *P* <0.001
		No-VKA vs. VKA Time period, days, 90–179	5.04 (3.43–7.40) vs. 1.87 (0.84–4.16) AIRR (95% CI) 2.65 (1.08–6.51) *P* = 0.03
	CV mortality Event rate (95% CI)	No-VKA vs. VKA Time period, days, 30–89	31.74 (24.69–40.70) vs. 3.97 (2.43–6.48) AIRR (95% CI) 7.61 (4.37–13.26) *P* <0.001
		No-VKA vs. VKA Time period, days, 90–179	6.50 (4.67–9.06) vs. 2.08 (0.99–4.36) AIRR (95% CI) 3.51 (1.54–8.03) *P* = 0.003
		Time period, days, 180–364	3.07 (2.27–4.16) vs. 0.65 (0.16–2.61) AIRR (95% CI) 4.57 (1.09–19.13) *P* = 0.04
	Bleeding Event rate (95% CI)	No-VKA vs. VKA Time perio, days, 30–89	11.86 (7.81–18.01) vs. 5.37 (3.54–8.16) AIRR (95% CI) 2.32 (1.28–4.22) *P* = 0.006

Abbreviations: AIRR, adjusted incidence rate ratio; ARR, adjusted relative risk; CI, confidential interval; NSD, non-significant difference; other — see Table 1

A state-of-the-art review by Pagnesi et al. [30] suggests considering an anticoagulation-based antithrombotic strategy to prevent the risk of valve thrombosis and thromboembolic events after any transcatheter mitral valve replacement procedure (valve-in-valve or valve-in-ring).

The current guidelines are limited by these uncertainties; however, they suggest a VKA prescription for 3 months following the transcatheter mitral intervention as it is the most common strategy applied in clinical practice [4].

Aortic valve

In the historical trials evaluating TAVI for severe aortic stenosis, a 6-month DAPT strategy following the procedure was used [31, 32]; so, until 2017, this approach was recommended by guidelines (IIa, level of evidence C) [33]. Several observational studies [30–34] and RCTs [35–37] demonstrated a better clinical safety profile of SAPT compared to DAPT, with no significant differences in terms of efficacy among TAVI patients.

In a pooled cohort of 4832 patients discharged with or without OAC after aortic BHV implantation (3889 TAVI and 943 surgical aortic BHV) [42], Chakravarty et al. showed a lower incidence of increased mean valvular gradient, over the first year after the procedure, among patients on OAC (mainly warfarin), with no significant differences in the stroke rate. In patients without an established indication for OAC after successful TAVI, a treatment strategy with aspirin and rivaroxaban 10 mg daily was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than with the DAPT strategy [41].

The latest European and American guidelines recommend lifelong SAPT with aspirin after TAVI in patients with no baseline indications for OAC (Class I A and IIa B, respectively) [4, 5]. Moreover, American guidelines approve DAPT or VKA strategy in low bleeding risk patients (class IIb B) [5].

Table 3. Results of the studies analyzing the clinical performance of non-vitamin K oral anticoagulants after bioprosthetic valve implantation in the general population

Author/reference	Study design	Results				
Ball et al. [43]	Retrospective Observational Apixaban in BHV	Hospital readmission, n (%)	18 (33)			
		Mortality, n (%)	3 (6)			
		Major bleeding, n (%)	1 (2)			
		Minor bleeding, n (%)	3 (6)			
		MBV vs. ABV (readmission), n (%)	10 (48) vs. 8 (24), $P = 0.07$			
		AF vs. SR (mortality), n (%)	(14) vs. (3), $P = 0.14$			
Pasciolla et al. [44]	Retrospective cohort study VKA vs. NOACs NOACs included apixaban rivaroxaban dabigatran	Thromboembolic events, n (%) (events per drug)	VKA	API	RIVA	DABI
			0	1(2.5)	2 (5)	0
		Thromboembolic events, n (%) (NOACs vs. VKA)	3 (2.4) vs. 0 $P = 0.20$			
		Major bleeding, n (%) (events per drug)	VKA	API	RIVA	DABI
			2(2.9)	7(8.1)	2(5)	0
		Major bleeding, n (%) (NOACs vs. VKA)	9 (7.1) vs. 2 (2.9); $P = 0.22$			
Shim et al. [45]	Prospective Randomized Edoxaban vs. VKA		Efficacy outcomes (Edoxaban vs. VKA)			
		Death, n (%)	0 in both groups			
		Thromboembolic events, n (%)	0 vs. 1 (0.92)			
		Asymptomatic intracardiac thrombus, n (%)	0 vs. 3 (2.75)			
		Subcl. leaflet thrombosis, n (%)	0 vs. 1 (0.92)			
		Thrombus within cardiac chambers, n (%)	0 vs. 1.83			
		Composite of all efficacy outcomes, n (%)	0 vs. 4 (3.67) RD (95% CI), 0.0367 (0.0720–0.0014); $P \leq 0.001$			
			Safety outcomes (Edoxaban vs. VKA)			
		Major bleeding, n (%)	3 (2.75) vs. 1 (0.92) RD (95% CI), 0.0183 (0.0172–0.0539); $P = 0.013$			
		CRNMB	1 (0.92) vs. 1 (0.92) RD (95% CI), 0 (0.0253–0.0253); $P = 0.002$			
		Major bleeding + CRNMB, n (%)	4 (3.67) vs. 2 (1.83) RD (95% CI); 0.0183 (0.0250–0.0617); $P = 0.018$			
Dangas 2020 [46]	Prospective Randomized Rivaroxaban10 mg+ASA vs. ASA+Clopidogrel	Primary efficacy outcome[a], n (%)	105 (12.7) vs. 78 (9.5) HR (95% CI), 1.35 (1.01–1.81)			
		Primary safety outcome[b], n (%)	46 (5.6) vs. 1 (3.8) HR (95% CI), 1.50 (0.95–2.37)			
Collet et al. [15]	Prospective Randomized Stratum 2[c]: Apixaban 5 mg BID Versus SAPT or DAPT	Primary endpoint[d], n (%)	89 (16.9) vs. 101 (19.3) HR (95% CI), 0.88 (0.66–1.17)			

[a]Composite of death from any cause or thromboembolic events, including any stroke, myocardial infarction, symptomatic valve thrombosis, systemic embolism (not involving the central nervous system), deep-vein thrombosis, or pulmonary embolism; [b]Composite of life-threatening, disabling, or major bleeding; [c]Patients with no indication to oral anticoagulation; [d]Composite of all-cause death, stroke, heart attack, valve thrombosis, pulmonary or systemic embolism, deep vein thrombosis or major bleeding

Abbreviations: ABV, aortic bioprosthetic valve; AF, atrial fibrillation; CRNMB, clinically relevant non-major bleeding; HR, hazard ratio; MBV, mitral bioprosthetic valve; NOACs, non-vitamin K antagonist oral anticoagulants; Subcl, subclinical; RD, risk difference; SR, sinus rhythm; other — see Tables 1 and 2

NOACs after surgical or transcatheter BHV replacement

Surgical BHV replacement

Current guidelines do not recommend the use of NOACs over VKAs when OAC is the preferred antithrombotic strategy after surgical BHVs replacement, especially in patients without AF [4, 5]. However, some data are being collected on the clinical performance of NOACs in patients with BHVs or previous valve repair, irrespective of the presence of a long-term indication for OAC (Table 3).

In a small single-center retrospective study [43] including 54 patients undergoing a BHV replacement (61% aortic, 39% mitral), the standard dose of apixaban was safe and well-tolerated with low incidences of major/minor bleeding and thrombotic events. The subgroup analysis comparing patients with and without AF showed a trend toward increased mortality in patients with AF, but results did not reach statistical significance (14% vs. 3%; $P = 0.135$).

In a small exploratory study including 197 patients undergoing BHV replacement (68% aortic, 21% mitral, 11% both aortic and mitral), Pasciolla et al. [44] evaluated the efficacy and safety of NOACs (n = 127, 64%) vs. warfarin (n = 70, 35.5%). Eighty-six patients received apixaban, 40 rivaroxaban and 1 dabigatran. More than half (51.8%) of the study population had a history of AF (NOACs, n = 57 and

VKAs, n = 45). The authors found a similar rate of thromboembolic complications (2.4% vs. 0%; $P = 0.20$) and major bleeding events (7.1% vs. 2.9%; $P = 0.22$) in the two groups.

The favorable results of observational studies were recently confirmed in the Explore the Efficacy and Safety of Edoxaban in Patients after Heart Valve Repair or Bioprosthetic Valve Replacement (ENAVLE) study [45], a prospective RCT exploring the effectiveness and safety of edoxaban for the first 3 months after surgical aortic and mitral BHV implantation and mitral repair. The study enrolled 218 patients (109 per group). Edoxaban was non-inferior to warfarin for preventing thromboembolism (risk difference –0.0367; $P < 0.001$) and potentially comparable for the risk of major bleeding (risk difference 0.0183; $P = 0.013$) during the first 3 months after surgical BHV implantation or valve repair.

TAVI

Among patients undergoing TAVI, the results of RCTs do not favor a NOAC treatment-based strategy over the antiplatelet therapy. In the Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes (GALILEO) trial, rivaroxaban 10 mg daily plus aspirin was compared to DAPT in TAVI patients with no indication to long-term OAC treatment. The study was prematurely terminated because of safety concerns. Indeed, after 17 months of follow-up, the composite endpoint of death or thromboembolic events (hazard ratio [HR], 1.53; $P = 0.04$), as well as major bleeding events (HR, 1.50; $P = 0.08$), were found higher in the rivaroxaban group [46].

Similar results were shown by the Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis (ATLANTIS) trial which compared apixaban 5 mg twice daily to aspirin alone or DAPT after TAVI (stratum 2 — no indication for long term OAC) [15]. At one year follow-up, no significant difference in the primary efficacy endpoints was shown (Table 3). However, the authors found higher numbers of secondary endpoints including death, stroke, heart attack, or systemic embolism in the apixaban group.

In summary, among patients undergoing surgical BHV replacement, NOACs can be at least as effective and safe as warfarin. However, in the clinical setting of patients with TAVI, due to the unfavorable results of the GALILEO and ATLANTIS trials, the ESC/EACTS guidelines contraindicated the routine use of OAC in TAVI patients without baseline indication to long term OAC (class III B) and the American guidelines specifically warrant the use of NOACs in these patients [4, 5].

ORAL ANTICOAGULATION IN AF PATIENTS WITH BHVS REPLACEMENT

Patients with AF and BHVs have a non-significantly higher risk of thromboembolic events compared to those with AF only. However, in BHV patients with AF, the VKA use is independently associated with a lower risk of thromboembolic events (HR, 0.83; $P = 0.03$) [47]. The optimal OAC therapy in AF patients with BHVs is still debated. According to the current guidelines [4], life-long therapy with OAC is recommended for AF patients undergoing BHVs replacement (class IC). Moreover, NOACs may be used as an alternative to VKA only after 3 months from the BHV replacement among AF patients with different classes of recommendation [4, 5]. Considering the results of the RIvaroxaban for Valvular heart diseasE and atRial fibrillation (RIVER) trial [13], according to the ESC/EACTS guidelines, NOACs may be considered over VKA also in the first three months following surgical BHV implantation in mitral position in patients with AF (class IIb C) [4].

NOACs in AF patients with BHVs replacement: preliminary studies

Two preliminary studies [44, 45] reported the clinical performance of NOACs in AF patients with BHVs replacement or valve repair.

In a retrospective single-center cohort study including 73 AF patients undergoing aortic (n = 61) or mitral (n = 12) BHV replacement, Yadlapati et al. [48] collected data on thromboembolic and major bleeding events during NOAC therapy (dabigatran, n = 44; rivaroxaban, n = 25; apixaban, n = 4). During the follow-up period of 511.8 ± 400.8 days, they recorded 1 transient ischemic attack (TIA; 1.4%), 5 major bleeding (6.9%), and 6 minor bleeding (8.2%) events, 1 hemorrhagic stroke, and 3 deaths (4.1%). Based on these results, the authors concluded that NOACs therapy appears effective in the prevention of thromboembolic events, albeit at the expense of increased bleeding. However, it is worth mentioning that 72% of the study population was taking concomitant aspirin treatment [48].

In a retrospective multicenter observational study including 122 AF patients with a prior BHV replacement or valve repair, Russo et al. [49] investigated the incidence of thromboembolic and major bleeding events with NOAC treatment. Patients were treated with apixaban (53.1%), dabigatran (31%), or rivaroxaban (15.5%). During a follow-up of 835 ± 203 days, 2 patients (1.7%) experienced thromboembolic events, and 4 patients (3.3%) had major bleeding events. The authors concluded that NOACs seem to be an effective and safe alternative therapy in patients with BHVs replacement or valve repair. Notably, only 20% of patients were under concomitant antiplatelet therapy. Table 4 shows details of the abovementioned studies.

NOACS vs. VKAs in AF patients with BHVs replacement

Of the 4 major clinical trials comparing NOACs to warfarin in patients with AF for the prevention of stroke and systemic embolism [50–53], only the Effective Anticoagulation with Factor Xa Next Generation in AF-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial and the Apixaban

Table 4. Clinical performance of non-vitamin K antagonist oral anticoagulants after bioprosthetic heart valve replacement

First author/ /reference	Study design	Number of patients	Follow-up, days	NOAC, n (%)	Procedure, n (%)	Results	
Yadlapati et al. [48]	Obs. Rtsp SC	73	511.8 400.8	Dabigatran 44 (60.3) Rivaroxaban 25 (34.2) Apixaban 4 (5.5)	ABV 61 (83.6) MBV/MVR 12 (16.4)	TE events Bleeding events Mortality	1 TIA (1.4) 5 MB (6.9) 6 MB (8.2), 2 ICH (2.7) 3 (4.1)
Russo et al. [49]	Obs. Rtsp MC	122	835 203	Dabigatran (31) Rivaroxaban (15.5) Apixaban (53.1)	ABV 52 (43) MBV 24 (20) MSR 41 (34) AVR 5 (4)	TE events Bleeding events Mortality	2 (1.7) M.A.I: 0.8% 4 (3.3) M.A.I: 1.3% 0 (0)

Abbreviations: AVR, aortic valve repair; M.A.I, mean annual incidence; MC, multicenter; MB, major bleeding, mB, minor bleeding; MVR, mitral valve repair; Obs, observational; Rtsp, retrospective; SC, single-center; TIA, transient ischemic attack; other — see Tables 1 and 3

for Reduction in Stroke and Other Thromboembolic Events in AF (ARISTOTLE) trial included AF patients with BHV replacement [51, 53].

In a *post hoc* analysis from the ENGAGE AF-TIMI 48 [53] including 191 AF patients with BHV replacement (68.6% mitral; 31.4% aortic), Carnicelli et al. [54] showed similar rates of stroke/systemic embolism (HR, 0.37; $P = 0.15$) and major bleeding (HR, 0.5; $P = 0.26$) compared to warfarin. Moreover, patients on edoxaban showed significantly lower rates of myocardial infarction, stroke, or cardiovascular death (HR, 0.36; $P = 0.03$). The authors concluded that edoxaban appears to be a reasonable alternative to warfarin in AF patients with previous BHV replacement.

No significant differences between apixaban and warfarin were found for any outcome analyzed in the *post-hoc* analysis of the ARISTOTLE trial [55] including 156 patients with AF and BHVs or valve repair (see Tables 5 and 6 for details).

Two multicenter observational studies [56, 57] showed a more favorable effect of NOACs over warfarin in AF patients with BHV replacement. In particular, Russo et al. [56] in a propensity score matching study including 260 AF patients with BHVs (130 patients in each treatment group) showed a low rate of major bleeding among the NOACs group leading to a positive (+1.87) net clinical benefit of NOACs over VKAs.

Among 2 672 AF patients with BHVs included in a large integrated health care delivery system in California, Duan et al. [57] did not find significant differences between NOACs-users and VKAs-users in terms of thromboembolic events (composite of ischemic stroke, transient ischemic attack, or systemic embolism). Moreover, a lower risk of major bleeding (HR, 0.69; $P < 0.001$) was shown in the NOAC group. These results were consistent across subgroups (dabigatran versus warfarin; aortic versus mitral valve replacement). Tables 5 and 6 show the characteristics and results of the studies. The preliminary results of the observational studies were confirmed in several RCTs [11–13].

The DAWA pilot study [11] was the first trial designed to compare the effectiveness and safety of dabigatran 110 mg twice daily vs. warfarin in patients undergoing mitral and aortic BHV replacement. The primary endpoint was the presence of a newly diagnosed intracardiac thrombus at 90 days; the secondary outcomes were the development of dense spontaneous echo contrast and the incidence of any stroke, myocardial infarction, valve thrombosis, and peripheral embolic events. The study was terminated prematurely because of the low enrollment (34 patients). During the 90 days of follow-up, no significant differences were found either for the primary or secondary outcomes between the groups.

In a recent small trial [12], 50 AF patients undergoing aortic BHV replacement were randomized to receive apixaban (n = 25 patients) or warfarin (n = 25 patients) in a 1:1 ratio for the first 3 months after surgery. At 3 months follow-up, no valvular dysfunction was recorded; major bleeding events occurred in 3 patients (12%) among the warfarin group and none in the apixaban group. The only death reported was in the warfarin group early after surgery (9 days) due to massive pericardial bleeding effusion. The authors concluded that apixaban was non-inferior to warfarin in the first 3 months after surgical aortic BHV replacement and safer with respect to major bleeding and death.

The RIVER trial [13] was a large multicenter RCT in which 1005 AF patients undergoing surgical mitral BHV replacement were enrolled and randomized to receive rivaroxaban or warfarin. At twelve months follow-up, no significant differences in the incidence of stroke (3% vs. 2.4%), major bleeding (1.4% vs. 2.6%), or death (4% vs. 4%) were reported between rivaroxaban and warfarin. This trial brought solid data on the non-inferiority of rivaroxaban compared to warfarin with respect to the mean time until the occurrence of death, major cardiovascular events, or major bleeding at 12 months in AF patients with mitral BHV replacement.

Tables 7 and 8 summarize RTCs evaluating NOACs vs. VKAs in AF patients with BHVs replacement.

Table 5. Overview of the studies characteristics comparing non-Vitamin K oral anticoagulants with Vitamin K antagonist oral anticoagulants in AF patients with bioprosthetic valves or prior surgical valve repair

Author/reference	Study design	Number of patients	Mean FU, years	NOAC, n (%)	Procedure, n (%)	Primary outcomes	
Carnicelli et al. [54]	Posthoc analysis phase III trial	191	2.8	Edox. 121 (63.4)	ABV 60 (31.4) MBV 131(68.6)	Efficacy outcome	S/SE
						Safety outcome	MB
						Other	Primary net clinical outcome (S/SE, MB, death)
Guimarães et al. [55]	Posthoc analysis phase III trial	156	1.8	Apix. 87 (55.8)	ABV 73 (46.8) MBV 26 (16.7) ABV +MBV 5 (3.2) MVR 50 (32.1) AVR 2 (1.3)	Efficacy outcome	S/SE ACS IS MI Death CVM
						Safety outcome	MB, MB/CRNMB ICH GI bleeding Any bleeding
Russo et al. [56]	Retrosp. Propensity S-matched	260 130 for each group	1.1	Apix. 72 (55.4) Rivarox. 39 (30.0) Dabig. 17 (13.1) Edox. 2 (1.4)	ABV 128 (49.2) MBV 132 (50.8) ABV +MBV 66 (25.4)	Efficacy outcome	S/SE TIA
						Safety outcome	MB
						Other	ICH
Duan et al. [57]	Retrosp. cohort study	2672	2.9	Dabig. 362 (13.5) Apix. 60 (2.2) Rivarox. 17 (0.6)	ABV 1,724 (64.5) MBV 943 (35.3) N/A 5 (0.2)	Efficacy outcome	Composite of IS TIA/SE
						Safety outcome	Composite of MB[a]

[a]Gastrointestinal bleeding, intracranial hemorrhage, and bleeding from other sites

Abbreviations: Apix, apixaban; ACS, all-cause stroke; Dabig, dabigatran; Edox, edoxaban; GI, gastrointestinal; ICH, intracranial hemorrhage; IS, ischemic stroke; MI, myocardial infarction; S-matched, score-matched; S/SE, stroke/systemic embolism; Rivarox, rivaroxaban; other — see Tables 1, 3 and 4

Oral anticoagulation in AF patients with TAVI

VKA

Results from studies evaluating the role of OAC alone or with an antiplatelet agent after TAVI are controversial. Early observational studies showed an increased bleeding risk with the association therapy of VKAs with SAPT or DAPT, with no differences in the occurrence of thrombotic events [58, 59].

A recent subanalysis of the Placement of Aortic Transcatheter Valve II (Partner II) trial and associated registries [60] showed that antiplatelet therapy with (HR, 0.43; $P = 0.015$) or without (HR, 0.32; $P = 0.002$) OAC reduced the 2-year risk of stroke among patients with prior AF undergoing TAVI, implicating multifactorial stroke mechanism in these patients.

The POPular TAVI [61] was a randomized trial of clopidogrel in patients undergoing TAVI who were taking oral anticoagulation (warfarin) for appropriate indications. Patients before TAVI were assigned in a 1:1 ratio into two groups: one not receiving clopidogrel (n = 157) and the other receiving clopidogrel (n = 156) for 3 months. Patients with OAC alone showed a lower incidence of serious bleeding (relative risk, 0.64; $P = 0.02$) than those on OAC plus clopidogrel. No significant differences in death from cardiovascular causes, non-procedure-related bleeding, stroke from any cause, or myocardial infarction were found.

Based on these results, when long-term OAC is indicated, the current guidelines suggest using life-long OAC alone in TAVI patients with AF (class of recommendation I B in the ESC guidelines and IIaB in the American guidelines). To date, VKAs are the first-line treatment within the first 3 months following TAVI; at the end of this period, NOACs can be evaluated as an alternative [4, 5].

NOACs

The role of NOACs in AF patients undergoing TAVI is still uncertain. In a large propensity score matching study involving 962 AF patients undergoing TAVI who were discharged

Table 6. Results of the studies comparing non-vitamin K oral anticoagulants with vitamin K antagonist oral anticoagulants in atrial fibrillation patients with bioprosthetic valves or surgical valve repair

Author/reference	Events		Statistics (NOACs vs. VKA)
Carnicelli et al. [54]	S/SE	Warfarin = 8 HDE = 3 LDE n = 4	HDE vs. warfarin: HR, 0.37; 95% CI, 0.10–1.42; $P = 0.15$ LDE vs. warfarin HR, 0.53; 95% CI, 0.16–1.78; $P = 0.31$
	MB	Warfarin = 9 HDE = 4 LDE = 1	HDE vs. warfarin: HR, 0.5; 95% CI, 0.15–1.67; $P = 0.26$ LDE vs. warfarin HR, 0.12; 95% CI, 0.01–0.95; $P = 0.045$
	Primary net clinical outcome	N/A	HDE vs. warfarin: HR, 0.46; 95% CI, 0.23–0.91; $P = 0.03$ LDE vs warfarin HR, 0.43; 95% CI, 0.21–0.88; $P = 0.02$
Guimarães et al. [55]	Efficacy outcomes		Efficacy outcomes
	S/SE	Warfarin = 2 Apixaban = 4	HR, 1.714; 95% CI 0.313–9.372; $P = 0.53$
	ACS	Warfarin = 2 Apixaban = 4	HR, 1.714, 95% CI 0.313–9.372; $P = 0.53$
	IS	Warfarin = 1 Apixaban = 4	HR, 3.286, 95% CI 0.37–29.4; $P = 0.29$
	MI	Warfarin = 1 Apixaban = 1	HR, 0.825, 95% CI 0.367–29.40; $P = 0.29$
	Death	Warfarin = 6 Apixaban = 7	HR, 1.017, 95% CI 0.341–3.037; $P = 0.98$
	CVM	Warfarin = 2 Apixaban = 2	HR, 0.827, 95% CI 0.123–6.201; $P = 0.89$
	Safety outcome		Safety outcome
	MB	Warfarin = 7 Apixaban = 7	HR, 0.882, 95% CI 0.309–2.519; $P = 0.82$
	MB/CRNMB	Warfarin = 10 Apixaban = 9	HR, 0.781, 95% CI 0.317–1.925; $P = 0.59$
	ICH	Warfarin = 2 Apixaban = 1	HR, 0.467, 95% CI 0.042–5.187; $P = 0.54$
	GI bleeding	Warfarin = 2 Apixaban = 3	HR, 1.244, 95% CI 0.208–7.448; $P = 0.81$
	Any bleeding	Warfarin = 28 Apixaban = 30	HR, 0.866, 95% CI 0.517–1.451; $P = 0.59$
Russo et al. [56]	S/SE TIA	VKA = 5 NOAC = 3	HR, 0.49, 95% CI, 0.19–1.22; $P = 0.14$
	MB	VKA = 12 NOAC = 6	HR, 0.59, 95% CI, 0.15–2.4; $P = 0.47$
	ICH	VKA = 3 NOAC = 1	HR, 0.33, 95% CI, 0.05–2.34; $P = 0.3$
Duan et al. [57]	Composite of IS TIA/SE	N/A	HR, 1.19, 95% CI, 0.96–1.48; $P = 0.106$
	Composite of MB[a]	N/A	HR, 0.69, 95% CI 0.56–0.85; $P < 0.001$

Abbreviations: HDE, high dose edoxaban; LDE, low dose edoxaban; a: composite of major bleeding including gastrointestinal bleeding, intracranial hemorrhage, and bleeding from other sites; other — see Tables 1, 3–5

on NOACs (n = 326; 53.7 % rivaroxaban, 39.2% apixaban, and 7.1% dabigatran) or warfarin (n = 626), Jochheim et al. [62] did not show any significant differences in the primary safety outcomes (bleeding according to the Bleeding Academic Research Consortium) or all-cause mortality between the two groups at 1-year follow-up. However, the incidence of the primary efficacy outcomes (all-cause mortality, myocardial infarction, and any cerebrovascular events) was higher in the NOACs group (21.2% vs. 15%; HR, 1.44; $P = 0.05$).

Conversely, in the prospective study of Seeger et al. [63], TAVI patients with AF treated with apixaban experienced a significantly lower rate of the safety endpoints (a composite of all-cause mortality, all stroke, life-threatening bleeding, acute kidney injury, coronary obstruction, major vascular complications, and valve dysfunction requiring re-intervention) at 30 days follow up (13.5% vs. 30.5%; $P < 0.01$). No significant differences were found in the rate of stroke at 30 days (2.1% vs. 5.3%; $P = 0.17$) and 12 months follow-up between treatment groups (1.2% vs. 2.0%; $P = 0.73$).

Among 2588 patients who underwent TAVI, enrolled in the prospective multicenter observational Optimized Transcatheter Valvular Intervention (OCEAN) study [64], 403 (15.6%) patients had AF on anticoagulation therapy

Table 7. Characteristics of randomized clinical trials comparing non-vitamin K oral anticoagulants with vitamin K antagonist oral anticoagulants in AF patients with bioprosthetic valves or surgical valve

Author/reference	Study design	Procedure	Study groups	Number of patients (NOACs/VKAs)	Primary outcomes
Durães et al. [11]	Phase 2 RCT Pilot study — FU At 90 days	ABV = N/A MBV = 20	Dabigatran 110 mg vs. Warfarin	Overall = 27 Dabigatran = 15 Warfarin = 12	New intracardiac thrombus (TEE)
Piepiorka-Broniecka et al. [12]	Prospective RCT — At 30 days And At 90 days	ABV	Apixaban vs. Warfarin	Overall = 50 Apixaban = 25 Warfarin = 25	Death Bleeding (1 and 3 months) BV function (3 months)
Guimarães et al. [13]	Multicenter RCT — FU 365 days	MBV	Rivaroxaban vs. Warfarin	Overall = 1005 Rivaroxaban = 500 Warfarin = 505	[a]Composite of Death MACE[b] MB — Bleeding events[c]

[a]Mean time until a primary-outcome event in days; [b]Ischemic attack, valve thrombosis, systemic embolism not related to the central nervous system, or hospitalization for heart failure; [c]According to the criteria of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF): Any bleeding; Major bleeding; Intracranial bleeding; Fatal bleeding; Clinically relevant nonmajor bleeding; Minor bleeding

Abbreviations: BV, bioprosthetic valve; RCT: randomized clinical trial; TEE: transesophageal echocardiography; other — see Table 1, 3 and 4.

Table 8. Results of the randomized clinical trials comparing non-vitamin K oral anticoagulants with vitamin K antagonist oral anticoagulants in AF patients with bioprosthetic valves or surgical valve

Author/reference	Results (n of events)		Statistics
Durães et al. [11]	New intracardiac thrombus (TEE)	Warfarin = 1 Dabigatran = 0	RR, 1.1; 95% CI, 0.9–1.3; *P* = 0.42
Piepiorka-Broniecka et al. [12]	Cumulative death	Warfarin = 1 Apixaban = 0	*P* = 0.31
	Cumulative bleeding	Warfarin = 3 Apixaban = 0	*P* = 0.07
	Valve dysfunction	Warfarin = 0 Apixaban = 0	N/A
Guimarães et al. [13]	Efficacy outcome		Efficacy outcome
	[a]Composite of Death MACE[b] MB[c]	Warfarin = 340.1 Rivaroxaban = 347.5	RMST difference, 7.4 days (–1.4–16.3) *P* <0.001 for noninferiority *P* = 0.10 for superiority
	Safety outcomes		Safety outcomes
	MB	Warfarin = 13 Rivaroxaban = 7	HR, 0.54; 95% 0.21– 1.35; *P* = N/A
	ICH	Warfarin = 5 Rivaroxaban = 0	N/A
	Fatal bleeding	Warfarin = 2 Rivaroxaban = 0	N/A
	CRNMB	Warfarin = 24 Rivaroxaban = 23	HR, 1.05; 95% CI, 0.60–1.87; *P* = N/A
	mB	Warfarin = 49 Rivaroxaban = 37	HR, 0.75; 95% CI, 0.49–1.15; *P* = N/A

[a]Mean time until a primary-outcome event in days; [b]Ischemic attack, valve thrombosis, systemic embolism not related to the central nervous system, or hospitalization for heart failure; [c]According to the criteria of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF): Any bleeding; Major bleeding; Intracranial bleeding; Fatal bleeding; Clinically relevant nonmajor bleeding; Minor bleeding

Abbreviations: RR, relative risk; RMST, restricted mean survival time; other — see Tables 1–5 and 7

(NOACs, n = 227; VKAs, n = 176). Compared with VKAs, NOACs were associated with a low incidence of all-cause mortality (10.2% vs. 20.6%; HR, 0.53; *P* = 0.036) during a median follow-up of 568 days. Similarly, Butt et al. [65] did not find differences in terms of 3-year incidence of arterial thromboembolism, bleeding, or mortality among 219 (29.8%) AF patients treated with NOACs and 516 (70.2%) treated with VKAs following TAVI.

In the multicenter, prospective, randomized, open-label ENVISAGE-trial [14], edoxaban was non-inferior to VKAs for the efficacy endpoints (composite of death from any cause, myocardial infarction, ischemic stroke, systemic thromboembolism, valve thrombosis) (HR, 1.05; *P* = 0.01) or major bleeding (HR, 1.05; *P* = 0.01). However, it was associated with a higher rate of major bleeding events (HR, 1.40; P = 0.93), mainly due to gastrointestinal bleeding.

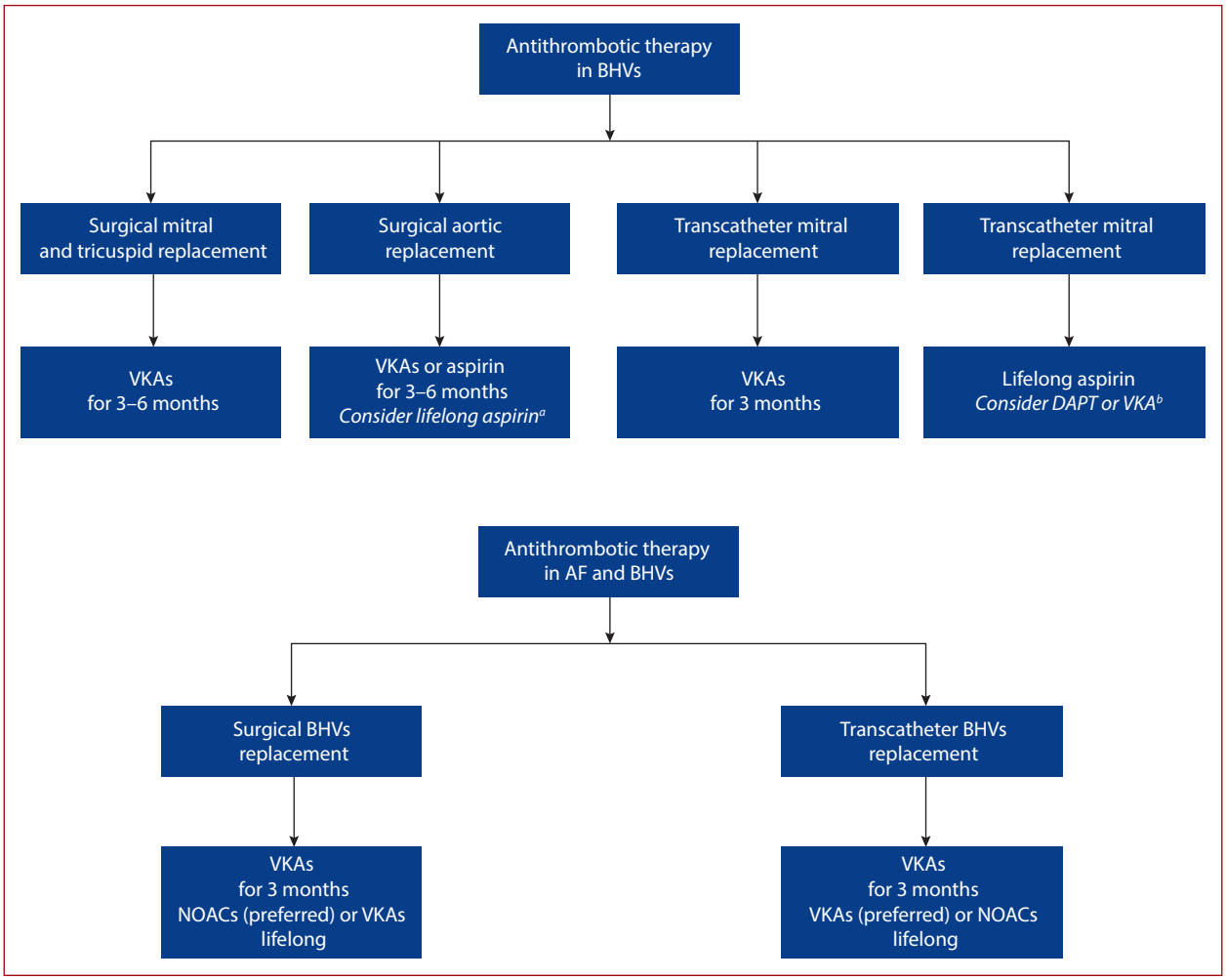

Figure 1. Proposed approach to antithrombotic therapy after bioprosthetic valve replacement
[a]Even in patients treated with VKAs in the first 3–6 months; [b]In low bleeding risk patients

Abbreviations: AF, atrial fibrillation, BHVs, bioprosthetic heart valves; DAPT, dual antiplatelet therapy (aspirin plus clopidogrel); NOACs, non-vitamin K antagonist and anticoagulants; VKA, vitamin K antagonist oral anticoagulants

On the other hand, in the AF cohort of the ATLANTIS trial (stratum 1) [15], apixaban 5 mg twice daily was found non-inferior for both the primary (composite of all-cause death, stroke, heart attack, valve thrombosis, pulmonary or systemic embolism, deep vein thrombosis or major bleeding; 21.9% vs. 21.9%; *P* = NS) and safety outcomes (0.9% vs. 1.3%; *P* >0.05) compared to warfarin.

Even if these preliminary results suggest that NOACs are comparable for the safety profile to VKAs in AF patients undergoing TAVI [47, 63–65], some concerns remain about the incidence of adverse ischemic and bleeding events [14, 62]. Finally, until more data are available, the VKA-based strategy should be preferred early after TAVI in AF patients.

DISCUSSION

There is increasing evidence that OAC therapy can play a key role in the prevention of early and late thrombotic complications in patients with BHVs, especially in those undergoing mitral or tricuspid replacement [4, 5, 16, 18, 19, 66]. The optimal duration of OAC therapy is still debated (three or six months). The life-long treatment with aspirin alone is still the standard of care for TAVI patients with no indication for long-term OAC [4, 5].

According to the international guidelines [4, 5], OAC-alone therapy is the favored strategy among AF patients undergoing BHVs replacement.

Several studies suggest a preference for NOACs over VKAs among AF patients undergoing surgical BHV replacement [7, 54, 57, 63–65]; however, most of them [48, 49, 54, 55, 57, 62–65] included patients with concomitant antiplatelet therapy leading to several biases both for thromboembolic and bleeding outcomes. Three recent metanalyses [67–69] support the use of NOACs over VKAs in AF patients with BHVs, however, the large heterogeneity of the study populations (especially for age and comorbidities) and the inclusion of different valve surgeries make it difficult to generalize the results [67]. Few data support the early use of NOACs even in the first three months [14,

54, 55]; however, the number of patients randomized in the first 3 months after the procedure is too small to draw definitive conclusions.

Among AF patients undergoing TAVI, the choice of the optimal oral anticoagulant therapy is still uncertain, due to heterogeneous results of the available studies [4, 15, 62–65]. Moreover, the conflicting results of the ENVISAGE [64] and ATLANTIS trials [46] suggest that comparative RCTs for each NOACs are needed to draw definitive conclusions since the clinical results can vary from one NOAC to another. Figure 1 shows our proposed approach for antithrombotic therapy after both surgical and transcatheter BHV replacement, in light of the data available in the literature.

CONCLUSION

Finding an optimal oral anticoagulant therapy among patients with BHVs and AF is still challenging. Despite the increasing data suggesting a preference to NOACs over VKAs among AF patients undergoing surgical BHVs replacement, further confirmatory studies are needed to clarify the clinical profile of NOACs among AF patients with BHVs in the first 3 months after intervention and among those with TAVI.

Article information

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