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Non-vitamin K antagonist oral anticoagulants in patients with valvular heart disease

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The non-vitamin K antagonist oral anticoagulants (NOACs) dabigatran, rivaroxaban, apixaban, and edoxaban have transformed the management of atrial fibrillation (AF), but are only approved by regulatory authorities for stroke prophylaxis in patients with so-called "non-valvular AF." This terminology has spawned confusion about which patients with valvular heart disease benefit from NOACs and which should be treated with vitamin K antagonists (VKAs) instead. Patients with valvular heart disease other than mechanical prosthetic valves or severe mitral stenosis (including those with bioprosthetic valves) were included in pivotal trials demonstrating the benefit of NOACs over VKAs, and consensus guidelines recommend NOACs over VKAs in these patients. Subsequent devoted randomized controlled trials in patients with AF and bioprosthetic valves, including transcatheter valves, have confirmed the safety of NOACs in this population. In patients with rheumatic mitral stenosis, observational studies indicate that NOACs may be safe and effective, but randomized controlled trials are ongoing. By contrast, a randomized controlled trial showed that dabigatran is harmful in patients with mechanical prosthetic mitral valves; however, these data may not extrapolate to patients with mechanical valve prostheses in other locations or to other NOACs, and randomized controlled trials are ongoing. In this review, we discuss these data in greater depth, and make recommendations for the use of NOACs in patients with valvular heart disease.

Introduction

The non-vitamin K antagonist oral anticoagulants (NOACs)—including the direct thrombin inhibitor dabigatran and factor Xa inhibitors rivaroxaban, apixaban, and edoxaban—transformed the management of atrial fibrillation (AF) upon their regulatory approval in the first half of the 2010s. Pivotal clinical trials demonstrated that each NOAC was non-inferior to vitamin K antagonists (VKAs) for the prevention of stroke and systemic embolism, and that apixaban, edoxaban, and dabigatran caused fewer episodes of major bleeding.[1-4] Moreover, NOACs' predictable pharmacokinetics eliminated the need for routine monitoring of anticoagulant activity, which is necessary for patients treated with VKAs. However, all pivotal trials of NOACs excluded patients with mechanical mitral valves or severe mitral stenosis, an artefact of the non-inferiority design of these trials, which required that they enroll the same patient population as pivotal trials demonstrating the efficacy of VKAs vs. placebo for stroke prophylaxis in

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patients with AF. For this reason, regulatory authorities around the world approved NOACs for stroke and systemic embolism prophylaxis only in patients with 'non-valvular AF', defined, based on exclusion criteria in the pivotal trials comparing NOACs and VKAs, as moderate or severe mitral stenosis or a mechanical mitral valve.

However, the term non-valvular AF has spawned confusion, with many believing that the coexistence of AF and any valvular heart disease makes a patient ineligible for treatment with NOACs. This confusion is particularly significant because it limits the application of evidence-based treatment in patients with valvular heart disease, an area of cardiology with particularly limited evidence from randomized clinical trials to guide care.[5] In reality, many patients with valvular heart disease were included in pivotal trials comparing NOACs vs. VKAs and can realize the same benefits of NOACs with respect to bleeding and convenience as other patients included in these trials. For these reasons, the most recent version of the European Society of Cardiology guidelines for the management of patients with AF, published in 2020, indicates that the term 'non-valvular AF' should be abandoned.[6] In this state-of-the-art review, we will discuss the types of patients with valvular heart disease excluded from pivotal trials comparing NOACs and VKAs and the rationale for these exclusions, correct misconceptions surrounding the terms valvular and non-valvular AF, describe the evidence for the safety and efficacy of NOACs in patients with valvular heart disease other than moderate to severe mitral stenosis and mechanical mitral valves, and highlight ongoing studies that aim to assess the potential role of NOACs in valvular heart disease settings that were excluded from the pivotal NOAC trials.

Valvular atrial fibrillation in historical context

The efficacy of anticoagulation vs. placebo for stroke prevention in patients with AF was first established in a series

Table 1 Valve-related exclusion criteria in trials of anticoagulants in patients with AF

Trial	Publication year	Comparison	Exclusion criteria
AFASAK[12]	1989	VKA vs. placebo	• Heart surgery with valve replacement • Rheumatic heart disease
BAATAF[13]	1990	VKA vs. placebo	• Evidence of mitral stenosis on two-dimensional echocardiography • Prosthetic heart valve
SPAF-1[14]	1991	VKA vs. placebo	• Mitral stenosis by echocardiography • Prosthetic heart valve • Mitral regurgitation with heart failure and left atrial diameter of >5.5 cm
CAFA[15]	1991	VKA vs. placebo	• Mitral or aortic valve prosthesis • Mitral valve stenosis on two-dimensional echocardiography
SPINAF[16]	1992	VKA vs. placebo	• Mitral stenosis • Prosthetic heart valve
EAFT[17]	1993	VKA vs. placebo	• Rheumatic heart disease • Prosthetic heart valve
RE-LY[1]	2009	Dabigatran vs. VKA	• Prosthetic valve • Haemodynamically relevant valve disease
ROCKET-AF[2]	2011	Rivaroxaban vs. VKA	• Haemodynamically significant mitral valve stenosis • Prosthetic heart valve (annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty are permitted) • Active endocarditis
ARISTOTLE[3]	2011	Apixaban vs. VKA	• Clinically significant (moderate or severe) mitral stenosis • Prosthetic mechanical heart valve • Active infective endocarditis
ENGAGE AF[4]	2013	Edoxaban vs. VKA	• Moderate or severe mitral stenosis • Mechanical heart valve (patients with bioprosthetic heart valves and/or valve repair can be included)

of randomized clinical trials conducted in the 1980s and published in the early 1990s. Importantly, patients with rheumatic heart disease were excluded from these studies. Autopsy and cohort studies published in the 1940s through early 1980s had demonstrated a very high risk of thromboembolic stroke in patients with rheumatic heart disease—17-fold higher than the risk in the general population, in an analysis of the Framingham cohort—and anticoagulation had become the standard of care.[7-10] Similarly, it was rapidly recognized after the advent of prosthetic valves in the 1960s that failure to treat these patients with anticoagulation invariably led to valve thrombosis and death.[11] For these reasons, investigators did not believe that it was ethical to randomize patients with rheumatic heart disease or prosthetic valves to a treatment other than anticoagulation. Ultimately, six trials were done comparing VKA vs. placebo for the prevention of stroke, transient ischaemic attack, or systemic embolism. The first of these trials, the Copenhagen AFASAK (Atrial Fibrillation, Aspirin, Anticoagulation) study, enrolled 1007 patients with chronic AF without rheumatic heart disease, and randomized them to VKA, low-dose aspirin, or placebo for 12 months.[12] The yearly incidence of thromboembolic complications was 2.9% [95% confidence interval (CI) 0.6-4.8%] in patients randomized to VKA and 5.5% (95% CI 2.9-9.4%) in patients randomized to both aspirin and placebo. Five additional trials—SPAF I (Stroke Prevention in Atrial Fibrillation), BAATAF (Boston Area Anticoagulation Trial for Atrial Fibrillation), CAFA (Canadian Atrial Fibrillation Anticoagulation), SPINAF (Stroke Prevention in Nonrheumatic Atrial Fibrillation), and EAFT (European Atrial Fibrillation Trial)—compared VKA vs. placebo, and all found that VKAs reduced the risk of thromboembolism.[13-17] Like AFASAK, these trials all excluded patients with rheumatic heart disease (Table 1). In a meta-analysis of these six trials, Hart et al.[18] found that VKAs reduced the risk of thromboembolism by 64% vs. placebo in patients with non-valvular AF.

Based on the results of these trials, VKAs became the mainstay for stroke and systemic embolism prevention in patients with AF in the absence of rheumatic heart disease. Since it had previously been the standard of care for patients with rheumatic heart disease, it was thus indicated for all patients with AF, with or without rheumatic heart disease. However, VKAs have a number of limitations. First, their use is associated with a high risk of bleeding, which can be quite serious. In the meta-analysis by Hart et al.,[18] treatment with VKA vs. control was associated with an 0.2%/year increased risk of intracranial haemorrhage and a 0.3%/year increased risk of major extracranial haemorrhage. The risk of bleeding is compounded by VKAs' small therapeutic window: patients with international normalized ratio (INR) <2 have a substantially higher stroke risk than those with INR ≥2, and patients with INR >3 have a higher risk of intracranial haemorrhage with no further reduction in stroke risk.[19] Even within the therapeutic window, VKAs are not perfect; in one study, ~75% of patients with major bleeding and intracranial haemorrhage on VKA had INR < 3, and 50% of patients with ischaemic stroke on VKA had INR >2.[20,21] Maintaining patients within that

narrow therapeutic window is further complicated by VKAs' indirect effect on coagulation via prevention of the synthesis of coagulation factors II, VII, IX, and X. VKAs' effect on coagulation are therefore mediated by dietary vitamin K, genetic polymorphisms that affect VKAs' affinity for its target enzyme, and cytochrome p450 interactions with a number of common drugs and foods.[22] Together, these interactions can cause VKAs' effect on coagulation to fluctuate, and time spent outside of the therapeutic window will reduce VKAs' efficacy or safety. Treatment with VKAs therefore requires patients to undergo frequent INR checks to ensure safe and effective anticoagulation.

For these reasons, despite VKAs' efficacy in prevention of thromboembolism across multiple randomized controlled trials, there was considerable interest in the development of oral anticoagulants (OAC) that exerted a more direct effect on coagulation and would not require frequent monitoring. Ultimately, this interest led to the development of the NOACs dabigatran, rivaroxaban, edoxaban, and apixaban in the late 1990s and early 2000s. When designing trials to determine the efficacy of NOACs for the prevention of stroke and systemic embolism in patients with AF, VKAs' demonstrated effectiveness for the prevention of this serious endpoint meant that it would be unethical to compare NOACs with placebo; instead, the pivotal trials evaluating NOACs' efficacy all compared NOACs with VKAs. However, regulatory authorities also recognized a clinical need for OACs that were as (or nearly as) effective at preventing stroke as VKAs without VKAs' other, well-recognized limitations. For this reason, pivotal clinical trials of NOACs vs. VKAs were designed as non-inferiority trials.

A non-inferiority study is designed to test the hypothesis that a new treatment is not worse than an existing treatment by a pre-specified amount, which is termed the non-inferiority margin.[23] The non-inferiority margin is selected to preserve some fraction of the efficacy of existing treatment vs. placebo. Because non-inferiority studies make an implied comparison between NOACs and placebo via the comparison between VKAs and placebo, the population enrolled in the pivotal trials of NOAC vs. VKA needed to match the population enrolled in the pivotal trials of VKAs vs. placebo. Patients with haemodynamically significant mitral valve disease and mechanical prosthetic valves were therefore excluded from all of the pivotal trials comparing NOACs vs. VKA, and trials' primary publications referred to their study population as patients with non-valvular AF. Ultimately, regulatory authorities also adopted this terminology, approving dabigatran, rivaroxaban, apixaban, and edoxaban for the treatment of non-valvular AF. The 2012 European Society of Cardiology and 2014 American College of Cardiology/American Heart Association (ACC/AHA) guideline for the management of patients with AF also adopted valvular/non-valvular AF terminology.[19,24] The ACC/AHA guideline defined non-valvular AF as 'AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair', and the ESC guideline defined valvular AF as 'imply[ing] that AF is related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves'. Both guidelines

Table 2 Patients with valvular heart disease in pivotal trials comparing NOAC vs. VKA

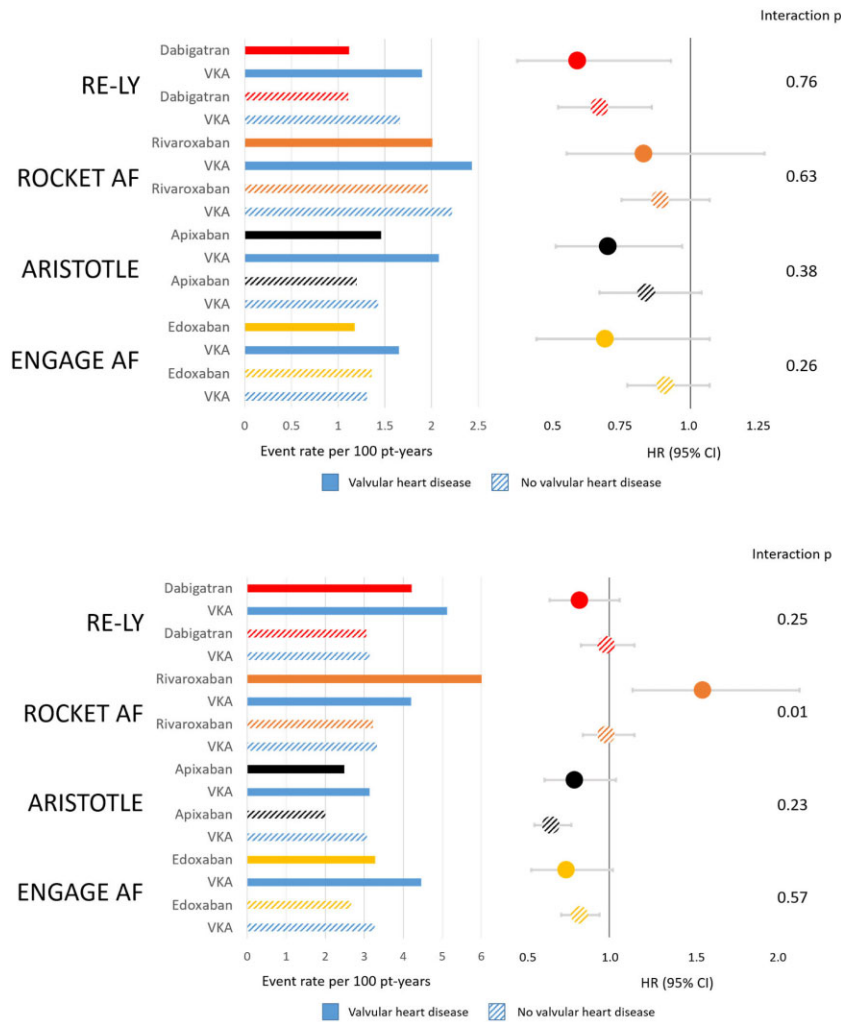|	RE-LY (N = 18 113)[27]		ROCKET-AF (N = 14 171)[28]		ARISTOTLE (N = 18 201)[29]		ENGAGE AF (N = 21 046)[30]		Total (N = 71 531)	
	N	%	N	%	N	%	N	%	N	%
Any moderate or severe valvular disease	3950	21.8	2003	14.1%	4808	26.4%	2824	13.4%	13 585	19.0%
Mitral regurgitation	3101	17.1%	1756	12.4%	3526	19.4%	2250	10.7%	10 633	14.9%
Mitral stenosis (mild)	193	1.1%	—	—	131	0.7%		—	324	0.5%
Aortic regurgitation	817	4.5%	486	3.4%	887	4.9%	369	1.7%	2559	3.6%
Aortic stenosis	471	2.6%	215	1.5%	384	2.1%	165	0.8%	1235	1.7%
Tricuspid regurgitation	1179	6.5%	—	—	2124	11.7%	—	—	3303	4.6%
Prior valve surgery or procedure	—	—	106	5.3%	251	1.4%	325	1.5%	682	1.0%

Figure 1 Interaction between valvular heart disease and treatment effect of NOACs vs. VKA on stroke and systemic embolism and major bleeding. (*A*) Stroke and systemic embolism and (*B*) major bleeding. Bar graphs show the rate of stroke and systemic embolism per 100 patient-years in patients with valvular heart disease (solid bars) and without valvular heart disease (hatched bars) in patients treated with VKAs (blue) and NOACs (other colours), and forest plot shows the hazard ratios (NOAC vs. VKA) in patients with valvular heart disease (solid circle) and without valvular heart disease (hatched circle) in the pivotal trials of NOACs versus VKAs in patients with atrial fibrillation.

recommended use of NOACs only in patients with non-valvular AF.

This terminology, however, proved confusing to practicing cardiologists.[25] In a survey of 513 cardiologists and internists conducted in 2011 and 2012, just 57% reported that existing definitions of non-valvular AF were sufficiently clear. When surveyed about whether various scenarios would be classified as valvular AF, only 30% knew

Table 3 Effect of NOAC vs. VKA on stroke and systemic embolism and major bleeding in patients with and without valvular heart disease enrolled in pivotal NOAC trials

	Stroke and systemic embolism		Major bleeding	
	HR, NOAC vs. VKA (95% CI)		HR, NOAC vs. VKA (95% CI)	
Trial	Valvular heart disease	No valvular heart disease	Valvular heart disease	No valvular heart disease
RE-LY	0.59 (0.37-0.93)	0.67 (0.52-0.86)	0.82 (0.64-1.06)	0.98 (0.83-1.15)
ROCKET-AF	0.83 (0.55-1.27)	0.89 (0.75-1.07)	1.56 (1.14-2.14)	0.98 (0.84-1.15)
ARISTOTLE	0.70 (0.51-0.97)	0.84 (0.67-1.04)	0.79 (0.61-1.04)	0.65 (0.55-0.77)
ENGAGE AF	0.69 (0.44-1.07)	0.91 (0.77-1.07)	0.74 (0.53-1.02)	0.82 (0.71-0.94)

Table 4 Effect of NOAC vs. VKA on stroke and systemic embolism and major bleeding in major trials enrolling patients with valvular heart disease

Trial	Population	NOAC arm	Comparator arm	Death or thromboembolism HR, 95% CI	Major bleeding HR (95% CI)
RE-ALIGN[37]	Mechanical aortic or mitral valve (79% immediately post-op)	Dabigatran 150, 220, or 300 mg twice daily, adjusted based on plasma drug level	VKA, dose adjusted to INR 2.5-3.5 or 2.0-3.0	1.94 (0.64-5.86)	1.76 (0.37-8.46)
RIVER[56]	Atrial fibrillation + bioprosthetic mitral valve	Rivaroxaban 20 mg daily	VKA, dose adjusted to INR 2.0-3.0	0.65 (0.35-1.20)	0.54 (0.21-1.35)
ATLANTIS (stratum 1)[61]	Atrial fibrillation + transcatheter aortic valve	Apixaban 5 mg twice daily	VKA, dose adjusted to INR 2.0-3.0	1.02 (0.68-1.05)	0.92 (0.52-1.60)
ENVISAGE-TAVI AF[62]	Atrial fibrillation + transcatheter aortic valve	Edoxaban 60 mg daily	VKA, dose adjusted to INR 2.0-3.0	1.02 (0.76-1.39)	1.40 (1.03-1.91)
GALILEO[66]	Transcatheter aortic valve without atrial fibrillation	Rivaroxaban 10 mg daily + aspirin	Clopidogrel 75 mg daily + aspirin	1.35 (1.01-1.81)	1.50 (0.95-2.37)
ATLANTIS (stratum 2)[61]	Transcatheter aortic valve without atrial fibrillation	Apixaban 5 mg twice daily	Antiplatelet therapy	1.56 (1.01-2.43)	1.09 (0.69-1.69)
PROACT-Xa[48]	Mechanical On-X aortic valve (> 3 months post-op)	Apixaban 5 mg twice daily	VKA, dose adjusted to INR 2.0-3.0	Ongoing	Ongoing
DAVID-MS[54]	Moderate or severe rheumatic mitral stenosis	Dabigatran 110 or 150 mg twice daily	VKA, dose adjusted to INR 2.0-3.0	Ongoing	Ongoing
INVICTUS[50]	Moderate or severe rheumatic mitral stenosis and atrial fibrillation	Rivaroxaban 20 mg daily	VKA, dose adjusted to INR 2.0-3.0	Ongoing	Ongoing

that AF in the presence of valvular disease other than mitral should be characterized as non-valvular, 24% knew that AF in the presence of mitral regurgitation should be characterized as non-valvular AF, 29% knew that AF in the presence of an aortic bioprosthesis should be characterized as non-valvular AF, and just 13% knew that the degree of

mitral valve stenosis (moderate-severe vs. mild) was relevant for distinguishing between valvular and non-valvular AF.[26]

Efficacy and safety of NOACs in patients with valvular heart disease other than mitral stenosis or mechanical prosthetic valves

The pivotal trials of NOACs vs. VKA did include a number of patients with other types of valvular heart disease. Of 71 531 patients enrolled in RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy), ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), and ENGAGE AF (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation), the pivotal trials evaluating NOACs vs. VKA, 13 585 (19.0%) had either moderate/severe valvular disease or a prior valve intervention or bioprosthesis (*Table 2*).[27-30] The vast majority of these patients ($N = 10\,633$; 78.2%) had mitral regurgitation, but significant numbers of patients had other valve lesions or prior valve procedures.

Across the four trials, compared with patients without valvular heart disease, patients with valvular heart disease were older and had more cardiovascular and non-cardiovascular comorbidities. They had higher rates of stroke and systemic embolism (the trials' primary endpoints) and major bleeding.[27-30] However, in all trials, the effect of NOAC vs. VKA on the primary efficacy endpoint of stroke and systemic embolism was similar for patients with and without valvular heart disease (*Figure 1A* and *Table 3*). The effect of NOAC vs. VKA on the major bleeding endpoint was similar for patients with and without valvular heart disease in all trials except ROCKET AF, in which patients with valvular heart disease were more likely to have major bleeding with rivaroxaban than VKA and patients without valvular heart disease has similar risks of bleeding with both treatments (*Figure 1B*). In all of the trials, there was no signal of heterogeneity between different valve lesions in their interaction with the effect of NOACs vs. VKAs on key clinical endpoints.[27-30] Though these trials were underpowered to assess the interaction between presence of valvular heart disease and the effect of NOAC vs. VKA on major bleeding, stroke, and systemic embolism, the tightly overlapping CIs and consistency across trials suggests that patients with valvular heart disease other than severe mitral stenosis and mechanical prosthetic heart valves derive the same benefit as patients without valvular heart disease from treatment with NOACs over VKAs. Based on the results from these subanalyses, European Society of Cardiology guidelines recommend NOACs in preference to VKAs in patients with AF and aortic stenosis, aortic regurgitation, or mitral regurgitation (Class I, Level of Evidence (LOE) A).[31] American College of Cardiology/American Heart Association (ACC/AHA) guidelines indicate that NOACs are 'an effective alternative to VKA' in this population (Class I, LOE A).[32]

Efficacy and safety of NOACs in patients with mitral stenosis and mechanical prosthetic valves

Since patients with moderate or severe mitral stenosis and mechanical prosthetic valves were excluded from the pivotal trials comparing NOACs vs. VKAs for reasons related to trial design rather than concerns that NOACs would be less effective in these populations, there remained equipoise to randomize patients with mitral stenosis and mechanical prosthetic valves to NOACs vs. VKA. By 2009, more than 4 million people had received a prosthetic valve, and 300 000 were implanted each year,[33] and NOACs' safety and effectiveness were unknown in this sizable group of patients. Moreover, in benchtop and swine models of mechanical prosthetic valves, dabigatran was as or more effective than VKAs or heparin in the prevention of thrombosis in mechanical valves placed in the aortic and mitral positions.[34-36] These findings informed the design of RE-ALIGN (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement), which planned to randomize 405 patients with mechanical prosthetic bileaflet heart valves in the aortic or mitral position to dabigatran or VKA.[37] The trial was stopped after enrolment of 252 patients due to an excess of both ischaemic and bleeding events in the dabigatran arm: 5% of patients in the dabigatran arm and 0% in the VKA arm had an ischaemic stroke, and 4% of patients in the dabigatran arm and 2% of patients in the VKA arm had a major bleeding event. RE-ALIGN showed that dabigatran was not as effective as VKA for the prevention of stroke and systemic embolism in patients with mechanical prosthetic valves, and as a result, consensus guidelines contain a Class III recommendation against the use of NOACs in these patients, with the strongest language contraindicating the use of dabigatran.[32,38]

Given well-recognized limitations of VKAs, there remains an unmet need for alternative anticoagulation strategies in this population, and some have argued that the results from RE-ALIGN should not be broadly applied to all types of mechanical valves and all NOACs.[39] They have argued that NOACs failed to be safe and effective for anticoagulation in patients with mechanical heart valves because RE-ALIGN enrolled patients at the wrong time, used the wrong mechanical valve type, and used the wrong NOAC.

First, 79% of patients enrolled in RE-ALIGN were enrolled immediately following mechanical prosthetic valve implantation, and early post-operative events this cohort of patients drove the worse outcomes with dabigatran.[39] Of nine patients with stroke in the dabigatran arm (vs. 0 in the VKA arm), the majority occurred within the first 90 days after surgery. Similarly, the seven instances of major bleeding in the dabigatran arm (vs. two in the VKA arm) were pericardial bleeds in the perioperative period. These findings suggest NOACs are not safe and effective for the immediate post-operative period, but that the safety and efficacy profile for patients >3 months from valve replacement may differ. This argument is supported by two hypotheses related to changing thrombogenicity of mechanical valves over time. First, prosthetic valve

components are highly thrombogenic, but develop a less thrombogenic neointimal covering over time.[40] Second, the trauma of surgery induces a transient hypercoagulable state, activating the extrinsic coagulation pathway, which is inhibited by VKAs but not dabigatran.[39,41]

The second reason advanced for dabigatran's failure to provide safe and effective anticoagulation in RE-ALIGN is related to dabigatran. Dabigatran is poorly bioavailable, and investigators adjusted the dose of dabigatran (up to 300 mg twice daily, or twice the dose approved for patients with non-valvular AF) to obtain a serum level of >50 ng/mL.[37] Though median time to reach therapeutic levels of anticoagulation was similar in the dabigatran and VKA groups (8 vs. 7 days), the interquartile range was broader for dabigatran (7-23 days) than VKA (5-11 days), suggesting that many patients were inadequately anticoagulated in the dabigatran arm during the critical postoperative period. In addition, there is poor correlation between serum levels of dabigatran and anticoagulant efficacy, so even patients reaching appropriate levels may not have been adequately anticoagulated.[42] This strategy of titrating dabigatran dose based on serum levels contrasts with how dabigatran was dosed in the RE-LY trial and how it is used in clinical practice, without need for monitoring of anticoagulant activity. Furthermore, the perceived need for monitoring anticoagulant activity in this population also limits the practical benefit of dabigatran compared with VKAs. More broadly, dabigatran's mechanism of action, as a direct thrombin inhibitor, may have made it a poor choice. Dabigatran inhibits thrombin, the final factor in the coagulation cascade, in a 1:1 manner. Mechanical heart valves continuously activate the coagulation cascade, leading to very high local concentrations of thrombin. In an *in vitro* study performed after RE-ALIGN, dabigatran concentrations <200 ng/mL (four-fold higher than the concentrations achieved in RE-ALIGN) had minimal effect on thrombin generation on mechanical heart valves; concentrations of 254 and 488 ng/mL (five- and nine-fold higher than the concentrations achieved in RE-ALIGN) were required to achieve inhibition of thrombus formation to the same extent as VKA at INR values of 2.0 and 3.5.[41] The 300 mg twice daily dose already led to substantially higher rates of bleeding in RE-ALIGN, making the higher doses required to achieve these serum concentrations of dabigatran prohibitively dangerous, and ruling out dabigatran as an effective anticoagulant in patients with mechanical heart valves. The greater anticoagulant efficacy of VKAs is partly related to their inhibition of multiple factors in both the extrinsic and intrinsic coagulation pathways and also to upstream inhibition. Each reaction in the coagulation cascade is repeated multiple times, generating many molecules of downstream factors for each upstream factor—each molecule of factor Xa, for example, generates ~1000 molecules of thrombin.[43] The Xa inhibitors, by acting upstream of thrombin, may therefore inhibit thrombin generation on mechanical heart valves at more reasonable serum concentrations. However, *in vitro* studies have suggested that apixaban and rivaroxaban doses >20 mg twice daily may be necessary to achieve anti-thrombin activity comparable to VKA dose-adjusted to achieve INR between 2.0 and 3.5.[44]

The last reason suggested for dabigatran's failure in RE-ALIGN is the choice and position of valves employed. RE-ALIGN allowed any mechanical bileaflet valve in the mitral or aortic position; however, mechanical valves in the mitral position are at substantially higher thromboembolic risk than mechanical valves in the aortic position. Moreover, some valves are more thrombogenic than others. The On-X valve, in particular, does not have any highly thrombogenic silicon in its construction and has a number of other features intended to reduce transvalvular gradients and increase laminar flow across the valve, thereby reducing thrombogenicity.[45] In the PROACT trial, which randomized patients with an On-X valve in the aortic position to high-intensity anticoagulation with VKA (INR 2.5-3.5) vs. lower intensity anticoagulation with VKA (INR 1.5-2.0), rates of embolic stroke and valve thrombosis were similar in both arms, with lower rates of bleeding in the lower intensity anticoagulation arm.[46]

Two randomized controlled trials testing the safety and efficacy of NOACs in patients with mechanical prosthetic valves—one completed, one ongoing—have used some or all of these major lessons from RE-ALIGN: avoid enrolling patients in the immediate post-operative period, use Xa inhibitors rather than dabigatran, and enroll patients with less thrombogenic valves in the aortic position. The RIWA trial (Rivaroxaban vs. Warfarin in Patients with Mechanical Heart Valves), which enrolled 44 patients with mechanical prosthetic heart valves and randomized them to rivaroxaban 15 mg twice daily (n = 23) or dose-adjusted VKA (n = 21), had similar instances of embolic events and bleeding between arms but was small and underpowered.[47] The ongoing PROACT-Xa trial employs all of the lessons learned from RE-ALIGN and should definitively answer the question of whether NOACs are safe and effective for the prevention of thrombotic complications in patients with mechanical prosthetic valves under optimal conditions. PROACT-Xa will enroll 1000 patients who underwent implantation of an On-X mechanical prosthetic valve in the aortic position >3 months prior, and randomize them to apixaban 5 mg twice daily or VKA dose-adjusted to achieve an INR 2.0-3.0.[48] All patients will be followed for at least 2 years for the incidence of the primary outcome, a composite of valve thrombosis or valve-related thromboembolic event. The trial will have >90% power to assess the non-inferiority of apixaban vs. VKA for this endpoint. While this trial is ongoing, current ESC and ACC/AHA guidelines recommend against the use of NOACs in patients with mechanical valve prostheses (Class III, LOE B).[31,32]

In patients with moderate or severe mitral stenosis, no randomized controlled trials of NOACs have been completed. The prevalence of mitral stenosis is low in the USA and Europe, but affects 33 million people worldwide, mostly in low- and middle-income countries.[49,50] Patients with AF and rheumatic heart disease are younger than those with AF in the absence of rheumatic heart disease, have fewer cardiovascular risk factors, and so may be at lower risk of stroke, despite the presence of severe mitral stenosis. In the REMEDY (Global Rheumatic Heart Disease) Registry, which enrolled 3343 patients with rheumatic heart disease from 14 countries in Africa and Asia, median age was 28, 21% had AF, and 33% had congestive heart

failure, most of whom had New York Heart Association Class III or IV symptoms.[51] Among patients with AF or mechanical valves, 77% were treated with VKAs, but 10% of these patients had no INR checks in the 6 months prior to enrolment and just 29% had INR within the therapeutic range, indicating a need for alternatives to VKAs in patients from low- and middle-income countries with AF and mitral stenosis. Despite this under-treatment, just 2.4% of patients with an indication for anticoagulation had a stroke over 2-year follow-up; however, 17% of patients died over the same time period, highlighting the challenges with competing risks in this population.[52]

Though there is no data from randomized controlled trials of NOACs in mitral stenosis, there is substantial clinical experience. In a nationwide, retrospective observational study of 7357 patients with AF and mitral stenosis treated with OAC between 2008 and 2017 in South Korea, 1917 (26.1%) were treated with a NOAC (367 dabigatran, 472 rivaroxaban, 192 apixaban, 84 edoxaban).[53] These patients were compared with VKA-treated patients using propensity score methods. Over a mean follow-up duration of 27 months, NOAC-treated patients had a stroke or systemic embolism rate of 2.22%/year compared with 4.19%/year in the VKA group [hazard ratio (HR) 0.28, 95% CI 0.18–0.45]. NOAC-treated patients also had a lower risk of intracranial haemorrhage and all-cause death. However, this study is limited by its retrospective nature, and particularly by an inability to ascertain the severity of mitral stenosis in administrative data and control for it in analyses, which may have biased the results.

There are two ongoing randomized clinical trials examining the role of NOACs in patients with rheumatic mitral stenosis. DAVID-MS (DAbigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis) will enroll 686 patients in Hong Kong or China with moderate or severe mitral stenosis and randomize them to dabigatran (110 or 150 mg twice daily) or VKA, dose-adjusted to achieve an INR of 2–3.[54] The trial is designed to evaluate the non-inferiority of dabigatran, as compared with VKA, in the prevention of the primary outcome of stroke or systemic embolism. The larger INVICTUS (INVestIgation of rheumatiC AF Treatment Using VKAs, rivaroxaban or aspirin Studies) programme will include both an observational registry of 17 000 patients with rheumatic mitral stenosis and AF as well as a 4500-patient randomized clinical trial.[50] Patients will be enrolled from sites in 23 countries in Africa, Asia, and South America. In the clinical trial, patients with AF, rheumatic mitral stenosis, and either CHA_2DS_2VASc score ≥ 2, mitral stenosis with mitral valve area (MVA) ≤ 2 cm^2, or the presence of left atrial spontaneous echo contrast or thrombus will be randomized to either VKA (dose adjusted to an INR of 2–3) or rivaroxaban 20 mg daily (15 mg daily in patients with reduced renal function). The study's primary endpoint is the composite of stroke and systemic embolism, for which the primary analysis will assess the non-inferiority of rivaroxaban vs. VKA; the primary safety endpoint is ISTH major bleeding. While this study is ongoing, ESC guidelines recommend against the use of NOACs in patients with AF and moderate to severe mitral stenosis (Class III, LOE C); ACC/AHA guidelines recommend use of a VKA without mentioning NOACs.[31,32]

Efficacy and safety of NOACs in patients with bioprosthetic valves

A small proportion of patients enrolled in pivotal trials of NOACs vs. VKAs in patients with AF had prior bioprosthetic valves: 191 patients in ENGAGE-AF (0.9% of the trial's total population) and 120 patients in ARISTOTLE (0.7%).[29,30] In these relatively small samples, efficacy and safety outcomes in patients with bioprosthetic heart valves were similar to the full trial population.

There have subsequently been two dedicated clinical trials in patients with AF undergoing surgical mitral or aortic valve replacement with a bioprosthetic valve. In a Brazilian study that enrolled 27 patients and terminated early due to low enrolment, dabigatran appeared to be similar to VKA following bioprosthetic mitral and/or aortic valve replacement in AF patients.[55] More recently, the RIVER (Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation) trial demonstrated non-inferiority of a rivaroxaban-based strategy compared with a traditional VKA strategy among AF patients with bioprosthetic mitral valve implanted at least 48 h prior to enrolment.[56] In a total of 1005 patients randomized to rivaroxaban compared with VKA, rates of cardiovascular death (3.4% vs. 5.1%, HR 0.65, 95% CI 0.35–1.20), stroke (0.6% vs. 2.4%, HR 0.25, 95% CI 0.07–0.88), and major bleeding (1.4% vs. 2.6%, HR 0.54, 95% CI 0.21–1.35) were all numerically lower in the rivaroxaban group compared with the VKA group, though the trial was powered for non-inferiority. In a meta-analysis combining data from RIVER, the Brazilian studies, and subgroup analyses from ENGAGE-AF and ARISTOTLE, there was no significant difference in the rates of major bleeding (HR 0.61, 95% CI 0.34–1.09) or stroke or systemic embolism (HR 0.47, 95% CI 0.17–1.29) for NOAC vs. VKA, but the point estimates favoured NOAC.[57]

As such, current ESC/EACTS guidelines recommend single-agent OAC (Class I, LOE C) for patients with surgical bioprosthetic valves and an indication for OAC, with a Class IIa recommendation to consider NOAC after 3 months in patients with AF (LOE B).[6,31] Based in large part on the RIVER Trial, NOAC can be considered over VKA in AF patients undergoing bioprosthetic mitral valve replacement (Class IIb).[31] ACC/AHA guidelines recommend either NOAC or VKA in patients with a bioprosthetic valve implanted ≥ 3 months prior (Class I, LOE A), and VKA in patients with new-onset AF < 3 months after bioprosthetic valve implantation (Class IIa, LOE B).[32] Interestingly, in the subgroup of patients enrolled within 3 months of bioprosthetic mitral valve implantation in RIVER ($n = 189$), the incidence of the composite of death, major cardiovascular events, or major bleeding was significantly lower with rivaroxaban than with VKA (6.4% with rivaroxaban vs. 18.9% with VKA). Though this is a small and underpowered subgroup, it may be reasonable to use rivaroxaban > 48 h after bioprosthetic mitral valve implantation, and further study is needed.[56]

There have also been a number of trials comparing NOACs vs. VKAs in patients undergoing transcatheter aortic valve implantation (TAVI), both with and without another indication for anticoagulation. These trials were preceded

by observational studies, which largely demonstrated lower bleeding with NOACs vs. VKAs. In a single-centre study of 272 patients with AF following TAVI, apixaban-treated patients had numerically lower incidences of life-threatening bleeding and stroke at 30 days, and a significantly lower incidence of the composite of mortality, stroke, life-threatening bleeding, coronary obstruction, major valvular complications, and valve dysfunction requiring re-intervention.[58] Similarly, in an analysis of the multi-centre France-TAVI and FRANCE-2 registries, 8962 of ~25 000 patients undergoing TAVI from 2010 to 2017 had an indication for OAC, of whom 2180 (24%) were treated with NOACs (53% apixaban, 35% rivaroxaban, and 12% dabigatran).[59] In a propensity-matched analysis, NOAC-treated patients had a lower risk of 3-year mortality and major bleeding with no significant difference in the risk of ischaemic stroke or acute coronary syndrome. By contrast, in a propensity-matched analysis of 962 patients who underwent TAVI at four European centres and were discharged on OAC, the composite of all-cause death, myocardial infarction (MI), or cerebrovascular event at 1 year was higher with NOACs vs. VKAs, with a comparable rates of bleeding between the groups.[60]

Though results of these observational studies have been discordant, there have been two recently presented randomized controlled trials in patients undergoing TAVI with an indication for anticoagulation. In ATLANTIS (Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischaemic and Hemorrhagic Events after TransAortic Valve Implantation for Aortic Stenosis) stratum 1, 451 patients undergoing TAVI with an indication for anticoagulation (mostly AF) were randomized to apixaban 5 mg twice daily or standard of care (VKA in 89%, antiplatelet therapy in the remainder).[61] The incidence of the primary outcome (a composite of death, stroke, MI, systemic embolism, or intracardiac/valve thrombosis) was similar in patients assigned to apixaban and usual care (HR 1.02, 95% CI 0.68–1.05), with similar rates of BARC ≥3 bleeding (HR 0.92, 95% CI 0.52–1.60). ATLANTIS enrolled patients both with and without an indication for anticoagulation, and the analysis of patients with an indication for anticoagulation was *post hoc* and not adequately powered to detect a difference between groups. By contrast, ENVISAGE-TAVI AF was a dedicated trial of edoxaban 60 mg daily vs. VKA (dose-adjusted to achieve INR 2.0–3.0) in 1426 patients with AF undergoing TAVI. Patients randomized to edoxaban had a similar rate of the trial's primary outcome, a composite of death, MI, ischaemic stroke, systemic embolism, valve thrombosis, or major bleeding (HR 1.05, 95% CI 0.85–1.31), but a higher rate of major bleeding (HR 1.40, 95% CI 1.03–1.91), with the difference driven by a higher rate of gastrointestinal bleeding with edoxaban.[62] The increase in major bleeding was primarily seen in patients taking high-dose edoxaban (60 mg daily) or concomitant antiplatelet therapy. The results of ENVISAGE TAVI are in contrast to ENGAGE AF, which found a significant reduction in major bleeding in patients randomized to edoxaban compared with VKA but is consistent with the higher rate of gastrointestinal bleeding seen in the ENGAGE AF edoxaban group.[4,62] However, ENVISAGE TAVI was nearly 15-fold smaller than ENGAGE AF, and it is possible that its

contradictory results with respect to major bleeding represent the play of chance. More data on the role of NOACs vs. VKAs in patients with AF undergoing TAVI are needed.

For patients undergoing TAVI with an indication for OAC, the role of clopidogrel in addition to OAC was clarified in the POPular TAVI study.[63] In cohort B of the study, 326 patients with an indication for anticoagulation were randomized to OAC alone vs. OAC + clopidogrel for 3 months. Although type of OAC was not specified by the study, ~30% of patients were treated with NOAC. The study found that OAC alone resulted in fewer bleeding events without a concomitant increase in ischaemic events, suggesting single-agent OAC may be sufficient in the management of these patients. The ongoing AVATAR (Anticoagulation Alone vs. Anticoagulation and Aspirin Following Transcatheter Aortic Valve Interventions) trial (NCT02735902), which will randomize patients undergoing TAVI who have an indication for OAC to OAC vs. OAC + aspirin may shed further light on the optimal antithrombotic strategy in this patient population.

In addition to these studies in patients with an indication for anticoagulation, other studies have evaluated NOACs in patients undergoing TAVI who do not have another indication for anticoagulation. These studies were initiated after observational studies in patients undergoing TAVI and surgical aortic valve replacement with bioprosthetic valves raised concerns about subclinical leaflet thrombosis,[64] which has been associated with need for valve replacement over 10-year follow-up.[65] The GALILEO (Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) study randomized patients after successful TAVI to a rivaroxaban-based strategy (rivaroxaban 10 mg daily and ASA daily for 90 days, followed by rivaroxaban 10 mg daily) with a traditional antiplatelet-based regimen (clopidogrel 75 mg daily and ASA for 90 days, followed by ASA only). Though the rivaroxaban-based strategy reduced the rate of subclinical leaflet thrombosis (rivaroxaban 2.1%, antiplatelet 10.9%; absolute risk difference 8.8%, 95% CI 1.9–16.5%), it also increased the rates of major bleeding (rivaroxaban 4.3 per 100 patient-years, antiplatelet 2.8 per 100 patient-years; HR 1.50, 95% CI 0.95–2.37) and death or thromboembolism (rivaroxaban 9.8 per 100 patient-years, antiplatelet 7.2 per 100 patient-years HR 1.35, 95% CI 1.01–1.81), and the study was stopped prematurely.[66,67] Similarly, in ATLANTIS stratum 2 (no indication for anticoagulation), apixaban 5 mg twice daily as compared with standard of care (92% antiplatelet therapy alone), reduced the risk of clinical or subclinical valve thrombosis (apixaban 1.1%, antiplatelet 6.1%; HR 0.19, 95% CI 0.08–0.47), but increased the risk of the composite of death, stroke, or systemic embolism (apixaban 9.5%, antiplatelet 6.3%; HR 1.56, 95% CI 1.01–2.43), with a similar risk of major bleeding (apixaban 7.8%, antiplatelet 7.3%; HR 1.09, 95% CI 0.69–1.69).[61]

As such, contemporary practice regarding the optimal antithrombotic strategy for patients undergoing TAVI is defined by whether the patient has prior indication for OAC. In patients without an indication for OAC, ESC guidelines recommend against the routine use of OAC (NOACs or VKA)
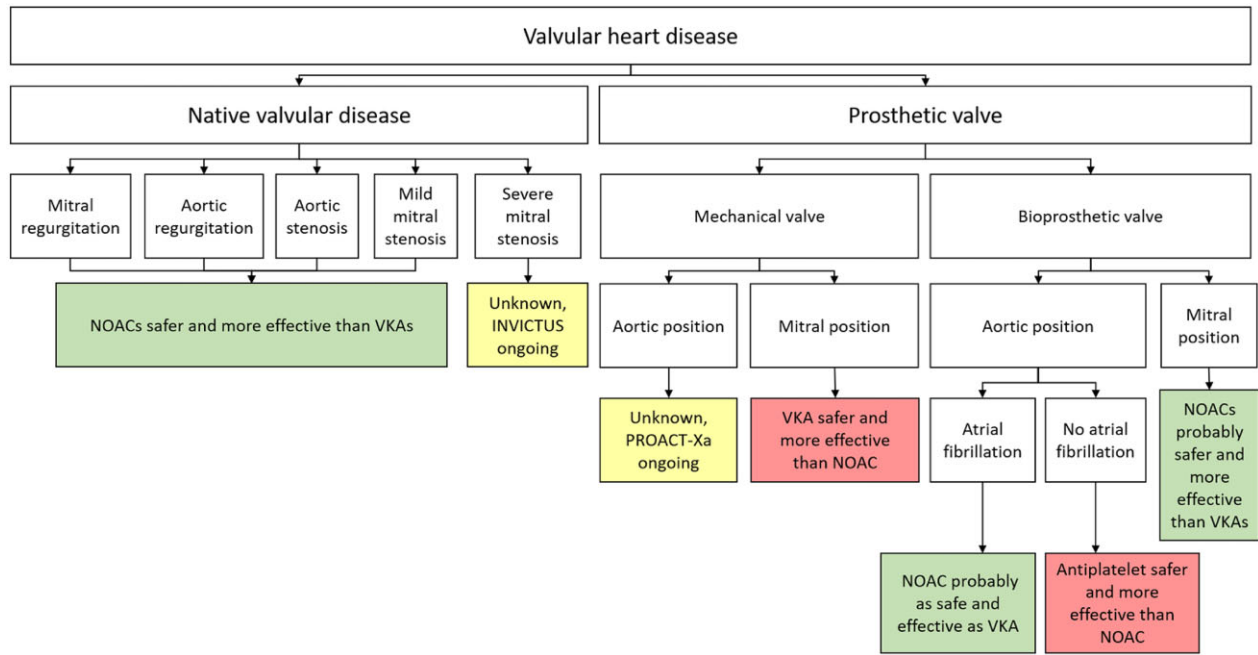
Figure 2 Recommendations for use of NOACs in patients with valvular heart disease. Flowchart shows valvular heart disease conditions in which the weight of evidence favours NOACs (green), does not favour NOACs (red), or is uncertain (yellow), with major ongoing trials highlighted for areas in which evidence is uncertain.

to prevent subclinical valve thrombosis (Class III, LOE B), based on GALILEO and ATLANTIS stratum 2, though OAC should be considered in patients who develop subclinical leaflet thrombosis (Class IIa, LOE B).[31] ACC/AHA guidelines recommend against routine use of rivaroxaban, in particular, to prevent subclinical valve thrombosis (Class III, LOE B), and specifically recommend VKAs in patients who develop valve thrombosis (Class IIa, LOE B).[32] For patients with an indication for OAC, lifelong OAC is recommended (Class I, LOE B) with no preference expressed for NOAC or VKA, consistent with the results of ENVISAGE-TAVI AF and ATLANTIS stratum 1.[31,32]

Summary and recommendations

Though patients with moderate or severe mitral stenosis and mechanical mitral valves were excluded from the pivotal trials that demonstrated the benefit of NOACs vs. VKAs, a number of trials have evaluated the safety and efficacy of NOACs in patients with valvular heart disease (*Table 4*). Patients with AF and aortic stenosis, aortic regurgitation, mitral regurgitation, and mild mitral stenosis were included in the pivotal trials comparing NOACs vs. VKAs, and NOACs should be used in preference to VKAs in these patients just as they would be used in patients without any valvular heart disease (*Figure 2*). Patients with AF and surgical bioprosthetic valves were also included in the pivotal NOAC trials, and the RIVER trial has subsequently confirmed the safety and efficacy of rivaroxaban in this population. In patients undergoing TAVI without AF or another indication for anticoagulation, NOACs reduce the risk of subclinical leaflet thrombosis, but increase the risk of major bleeding and thromboembolic events compared

with antiplatelet therapy and should be avoided. In patients with AF who undergo TAVI, outcomes appear to be similar for NOACs and VKAs, though more data are needed. In patients with moderate or severe mitral stenosis, no trials have evaluated the safety or efficacy of NOACs vs. VKA, though a large observational study suggests benefit, and two trials are ongoing. In patients with mechanical mitral valves, dabigatran increases the risk of thromboembolic events and major bleeding as compared with VKA, and NOACs are contraindicated in all patients with mechanical valves. However, the safety and efficacy of other NOACs in this population, and the safety and efficacy of NOACs in patients with mechanical valves in the aortic position are unknown, and the randomized PROACT-Xa trial is ongoing. Despite their original approval only for patients with 'nonvalvular AF', NOACs can be a good option for a large and growing number of patients with valvular heart disease.

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References

1. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139-1151.

2. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; the ROCKET AF Steering Committee. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883-891.

3. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FWA, Zhu J, Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981-992.

4. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093-2104.

5. Fanaroff AC, Califf RM, Windecker S, Smith SC, Lopes RD. Levels of evidence supporting American College of Cardiology/American Heart Association and European Society of Cardiology Guidelines, 2008-2018. *JAMA* 2019;**321**:1069-1080.

6. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan G-A, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau J-P, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL, Kirchhof P, Kühne M, Aboyans V, Ahlsson A, Balsam P; ESC Scientific Document Group. 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* 2021;**42**:373-498.

7. Wright IS, Foley WT. Use of anticoagulants in the treatment of heart disease: with special reference to coronary thrombosis, rheumatic heart disease with thromboembolic complications and subacute bacterial endocarditis. *Am J Med* 1947;**3**:718-739.

8. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;**22**:983-988.

9. Kane WC, Aronson SM. Cardiac disorders predisposing to embolic stroke. *Stroke Am Heart Assoc* 1970;**1**:164-172.

10. Szekely P. Systemic embolism and anticoagulant prophylaxis in rheumatic heart disease. *BMJ* 1964;**1**:1209-1212.

11. Callaghan JC. Total replacement of the mitral valve: results of insertion of a Starr-Edwards valve in five patients. *CMAJ* 1963;**88**:869-875.

12. Petersen P, Godtfredsen J, Boysen G, Andersen E, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK Study. *Lancet* 1989;**1**:175-179.

13. Singer DE, Hughes RA, Gress DR, Sheehan MA, Oertel LB, Maraventano SW, Blewett DR, Rosner B, Kistler JP; Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990;**323**:1505-1511.

14. Stroke prevention in atrial fibrillation study. Final results. *Circulation* 1991;**84**:527-539.

15. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian atrial fibrillation anticoagulation (CAFA) study. *J Am Coll Cardiol* 1991;**18**:349-355.

16. Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC, Krause-Steinrauf H, Kurtzke JF, Nazarian SM, Radford MJ. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med* 1992;**327**:1406-1412.

17. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet* 1993;**342**:1255-1262.

18. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**:857-867.

19. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;**64**:e1-e76.

20. Guimarães PO, Lopes RD, Alexander JH, Thomas L, Hellkamp AS, Hijazi Z, Hylek EM, Gersh BJ, Garcia DA, Verheugt FWA, Hanna M, Flaker G, Vinereanu D, Granger CB. International normalized ratio control and subsequent clinical outcomes in patients with atrial fibrillation using warfarin. *J Thromb Thrombolysis* 2019;**48**:27-34.

21. Lopes RD, Guimarães PO, Kolls BJ, Wojdyla DM, Bushnell CD, Hanna M, Easton JD, Thomas L, Wallentin L, Al-Khatib SM, Held C, Gabriel Melo de Barros E Silva P, Alexander JH, Granger CB, Diener H-C. Intracranial hemorrhage in patients with atrial fibrillation receiving anticoagulation therapy. *Blood* 2017;**129**:2980-2987.

22. Rasmussen MA, Skov J, Bladbjerg E-M, Sidelmann JJ, Vamosi M, Jespersen J. Multivariate analysis of the relation between diet and warfarin dose. *Eur J Clin Pharmacol* 2012;**68**:321-328.

23. Fanaroff AC, Ohman EM. Non-vitamin K antagonist oral anticoagulants in the treatment of atrial fibrillation. *Annu Rev Med* 2019;**70**:61-75.

24. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012;**33**:2719-2747.

25. Giancaterino S, Hsu JC. Valvular atrial fibrillation. *J Am Coll Cardiol* 2019;**73**:3360-3361.

26. Molteni M, Polo Friz H, Primitz L, Marano G, Boracchi P, Cimminiello C. The definition of valvular and non-valvular atrial fibrillation: results of a physicians' survey. *Europace* 2014;**16**:1720-1725.

27. Ezekowitz MD, Nagarakanti R, Noack H, Brueckmann M, Litherland C, Jacobs M, Clemens A, Reilly PA, Connolly SJ, Yusuf S, Wallentin L. Comparison of dabigatran versus warfarin in patients with atrial fibrillation and valvular heart disease: the RE-LY trial. *Circulation* 2016;**134**:589-598.

28. Breithardt G, Baumgartner H, Berkowitz SD, Hellkamp AS, Piccini JP, Stevens SR, Lokhnygina Y, Patel MR, Halperin JL, Singer DE, Hankey GJ, Hacke W, Becker RC, Nessel CC, Mahaffey KW, Fox KAA, Califf RM; ROCKET AF Steering Committee & Investigators. Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. *Eur Heart J* 2014;**35**:3377-3385.

29. Avezum A, Lopes RD, Schulte PJ, Lanas F, Gersh BJ, Hanna M, Pais P, Erol C, Diaz R, Bahit MC, Bartunek J, De Caterina R, Goto S, Ruzyllo W, Zhu J, Granger CB, Alexander JH. Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease. *Circulation* 2015;**132**:624-632.

30. De Caterina R, Renda G, Carnicelli AP, Nordio F, Trevisan M, Mercuri MF, Ruff CT, Antman EM, Braunwald E, Giugliano RP. Valvular heart disease patients on edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. *J Am Coll Cardiol* 2017;**69**:1372-1382.

31. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Gilard M, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, Wojakowski W; ESC/EACTS Scientific Document Group. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2021;ehab395. doi: 10.1093/eurheartj/ehab395.

32. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM, Thompson A, Toly C. 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. *Circ Am Heart Assoc* 2021;**143**:e72-e227.

33. Sun JCJ, Davidson MJ, Lamy A, Eikelboom JW. Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends. *Lancet* 2009;**374**:565-576.

34. Maegdefessel L, Linde T, Krapiec F, Hamilton K, Steinseifer U, Ryn JV, Raaz U, Buerke M, Werdan K, Schlitt A. In vitro comparison of dabigatran, unfractionated heparin, and low-molecular-weight heparin in preventing thrombus formation on mechanical heart valves. *Thromb Res* 2010;**126**:e196-e200.

35. McKellar SH, Abel S, Camp CL, Suri RM, Ereth MH, Schaff HV. Effectiveness of dabigatran etexilate for thromboprophylaxis of mechanical heart valves. *J Thorac Cardiovasc Surg* 2011;**141**:1410-1416.

36. Schomburg JL, Medina EM, Lahti MT, Bianco RW. Dabigatran versus warfarin after mechanical mitral valve replacement in the swine model. *J Invest Surg* 2012;**25**:150-155.

37. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, Blatchford J, Devenny K, Friedman J, Guiver K, Harper R, Khder Y, Lobmeyer MT, Maas H, Voigt J-U, Simoons ML, Van de Werf F; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013;**369**:1206-1214.

38. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Munoz D, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL; ESC/EACTS Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739-2791.

39. Aimo A, Giugliano RP, De Caterina R. Non-vitamin K antagonist oral anticoagulants for mechanical heart valves. *Circ Am Heart Assoc* 2018;**138**:1356-1365.

40. Noble S, Asgar A, Cartier R, Virmani R, Bonan R. Anatomo-pathological analysis after CoreValve Revalving system implantation. *Eurointervention* 2009;**5**:78-85.

41. Jaffer IH, Stafford AR, Fredenburgh JC, Whitlock RP, Chan NC, Weitz JI. Dabigatran is less effective than warfarin at attenuating mechanical heart valve-induced thrombin generation. *J Am Heart Assoc* 2015;**4**:e002322.

42. Speirs A, Deakin A. Dabigatran in patients with mechanical heart valves. *N Engl J Med* 2014;**370**:382.

43. Mann KG, Whelihan MF, Butenas S, Orfeo T. Citrate anticoagulation and the dynamics of thrombin generation. *J Thromb Haemost* 2007;**5**:2055-2061.

44. Jaffer IH, Fredenburgh JC, Stafford A, Whitlock RP, Weitz JI. Rivaroxaban and dabigatran for suppression of mechanical heart valve-induced thrombin generation. *Ann Thorac Surg* 2020;**110**:582-590.

45. Whitlock RP, Bhatt DL, Eikelboom JW. Reduced-intensity anticoagulation for mechanical aortic valve prostheses. *J Am Coll Cardiol* 2018;**71**:2727-2730.

46. Puskas JD, Gerdisch M, Nichols D, Fermin L, Rhenman B, Kapoor D, Copeland J, Quinn R, Hughes GC, Azar H, McGrath M, Wait M, Kong B, Martin T, Douville EC, Meyer S, Ye J, Jamieson WRE, Landvater L, Hagberg R, Trotter T, Armitage J, Askew J, Accola K, Levy P, Duncan D, Yanagawa B, Ely J, Graeve A; PROACT Investigators. Anticoagulation and antiplatelet strategies after on-X mechanical aortic valve replacement. *J Am Coll Cardiol* 2018;**71**:2717-2726.

47. Duraes AR, Souza Lima Bitar YD, Schonhofen IS, Travassos KSO, Pereira LV, Filho JAL, Neto MG, Junior RA, Roever L. Rivaroxaban versus warfarin in patients with mechanical heart valves: open-label, proof-of-concept trial-the RIWA study. *Am J Cardiovasc Drugs* 2021;**21**:363-371.

48. Jawitz OK, Wang TY, Lopes RD, Chavez A, Boyer B, Kim H, Anstrom KJ, Becker RC, Blackstone E, Ruel M, Thourani VH, Puskas JD, Gerdisch MW, Johnston D, Capps S, Alexander JH, Svensson LG. Rationale and design of PROACT Xa: a randomized, multicenter, open-label, clinical trial to evaluate the efficacy and safety of apixaban versus warfarin in patients with a mechanical On-X Aortic Heart Valve. *Am Heart J* 2020;**227**:91-99.

49. Chandrashekhar Y, Westaby S, Narula J. Mitral stenosis. *Lancet* 2009;**374**:1271-1283.

50. Karthikeyan G, Connolly SJ, Ntsekhe M, Benz A, Rangarajan S, Lewis G, Yun Y, Sharma SK, Maklady F, Elghamrawy AE, Kazmi K, Cabral TTJ, Dayi H, Changsheng M, Gitura BM, Avezum A, Zuhlke L, Lwabi P, Haileamlak A, Ogah O, Chillo P, Paniagua M, ElSayed A, Dans A, Gondwe-Chunda L, Molefe-Baikai OJ, Gonzalez-Hermosillo JA, Hakim J, Damasceno A, Kamanzi ER, Musuku J, Davletov K, Connolly K, Mayosi BM, Yusuf S; INVICTUS Investigators. The INVICTUS rheumatic heart disease research program: rationale, design and baseline characteristics of a randomized trial of rivaroxaban compared to vitamin K antagonists in rheumatic valvular disease and atrial fibrillation. *Am Heart J* 2020;**225**:69-77.

51. Zühlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B, Mauff K, Islam S, Joachim A, Daniels R, Francis V, Ogendo S, Gitura B, Mondo C, Okello E, Lwabi P, Al-Kebsi MM, Hugo-Hamman C, Sheta SS, Haileamlak A, Daniel W, Goshu DY, Abdissa SG, Desta AG, Shasho BA, Begna DM, ElSayed A, Ibrahim AS, Musuku J, Bode-Thomas F, Okeahialam BN, Ige O, Sutton C, Misra R, Abul Fadl A, Kennedy N, Damasceno A, Sani M, Ogah OS, Olunuga T, Elhassan HHM, Mocumbi AO, Adeoye AM, Mntla P, Ojji D, Mucumbitsi J, Teo K, Yusuf S, Mayosi BM. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J* 2015;**36**:1115-1122.

52. Zühlke L, Karthikeyan G, Engel ME, Rangarajan S, Mackie P, Cupido-Katya Mauff B, Islam S, Daniels R, Francis V, Ogendo S, Gitura B, Mondo C, Okello E, Lwabi P, Al-Kebsi MM, Hugo-Hamman C, Sheta SS, Haileamlak A, Daniel W, Goshu DY, Abdissa SG, Desta AG, Shasho BA, Begna DM, ElSayed A, Ibrahim AS, Musuku J, Bode-Thomas F, Yilgwan CC, Amusa GA, Ige O, Okeahialam B, Sutton C, Misra R, Abul Fadl A, Kennedy N, Damasceno A, Sani MU, Ogah OS, Elhassan TOHM, Mocumbi AO, Adeoye AM, Mntla P, Ojji D, Mucumbitsi J, Teo K, Yusuf S, Mayosi BM. Clinical outcomes in 3343 children and adults with rheumatic heart disease from 14 low- and middle-income countries. *Circ Am Heart Assoc* 2016;**134**:1456-1466.

53. Kim JY, Kim S-H, Myong J-P, Kim YR, Kim T-S, Kim J-H, Jang S-W, Oh Y-S, Lee MY, Rho T-H. Outcomes of direct oral anticoagulants in patients with mitral stenosis. *J Am Coll Cardiol* 2019;**73**:1123-1131.

54. Zhou M, Chan EW, Hai JJ, Wong CK, Lau YM, Huang D, Lam CC, Tam CCF, Wong YTA, Yung SYA, Chan KWK, Feng Y, Tan N, Chen J-Y, Yung CY, Lee KL, Choi CW, Lam H, Ng A, Fan K, Jim MH, Yiu KH, Yan BP, Siu CW. Protocol, rationale and design of DAbigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis (DAVID-MS): a randomised, open-label study. *BMJ Open* 2020;**10**:e038194.

55. Durães AR, Souza Roriz PD, Almeida Nunes BD, Albuquerque FPE, Bulhões FD, Souza Fernandes AD, Aras R. Dabigatran versus warfarin after bioprosthesis valve replacement for the management of atrial fibrillation postoperatively: DAWA pilot study. *Drugs R D* 2016;**16**:149-154.

56. Guimarães HP, Lopes RD, de Barros e Silva PGM, Liporace IL, Sampaio RO, Tarasoutchi F, Hoffmann-Filho CR, de Lemos Soares Patriota R, Leiria TLL, Lamprea D, Precoma DB, Atik FA, Silveira FS, Farias FR, Barreto DO, Almeida AP, Zilli AC, de Souza Neto JD, Cavalcante MA, Figueira FAMS, Kojima FCS, Damiani L, Santos RHN, Valeis N, Campos VB, Saraiva JFK, Fonseca FH, Pinto IM, Magalhães CC, Ferreira JFM, Alexander JH, Pavanello R, Cavalcanti AB, Berwanger O. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. *N Engl J Med* 2020;**383**:2117-2126.

57. Yokoyama Y, Briasoulis A, Ueyama H, Mori M, Iwagami M, Misumida N, Takagi H, Kuno T. Direct oral anticoagulants versus vitamin K antagonists in patients with atrial fibrillation and bioprosthetic valves: a meta-analysis. *J Thorac Cardiovasc Surg* 2021. doi: 10.1016/j.jtcvs.2021.07.034.

58. Seeger J, Gonska B, Rodewald C, Rottbauer W, Wöhrle J. Apixaban in patients with atrial fibrillation after transfemoral aortic valve replacement. *JACC Cardiovasc Interv* 2017;**10**:66-74.

59. Didier R, Lhermusier T, Auffret V, Eltchaninoff H, Le Breton H, Cayla G, Commeau P, Collet JP, Cuisset T, Dumonteil N, Verhoye JP, Beurtheret S, Lefèvre T, Teiger E, Carrié D, Himbert D, Albat B, Cribier A, Sudre A, Blanchard D, Bar O, Rioufol G, Collet F, Houel R, Labrousse L, Meneveau N, Ghostine S, Manigold T, Guyon P, Delepine S, Favereau X, Souteyrand G, Ohlmann P, Doisy V, Beygui F, Gommeaux A, Claudel J-P, Bourlon F, Bertrand B, Iung B, Gilard M.

TAVR patients requiring anticoagulation: direct oral anticoagulant or vitamin K antagonist? *JACC Cardiovasc Interv* 2021;**14**:1704–1713.

60. Jochheim D, Barbanti M, Capretti G, Stefanini GG, Hapfelmeier A, Zadrozny M, Baquet M, Fischer J, Theiss H, Todaro D, Chieffo A, Presbitero P, Colombo A, Massberg S, Tamburino C, Mehilli J. Oral anticoagulant type and outcomes after transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2019;**12**:1566–1576.

61. Collet J-P, Van Belle E, Thiele H, Portal J-J, Vicaut E, Montalescot G. Anti-thrombotic strategy to lower all cardiovascular and neurologic ischemic and hemorrhagic events after TransAortic Valve Implantation for Aortic Stenosis: a randomized, open-label, phase 3 trial [Conference presentation]. American College of Cardiology Scientific Sessions 2021, Virtual. http://clinicaltrialresults.org/wp-content/uploads/2021/08/Collet_ATLANTIS.pdf (22 December 2021).

62. Van Mieghem NM, Unverdorben M, Hengstenberg C, Möllmann H, Mehran R, López-Otero D, Nombela-Franco L, Moreno R, Nordbeck P, Thiele H, Lang I, Zamorano JL, Shawl F, Yamamoto M, Watanabe Y, Hayashida K, Hambrecht R, Meincke F, Vranckx P, Jin J, Boersma E, Rodés-Cabau J, Ohlmann P, Capranzano P, Kim H-S, Pilgrim T, Anderson R, Baber U, Duggal A, Laeis P, Lanz H, Chen C, Valgimigli M, Veltkamp R, Saito S, Dangas GD. Edoxaban versus vitamin K antagonist for atrial fibrillation after TAVR. *N Engl J Med* 2021;**385**:2150–2160.

63. Nijenhuis VJ, Bennaghmouch N, Kuijk JV, Capodanno D, Berg JT. Antithrombotic treatment in patients undergoing transcatheter aortic valve implantation (TAVI). *Thromb Haemost* 2015;**113**:674–685.

64. Chakravarty T, Søndergaard L, Friedman J, De Backer O, Berman D, Kofoed KF, Jilaihawi H, Shiota T, Abramowitz Y, Jørgensen TH, Rami T, Israr S, Fontana G, de Knegt M, Fuchs A, Lyden P, Trento A, Bhatt DL, Leon MB, Makkar RR, Ramzy D, Cheng W, Siegel RJ, Thomson LM, Mangat G, Hariri B, Sawaya FJ, Iversen HK; RESOLVE, SAVORY Investigators. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet* 2017;**389**:2383–2392.

65. Petrescu I, Egbe AC, Ionescu F, Nkomo VT, Greason KL, Pislaru C, Pellikka PA, Connolly HM, Pislaru SV. Long-term outcomes of anticoagulation for bioprosthetic valve thrombosis. *J Am Coll Cardiol* 2020;**75**:857–866.

66. Dangas GD, Tijssen JGP, Wöhrle J, Søndergaard L, Gilard M, Möllmann H, Makkar RR, Herrmann HC, Giustino G, Baldus S, De Backer O, Guimarães AHC, Gullestad L, Kini A, Lewinski D. V, Mack M, Moreno R, Schäfer U, Seeger J, Tchétché D, Thomitzek K, Valgimigli M, Vranckx P, Welsh RC, Wildgoose P, Volkl AA, Zazula A, van Amsterdam RGM, Mehran R, Windecker S; GALILEO Investigators. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med* 2020;**382**:120–129.

67. De Backer O, Dangas GD, Jilaihawi H, Leipsic JA, Terkelsen CJ, Makkar R, Kini AS, Veien KT, Abdel-Wahab M, Kim W-K, Balan P, Van Mieghem N, Mathiassen ON, Jeger RV, Arnold M, Mehran R, Guimarães AHC, Nørgaard BL, Kofoed KF, Blanke P, Windecker S, Søndergaard L; GALILEO-4D Investigators. Reduced leaflet motion after transcatheter aortic-valve replacement. *N Engl J Med* 2020;**382**:130–139.