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EHRA CONSENSUS DOCUMENT

Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE)

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Atrial fibrillation (AF) is a major worldwide public health problem, and AF in association with valvular heart disease (VHD) is also common. However, management strategies for this group of patients have been less informed by randomized trials, which have largely focused on 'non-valvular AF' patients.

Thrombo-embolic risk also varies according to valve lesion and may also be associated with CHA_2DS_2VASc score risk factor components, rather than only the valve disease being causal.

Given marked heterogeneity in the definition of valvular and non-valvular AF and variable management strategies, including non-vitamin K antagonist oral anticoagulants (NOACs) in patients with VHD other than prosthetic heart valves or haemodynamically significant mitral valve disease, there is a need to provide expert recommendations for professionals participating in the care of patients presenting with AF and associated VHD.

To address this topic, a Task Force was convened by the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Thrombosis, with representation from the ESC Working Group on Valvular Heart Disease, Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE) with the remit to comprehensively review the published evidence, and to publish a joint consensus document on the management of patients with AF and associated VHD, with up-to-date consensus recommendations for clinical practice for different forms of VHD.

This consensus document proposes that the term 'valvular AF' is outdated and given that any definition ultimately relates to the *evaluated practical use* of oral anticoagulation (OAC) *type*, we propose a *functional* Evaluated Heartvalves, Rheumatic or Artificial (EHRA) categorization *in relation to the type of OAC use* in patients with AF, as follows: (i) EHRA Type 1 VHD, which refers to AF patients with 'VHD needing therapy with a Vitamin K antagonist (VKA); and (ii) EHRA Type 2 VHD, which refers to AF patients with 'VHD needing therapy with a VKA or a Non-VKA oral anticoagulant (NOAC)', also taking into consideration CHA_2DS_2VASc score risk factor components.

This consensus document also summarizes current developments in the field, and provides general recommendations for the management of these patients based on the principles of evidence-based medicine.

Keywords Atrial fibrillation • Valvular heart disease • Mitral stenosis • Mechanical prosthetic heart valves • Thromboembolism • Stroke • Stroke prevention • Anticoagulation • Vitamin K antagonists • Non-vitamin K antagonist oral anticoagulants • Pregnancy

Preamble and valvular heart disease definition

Atrial fibrillation (AF) is a major public health problem[1] with global prevalence rates (per 1000000 population) in 2010 being 596.2 (95% uncertainty interval (UI), 558.4–636.7) in men and 373.1 (95% UI, 347.9–402.2) in women; the incidence rates increased to 77.5 (95% UI, 65.2–95.4) in men and 59.5 (95% UI, 49.9–74.9) in women.[2] Worldwide, AF in association with valvular heart disease (VHD) is also common, and management strategies for this group of patients have been less addressed by randomized trials. The latter have largely focused on 'non-valvular AF' patients leading to major uncertainties over how to define (and treat) such patients.

There is also an important heterogeneity in the definition of valvular and non-valvular AF.[3] Some physicians assume that any valve disease should be considered as 'valvular' AF. Others consider that only mechanical valve prosthesis and rheumatic mitral stenosis should be defined as 'valvular' AF.

The term valvular AF has been arbitrarily applied and the 2016 ESC guidelines have avoided the term 'valvular AF' and refer simply to 'AF related to hemodynamically significant mitral stenosis or prosthetic mechanical heart valves'.[4] AF clearly leads to an incremental risk for thromboembolism in patients with mitral valve stenosis, but there are limited data for other valvular diseases. Another proposal is to use the acronym MARM-AF as a simple acronym to designate 'Mechanical and Rheumatic Mitral AF' as an alternative to term 'valvular AF' to designate the clinical scenarios for which at the non-vitamin K antagonist oral anticoagulants (NOACs) are not indicated.[5]

For this document we recognize the uncertainty in terminology, and our scope largely relates to AF related to 'hemodynamically significant' rheumatic VHD (ie. severe enough to impact on patient's survival or necessitates an intervention or surgery) or prosthetic mechanical heart valves. Nonetheless, thrombo-embolic (TE) risk varies according to valve lesion and may be associated with CHA_2DS_2VASc score risk factor components, rather than the valve disease per se being causal.[6,7] TE risk may also be influenced not only by type but also the severity of the lesion. For example, the degree of mitral regurgitation may matter when it comes to risk of TE as some studies suggest that mild (Grade 1) mitral regurgitation is associated with a 2.7-fold increased risk of stroke/TE, while severe forms may possibly have a 'protective' effect (HR = 0.45 for stroke and 0.27 for LA stasis.[8] An appropriate definition of 'valvular AF' would need to identify a subgroup of patients with similar pathophysiology of thrombo-embolism, TE risk, and treatment strategies[6,9]; however, this would be challenging given the major heterogeneity of the condition.

This consensus document proposes that the term 'valvular AF' is outdated and given that any definition ultimately relates to the *evaluated practical use* of oral anticoagulation (OAC) *type*, we propose a *functional* EHRA (**E**valuated **H**eartvalves, **R**heumatic or **A**rtificial) categorization *in relation to the type of OAC use* in patients with AF, as follows:

Evaluated Heartvalves, Rheumatic or Artificial (EHRA) Type 1, which refers to AF patients with 'VHD needing therapy with a Vitamin K antagonist (VKA)'

- *Mitral stenosis (moderate-severe, of rheumatic origin)*
- *Mechanical prosthetic valve replacement*

[EHRA Type I VHD is broadly similar to the previously described MARM-AF.]

Evaluated Heartvalves, Rheumatic or Artificial (EHRA) Type 2 VHD, which refers to AF patients with 'VHD needing therapy with a VKA or a NOAC', also taking into consideration CHA_2DS_2VASc score risk factor components:

- *Mitral regurgitation*
- *Mitral valve repair*
- *Aortic stenosis*
- *Aortic regurgitation*
- *Tricuspid regurgitation*
- *Tricuspid stenosis*
- *Pulmonary regurgitation*
- *Pulmonic stenosis*
- *Bioprosthetic valve replacements*
- *Trans-aortic valve intervention (TAVI)*

This classification would have the advantage that it may easily evolve or be updated (type 1 may become type 2 or vice versa) when there are new results. For example, transcatheter mitral valve interventions (TMVI, e.g. to include both MitraClip and Mitral valve replacement) are emerging as a possible therapeutic options,[10] but more data are awaited especially in relation to OAC use.

A recent physicians survey[3] reported marked heterogeneity in the definition of valvular and non-valvular AF and variable management strategies, including NOACs in patients with VHD other than prosthetic heart valves or haemodynamically significant mitral stenosis. Thus, there is a need to provide expert recommendations for professionals participating in the care of patients presenting with AF and associated VHD. These may include rheumatic VHD, mechanical or biological prosthetic valves and percutaneous aortic valve implantation (TAVI), as well as those having undergone mitral valve repair. Whilst hypertrophic cardiomyopathy is sometimes discussed in association with valvular AF, this would not be addressed in this document, given specific guidelines on the management of this condition.[11]

To address this topic, a Task Force was convened by the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Thrombosis, with representation from the ESC Working Group on Valvular Heart Disease, Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE) with the remit to comprehensively review the published evidence, and to publish a joint consensus document on the management of patients with AF and associated VHD, with up-to-date consensus recommendations for clinical practice.

This document summarizes current developments in the field, and provides general recommendations for the management of these patients based on the principles of evidence-based medicine.

Rather than 'valvular AF' a more functional Evaluated Heartvalves, Rheumatic or Artificial (EHRA) categorization in relation to the type of OAC use is recommended in patients with AF, as follows:

(i) EHRA Type 1 VHD, which refers to AF patients with 'VHD needing therapy with a Vitamin K antagonist (VKA); and
(ii) EHRA Type 2 VHD, which refers to AF patients with 'VHD needing therapy with a VKA or a Non-VKA oral anticoagulant (NOAC), also taking into consideration CHA2DS2VASc score risk factor components.

Evidence review

Members of the Task Force were asked to perform a detailed literature review, weigh the strength of evidence for or against a particular treatment (or procedure), and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that might influence the choice of particular tests or therapies are considered, as are frequency of follow-up and cost effectiveness. In controversial areas, or with regard to issues without evidence other than usual clinical practice, a consensus was achieved by agreement of the expert panel after thorough deliberations. This document was prepared by the Task Force with representation from EHRA, HRS, APHRS, and SOLAECE. The document was peer-reviewed by official external reviewers representing EHRA, HRS, APHRS, and SOLAECE.

Consensus statements are evidence-based, and derived primarily from published data. Current systems of ranking level of evidence are becoming complicated in a way that their practical utility might be compromised.[12] We have, therefore, opted for an easier and, perhaps, more user-friendly system of ranking that should allow physicians to easily assess current status of evidence and consequent guidance (*Table 1*).

Thus, a 'green heart' indicates a recommended statement or recommended/indicated treatment (or procedure) and is based on at least one randomized trial, or is supported by large observational evidence that it is beneficial and effective. A 'yellow heart' indicates general agreement and/or scientific evidence favouring a statement or the usefulness/efficacy of a treatment or procedure. A yellow heart may be supported by randomized trials based on small number of patients or not widely applicable. Treatment strategies for which there have been scientific evidence that they are potentially harmful and should not be used are indicated by a 'red heart'.

EHRA grading of consensus statements does not have separate definitions of Level of Evidence. The categorisation used for consensus statements (used in consensus documents) should not be considered as being directly similar to that used for official society guideline recommendations which apply a classification (I–III) and level of evidence (A, B, and C) to recommendations in official guidelines.

Finally, this is a consensus document that includes evidence and expert opinions from several countries. The anticoagulation approaches discussed may, therefore, include drugs that do not have the approval of governmental regulatory agencies in all countries.

Relationships with industry and other conflicts

It is EHRA/ESC policy to sponsor position papers and guidelines without commercial support, and all members volunteered their time. Thus, all members of the writing group as well as reviewers have disclosed any potential conflict of interest in detail, at the end of this document.

Epidemiology of valvular atrial fibrillation and implications for stroke/thrombo-embolism

The reported prevalence of AF varies by geographical region.[2] In Australian, North American and European studies, approximately 1–2% of adults have AF.[13–15] In Asians, the reported prevalence of AF ranges from 0.1–4.0% in the community and 2.8–14% in hospital-based studies.[16]

Nonetheless, robust data on the epidemiology of patients with AF and associated VHD are limited. Examples of available data from some global registries and large trials are reported in Supplementary material online, *Table S1*. In the RE-LY AF Registry which enrolled patients presenting to an emergency department with AF at 164 sites in 46 countries, rheumatic heart disease was present in 2.2% of North American patients, in comparison with 21.5% in Africa and 31.5% in India[7]; interestingly thrombo-embolism rates were related to clinical risk profile, as expressed by $CHADS_2$ score, irrespective of the presence of rheumatic VHD. Detailed data on the geographic distribution of valvular AF are also reported in the Supplementary material online.

Table 1 Scientific rationale of recommendations

Definitions where related to a treatment or procedure	Consensus statement	Symbol
Scientific evidence that a treatment or procedure is beneficial and effective. Requires at least one randomized trial, or is supported by strong observational evidence and authors' consensus (as indicated by an asterisk).	Recommended/ indicated	
General agreement and/or scientific evidence favour the usefulness/efficacy of a treatment or procedure. May be supported by randomized trials based on small number of patients or not widely applicable.	May be used or recommended	
Scientific evidence or general agreement not to use or recommend a treatment or procedure.	Should NOT be used or recommended	

This categorization for our consensus document should not be considered as being directly similar to that used for official society guideline recommendations which apply a classification (I–III) and level of evidence (A, B, and C) to recommendations.

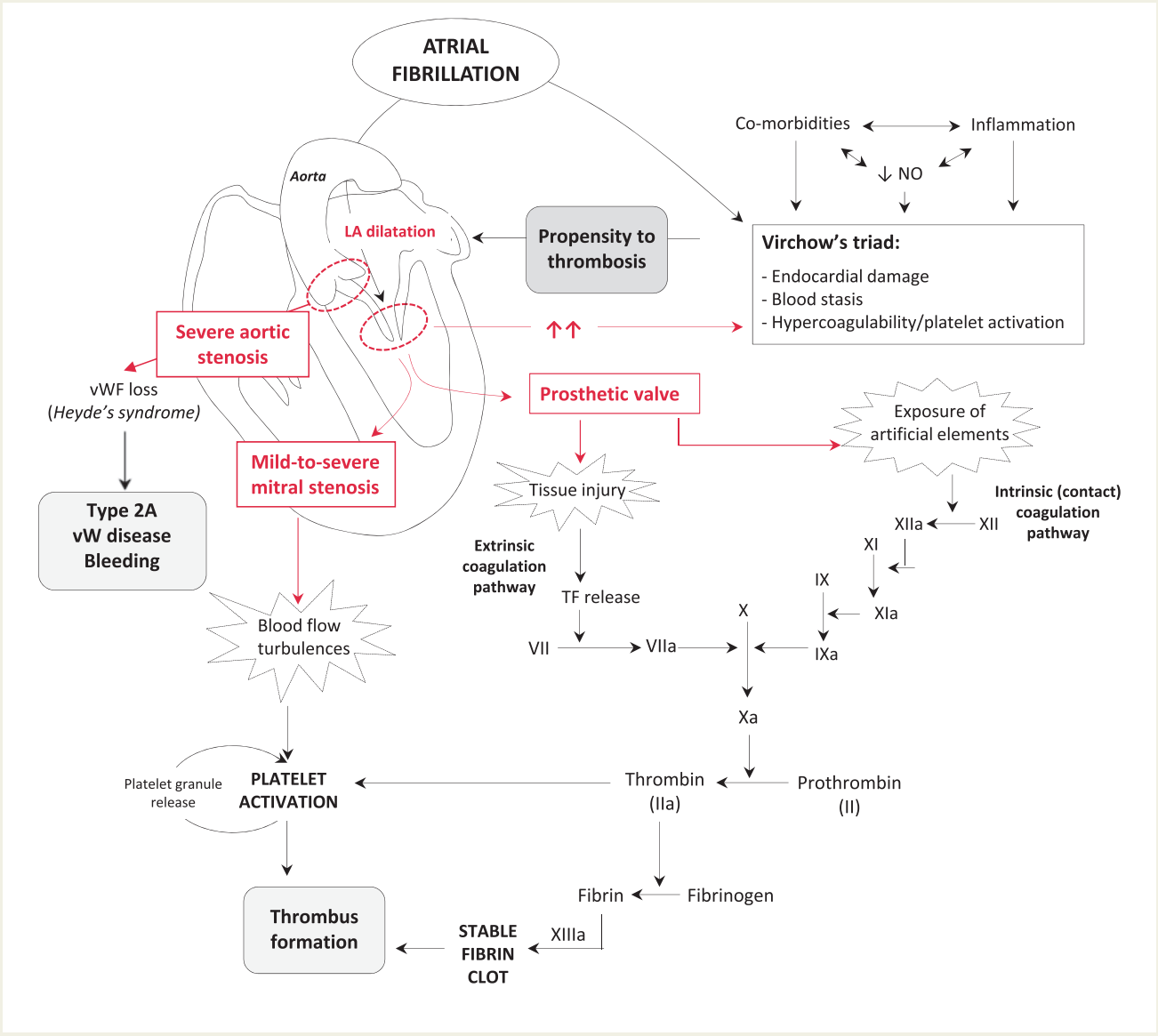

Figure 1 Pathophysiology of thrombogenesis in atrial fibrillation (AF) related prosthesis and/or mitral valve diseases. In valvular-AF there is a propensity to thrombosis because of the presence of the Virchow's triad components which, in turn, are found likely boosted by patients' co-morbid conditions. The risk of thrombosis, however, is enhanced because of the presence of prosthetic valves which activate the coagulation cascade (both the intrinsic and extrinsic pathway) leading to thrombin production (a strong platelet agonist); and, although to a lesser extent, because of the considerable degree of mitral stenosis which induces flow turbulences capable of inducing platelet activation. Finally, AF also frequently occurs in patients with severe aortic stenosis, which can be associated to the Heyde's syndrome due to Von Willebrand Factor (VWF) consumption leading to an acquired bleeding disorder.

Pathophysiology—a brief overview

There is a general agreement that AF is independently associated with thrombotic diathesis.[17] The drivers include the three elements of the Virchow's triad: blood flow alterations, endocardial injury and changes in blood constituents.[18] In fact, according to the recently published EHRA/HRS/APHRS/SOLAECE consensus document, atrial tissue in VHD is characterized, at a histopathological level, by a combination of cardiomyocyte and fibrotic changes.[19] Co-morbidities present in most AF patients may contribute to enhance thrombotic risk by pro-inflammatory/pro-atherogenic mechanisms. An overview of the pathophysiology of thrombogenesis in AF in haemodynamically significant mitral stenosis and/or mechanical heart valves prosthesisis shown in *Figure 1*.

The risk of TE is increased in patients with AF and mechanical valve, mild-to-severe mitral stenosis[20] and left atrium dilatation, as compared to non-valvular AF,[6] suggesting differences among the pathogenic mechanisms contributing to thrombosis in each of these AF conditions. It is generally thought that Virchow's triad is triggered by the turbulent flow and the endothelial injury that accompanies valvular AF. On top of this, AF prosthetic valves (particularly mechanical prosthesis) induce thrombin generation through the activation of both the tissue factor (TF) and the contact coagulation pathways.[21]

Surgical heart valve replacement surgery induces tissue damage with TF release leading to extrinsic coagulation pathway activation after binding to plasma Factor (F) VII/FVIIa. Moreover, the exposure of valve leaflets, struts and/or sewing ring to the circulating blood[22] can activate the contact (intrinsic) coagulation pathway. Both intrinsic and extrinsic pathways converge factor X (FX) activation and then the transformation of prothrombin into thrombin (FIIa) and formation of the fibrin mesh. The vitamin K antagonist (VKA), warfarin, by blocking the formation of the vitamin K-dependent clotting FVII, FIX, FX, and FII prevents the activation of the coagulation cascade at the extrinsic and intrinsic pathway levels.

In addition to the thrombogenic contribution of plasma coagulation in valvular AF, platelet activation may possibly contribute, although to a much lesser extent, to promote thrombogenesis, particularly in mild-to-severe mitral stenosis. It is also possible that moderate to severe mitral stenosis causes increased blood stasis, due to the severe dilatation of the left atrium occurring in this condition. Finally, acquired type IIA von Willebrand disease and bleeding complications can be associated with severe aortic stenosis due to high-molecular weight multimer consumption.[23]

Table 2 Target international normalized ratio for some examples of mechanical prosthesis

Prosthesis thrombogenecity	Valve type	Patient-related risk factors*
		Risk factor ≥ 1
Low	Carbomedics, Medtronic Hall, St Jude Medical, ON-X	3.0
Medium	Other bileaflet valves	3.5
High	Lillehei-Kaster, Omniscience, Starr-Edwards, Bjork-Shiley and other tilting-disc valves	4.0

*Risk factors: previous thromboembolism; AF; mitral stenosis of any degree; left ventricular ejection fraction < 35%. Reproduced from reference.[24]

Oral anticoagulation with vitamin K antagonists in patients with AF and prosthetic heart valves, including bioprostheses

Mechanical heart valves

Oral anticoagulation (OAC) with VKA is crucial for prevention of TE in patients with mechanical heart valves, regardless the presence or absence of AF. The ESC guidelines[24] establish the risk of TE in patients with mechanical valves according to valve type and position, and also according to the individual patient risk profile or comorbidities. Warfarin and other VKA are the most widely used OACs, and are titrated according to international normalized ratio (INR) range and target value which is also related with associated risk factors (*Table 2*).

The duration of antithrombotic therapy also varies according to a number of factors. Lifelong anticoagulant treatment is indicated for all patients with mechanical valves and those with bioprosthetic valves or native valve disease with ≥1 additional risk factors.

Clinical trials with VKA are sparse and recommendations are mostly based on old trials, with the oldest types of mechanical valve prostheses, and AF patients were excluded.

Patients with bioprostheses and additional risk factors for embolism (AF, venous TE, hypercoagulable state, or with a lesser degree of evidence, severely impaired left ventricular function) require life-long OAC. The use of NOACs instead of warfarin in this setting is accepted by the more recent document of recommendations by EHRA[25] in spite of a lack of randomized clinical trials (RCT)[26–28] (see Antithrombotic therapy in patients with AF undergoing TAVI or LAAO section for NOACs and bioprosthesis).

Bioprostheses

After biological valve replacement, thrombo-embolic risk is estimated between 0.6 to 3.3% per year without anticoagulation, after the third month.[29] The thrombo-embolic risk associated with a bioprosthesis and sinus rhythm is higher in the first 3 months after surgery, the risk being almost eliminated in anticoagulated patients for aortic bioprosthesis, but remaining higher in patients with a mitral bioprosthesis.[30,31] The benefit of an initial anticoagulant treatment following aortic valve replacement with a bioprosthesis and no AF is however debated.[32–34]

Overall AF patients with a bioprosthesis had a non-significantly higher risk of stroke/TE events compared with patients with non-valvular AF, and VKA use was independently associated with a lower risk of thrombo-embolic events (hazard ratio 0.83, 95% CI 0.71–0.98).[35]

One small pilot study compared Dabigatran Versus Warfarin After Bioprosthesis Valve Replacement for the Management of Atrial Fibrillation Postoperatively (DAWA Pilot Study) but small numbers preclude definitive conclusions.[36]

Recent small studies also suggest that NOACs can be a reasonable alternative to VKA in patients with AF and remote bioprosthetic valve implantation,[26,37] however larger studies are needed to define the safety and efficacy profile. Data on thromboprophylaxis in patients with AF and TAVI, which is actually the insertion of a bioprosthesis, are preliminary[38] and discussed in detail elsewhere in the document section.

Mitral valve repair

Patients undergoing mitral valve repair have a small risk of TE,[39] with the highest risk of TE occurring during the first year after surgery. Guidelines therefore recommend OAC during the first 3–6 months after surgery.[40] However, only limited data are available on the efficacy of warfarin therapy in the early stages after valve surgery, and the use of short-term VKAs in patients with mitral valve annuloplasty is also controversial. It is therefore not clear whether patients with AF in addition to valve repair are markedly different from the patients with AF and no VHD.[6,21]

North American and European guidelines have a different position on this issue, the former considering AF is 'valvular AF' whilst ESC guidelines do not.[32,41]

Consensus statements

	Coloured heart	Supporting references
• Well managed VKA monotherapy with good anticoagulation control (e.g. TTR >65–70%), is generally recommended, taking into account the type of valve, the position, and additional risk factor(s), including atrial fibrillation.		24
• Patients with a bioprosthetic valve and atrial fibrillation require lifelong OAC.		

Indications of 'add on' antiplatelet therapy in patients with atrial fibrillation and prosthetic mechanical heart valves

Arterial TE and valve thrombosis are ~12%/year and 22%/year, for mechanical valve prosthesis in the aortic and mitral position, respectively, in patients without VKA prophylaxis.[29] The residual risk ranges from 0.5%/year, to 2.5%/year,[29,42–44] in VKA-treated patients without additional cardiovascular risk factors such as AF. A higher incidence is associated with the mitral (~2%/year) vs. the aortic (~1%/year) position, depending also on the type of valve and VKA intensity.[29,43,44] AF and/or other risk factors (e.g. heart failure, even without AF) increase TE risk by four-fold, from 4% up to 8%/year,[45–47] even on adequate VKA treatment.[45,46]

Given this high residual TE risk, RCT have compared VKA alone vs. VKA combined with different aspirin doses and/or dipyridamole[29,48,49] (*Table 3*).

Despite major methodological limitations of these studies including small sample size, heterogeneities in thrombotic risk level at study entry and anticoagulation intensity, inconsistencies in safety and efficacy endpoint definitions,[48] there may possibly be some benefit of adding low-dose aspirin (between 75 and 200 mg daily) to VKA in patients with mechanical valve prosthesis and additional risk factors including AF[29,48,54] (*Table 3*). This approach lowered TE complications in the majority of studies,[29,45,46,48,54] and two meta-analyses showed ~60% relative risk reduction (RRR) of TE and ~50% RRR of all-cause mortality[48,49] (*Table 3*). Nonetheless, the relative risk of major bleeding with VKAs plus antiplatelet therapy increases by ~58% across studies including aspirin daily doses from 100 to 1000 mg[48,49] and high dose dipyridamole alone or with aspirin.[48] Importantly, major bleeding appears significantly affected by aspirin dose: the association with low dose (100 mg) shows a bleeding risk significantly lower than higher doses[50,52] and not significantly different from VKA alone (OR = 0.96; 95% CI 0.60–1.55; 2.58; 95% CI 1.43–2.55 for low and high doses vs. VKA, respectively, $P = 0.002$ for the high aspirin dose combination vs. VKA) with similar efficacy (*Table 3*).[48,50] Thus, VKA plus low-dose aspirin (75–100 mg daily) for the association of mechanical prosthetic valve and AF, is recommended by the AHA/ASA/ACCP as a class I (level A or B) recommendation,[42,44,55,56] but as a class IIb C recommendation by the ESC.

When the aspirin/VKA combination is used, anticoagulation should be titrated taking into account the type of valve, the position, and comorbidities. The target INR for AF patients with aortic mechanical prosthetic valve on VKA and low-dose aspirin should be 2.5 (range 2.0–3.0), with close attention to the quality of anticoagulation control, with time in therapeutic range (TTR) >65–70%. This applies to low-thrombogenicity valves, including Carbomedics, Medtronic Hall, St Jude Medical, ON-X; but there is insufficient data for other valves, even if bileaflet.

Whether the INR target should be 2.5 (range 2–3) or 3 (range 2.5–3.5) in AF patients with mitral prosthetic valve on both VKA and low-dose aspirin is less clear. High intensity VKA (i.e. INR range 3–4 or higher), combined with aspirin, has been consistently associated with higher major bleeding and comparable benefit as lower intensity VKA with aspirin.[51,52,57]

Consensus statements

	Coloured heart	Supporting references
• In patients with a mechanical prosthetic valve and concomitant AF with vascular disease, VKA plus low-dose aspirin (75–100 mg daily) may be considered in the absence of high bleeding risk.		53,54,56–69
• In patients with a mechanical prosthetic valve and AF, when VKA plus aspirin are used, the INR should be kept between 2.0 and 3.0 (target 2.5), given the high bleeding risk of the combination and the lack of evidence of greater protection with higher intensity VKA (INR range 3–5 or above).		51,56,63
• High doses of aspirin (≥325 mg) in association with VKA at any intensity must be avoided.		51,60

Evidence for non-vitamin K antagonist oral anticoagulants use in patients with atrial fibrillation and valvular heart disease

Subgroups from the recent non-vitamin K antagonist oral anticoagulant trials

The efficacy and safety of NOACs for the prevention of stroke/systemic embolic events (SSEE) in patients with non-valvular AF has been established by the pivotal randomized trials.[58,60–63] These trials excluded patients with significant mitral stenosis or prosthetic mechanical valves but enrolled participants (13–26%, depending on

Table 3 Randomized trials and meta-analyses comparing different intensities of VKA alone vs. VKA plus aspirin in patients with mechanical valve replacement since 1990

Reference	Design	Patients	AF and MVR position (%)	Efficacy	Safety	Comments or additional data
Turpie *et al.*[45]	RCT: VKA (INR target 3–4.5) + ASA 100 mg daily vs. VKA (INR target 3–4.5) + placebo mean f.u. 2.5 years	370 patients with MVR or tissue valve replacement + AF or TE; mean age 58 years males 50%	AF: 45% per arm; Mitral 44%, Aortic 46% Multiple 10%	Major systemic embolism or vascular death: 1.9%/year ASA vs. 8.5%/year placebo *NNT = 15*	Major bleeding: 8.5%/year ASA, 6.6%/year placebo *P* = 0.43; *NNH = 52*	Mean INR: 3 in each arm. Net beneficial effect favoured ASA (RRR 61%)
Altman *et al.*[50]	RCT: VKA (INR target 2–3) plus: ASA 100 mg or ASA 650 mg daily mean f.u. 20 months	416 patients with mechanical MVR; mean age 60 years males 50%	AF: ~23% per arm Mitral 26%, Aortic 74%	Major TE: 0.5%/year in low-ASA and 1.1%/year high ASA; Vascular death 1.2%/ year low-ASA vs. 0.5%/year high-ASA, *P* = 0.3	Major bleeding: 3.6%/year low-ASA vs. 5.1%/year high-ASA; any bleeding: 7.9%/year low-ASA vs.13.4%/year high-ASA, p = 0.03;	Vascular mortality and non-fatal TE: 3.4% low-ASA and 2.9% high ASA, *P* = n.s.
Meschengieser *et al.*[51]	RCT: high intensity VKA (INR 3.5-4.5) vs. less intense VKA (INR 2.5-3.5) + ASA 100 mg median f.u.: 23 months	503 patients with MRV; ~30% mitral MVR median age 53 years males 58%	AF: 15% high VKA arm; 20% VKA+ ASA arm; p = 0.04 Mitral 29% Aortic 66% Multiple 4%	Major TE: 1.48%/year high VKA vs. 1.32%/year VKA + ASA, *P* = n.s.	Major bleeding: 2.23%/year high VKA vs. 1.13%/year VKA+ASA; p=ns GI bleeding: 2.12%/year high VKA vs. 0.76%/year VKA+ASA, *P* = 0.14	Mean INR: high VKA arm 3.98. VKA+ASA 3.1 p < 0.001 Mortality: high VKA 8.1% vs. VKA+ASA 3.5% (RR for VKA+ASA 0.41, 95% CI 0.23-0.81)[62]
Laffort *et al.*[46]	RCT: VKA + ASA 200 mg daily vs. VKA alone INR target 3 (2.5-3.5) f.u.: 1 year	229 patients with MVR; mean age 63 years males 50%	Non-sinus rhythm: ~49% per arm Mitral: 100%	Major TE: 0.9% ASA+VKA vs. 4.1% VKA, *P* = ns. Total TE: 9% ASA+VKA vs. 25% VKA, *P* = 0.004; *NNT= 6* Echocardiographic thrombi day 9: 4.8% ASA+VKA vs. 13.1% VKA, *P* = 0.03	Major bleeding: 19.2% ASA+VKA vs. 8.3% VKA, *P* = 0.02 *NNH = 10*	No significant differences in mortality (few events)
Larson and Fisher[49]	Meta-analysis of 4 trials using aspirin	869 patients	Variable depending on the study	Major TE: 3.5% VKA + ASA vs. 11.3% VKA only *NNT: 13*	Major bleeding: 13.1% VKA + ASA vs. 8.1% VKA only *NNH: 20*	All-cause mortality: 5.4% VKA + ASA vs. 7.9% VKA only Aspirin daily dose ranged from 100 to 1000 mg

Continued

Table 3 Continued

Reference	Design	Patients	AF and MVR position (%)	Efficacy	Safety	Comments or additional data
Pengo *et al.*[52]	RCT: low-intensity VKA (INR 2–3) + ASA 100 mg vs. higher intensity VKA (INR 2.5–3.5) for 6 months f.u.: 1.5 years	198 patients with MVR; mean age 60 years males 46%	∼28% per arm Mitral 28% Aortic 63% Multiple ∼10%	VKA+ASA: 4 major bleeding and 1 ischaemic stroke; VKA: 2 major bleeding and 2 ischaemic stroke, $P = 0.6$	Cumulative endpoint of major bleeding and thrombosis	Very small study with short treatment and low number of events
Dong *et al.*[53]	RCT: VKA + ASA 75–100 mg vs. VKA alone mean f.u.: 24 ± 9 months	1496 patients with mechanical MVR; mean age 35 years males 40%	AF: 40% per arm Mitral 83% Aortic 43% Multiple:16%	Major TE: 2.1% VKA + ASA vs. 3.6% VKA alone, $P = 0.04$ *NNT* = 66	Major bleeding: 3.5 VKA + ASA vs. 3.7% in VKA alone; P = ns *NNH* = 500	Warfarin dose: 2.92 ± 0.87 mg in VKA+ASA and 2.89 ± 0.79 mg in VKA alone. No differences in mortality rate
Massel and Little[48]	Meta-analysis of RCT comparing VKA alone vs. VKA and antiplatelets	4122 patients with MVR in aortic or mitral position or both	Variable depending on the study	Major TE: ASA+VKA vs. VKA alone OR 0.43 [95% CI 0.32-0.5] $P < 0.001$	Major bleeding: Antiplatelet + VKA vs. VKA alone OR 1.58 [95% CI 1.14–2.18] $P < 0.001$ ASA high: OR 2.58 [95% CI 1.43–1.55] ASA 100 mg: OR 0.96 [95% CI 0.6–1.55] Statistical interaction high vs. low $P = 0.04$	Overall mortality: OR 0.57 [95% CI 0.42-0.78] Major bleeding in studies pre-1990: OR 2.34 [95% CI 1.34–4.08] after-1990: OR 1.26 [95% CI 0.84–1.89]

Data are presented as %/year, whenever possible. NNT and NNH per year are calculated for the comparisons including the combined VKA + antiplatelet treatment vs. VKA alone, whenever possible.
AF, atrial fibrillation; ASA, aspirin; f.u., follow-up; INR, international normalized ratio; MVR, mechanical valve replacement; NNT, number needed to treat; NNH, number needed to harm; OR, odds ratio; RCT, randomized clinical trial; RRR, relative risk reduction; TE, thromboembolism; VKA, vitamin K antagonists.

Table 4 Inclusion/exclusion criteria pertinent to valvular heart disease in the pivotal NOAC trials in patients with 'non-valvular' AF and valvular disease type distribution across the trials

Inclusion (√)/exclusion (–) criteria	RE-LY[61]	ROCKET-AF[58]	ARISTOTLE[60]	ENGAGE-AF[62]	AVERROES[63]
Prosthetic heart valve(s)					
Mechanical	–	–	–	–	–
Bioprosthesis	–	–	√	√	√
Prior surgical repair[a]	–	√	√	√	√
Moderate-to-severe MS	–	–	–	–	–
Other significant valve disease[b]	–	√	√	√	–
Mild-to-moderate valve disease	√	√	√	√	√
Subgroups with a cardiac valve disease[c]	RE-LY[58]	ROCKET-AF[64]	ARISTOTLE[67]	ENGAGE-AF[28]	
Total *n* (%)	**3950 (21.8)**	**2003 (14.1)**	**4808 (26.4)**	**2824 (13.4)**	**NR**
Moderate/severe MR	3101 (78.5)	1756 (87.7)	3526 (73.3)	2250 (79.6)	NR
Moderate/severe AR	817 (20.7)	486 (24.3)	887 (18.4)	369 (13.0)	NR
Moderate/severe AS	471 (11.9)	215 (10.7)	384 (8.0)	165 (5.8)	NR
Other	1179 (6.5)	11 (0.6)[d]	2124 (44.2)	NR	NR
Mild MS	193 (4.9)	NR	131 (2.7)	254 (9.0)	NR
Prior valve surgery (excluding mechanic prosthetic heart valve)	Not applicable	106 (5.3)	251 (5.2)	325 (11.5)	NR
Valve repair	—	42 (2.1%)	NR	123 (4.3)	NR
Valvuloplasty	—	64 (3.2%)	NR	19 (0.7)	NR
Bioprosthetic valves	—	Not applicable	82 (1.7)	191 (6.8)	NR

AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; MR, mitral regurgitation; MS, mitral stenosis; NOAC, non-vitamin K antagonist oral anticoagulant; NR, not reported.
[a]Annuloplasty, Commisurotomy, Valvuloplasty, etc.
[b]Clinically significant, but not requiring immediate surgery repair.
[c]Categories are not mutually exclusive.
[d]Without any of the preceding.

the trial)[28,59,64,65] with other clinically significant non-rheumatic VHD, including mitral regurgitation (MR), aortic regurgitation (AR), aortic stenosis (AS), mild mitral stenosis (MS) or prior valve surgery (bioprosthetic valves or valve repair) (*Table 4*). There are limited or no data on other options, such as MitraClip or other TMVI, and thus, NOACs should not be used in these patients.

Variable inclusion/exclusion criteria across the NOACs trials reflect the prevailing lack of a clear-cut definition of valvular AF.[6] Patients with VHD of non-rheumatic origin are prevalent in clinical practice,[66] and physicians may often deny NOACs to eligible AF patients due to uncertainty over whether the patient has valvular or non-valvular AF.[3]

There are no randomized trials on NOACs in AF patients with VHD. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY),[59] 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),[64] Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)[65] and Effective Anticoagulation with factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48)[28] trial subgroup analyses, non-valvular AF patients with VHD were older, had more comorbidities (including renal dysfunction), more persistent/permanent AF and higher cardioembolic and bleeding risks than patients without VHD. Whilst the use of aspirin was broadly similar, prior VKA use was more common among patients with VHD. Irrespective of the treatment arm (i.e. warfarin or a NOAC), VHD patients generally experienced worse outcomes (stroke and systemic TE, major bleeding or all-cause death) in comparison to non-VHD patients (*Table 5*). Nonetheless, the efficacy of NOACs in reduction of SSEE or all-cause mortality was consistent among patients without or with VHD (irrespective of the VHD subtype). Likewise, the safety of NOACs in terms of lower risk of major bleeding or ICH was consistent irrespective of VHD status, excluding the significantly higher rates of major bleeding in VHD patients (particularly those with aortic stenosis, or mitral or aortic regurgitation)[69] treated with rivaroxaban compared to warfarin (*Table 5*). Importantly, there are no head-to-head comparisons for any NOAC vs. VKA in AF patients with moderate to severe mitral stenosis; as mentioned, these patients were not enrolled in the NOACs trials.

The number of patients with any prior valve surgery (i.e. bioprosthetic valves or valve repair) exposed to rivaroxaban, apixaban or edoxaban in the ROCKET-AF, ARISTOTLE or ENGAGE AF-TIMI 48 trials, respectively, was very low (*Table 4*). Nevertheless, as reported for apixaban and edoxaban,[26,68] there was no statistically significant interaction between the presence of a bioprosthetic heart valve and the respective NOAC effects (*Table 5*), thus suggesting that apixaban or edoxaban may possibly be alternatives to warfarin in AF patients with bioprosthetic valves implanted ≥3 months ago.

Table 5 Major outcomes in AF patients by valvular heart disease status and treatment

Outcome trial	NOAC/Warfarin	VHD (Rate %/year)	No VHD (Rate %/year)	VHD NOAC vs. warfarin HR (95% CI)	No VHD NOAC vs. warfarin HR (95% CI)	Interaction *P*
Stroke/SE						
ROCKET-AF[64]	Rivaroxaban/Warfarin	2.01/2.43	1.96/2.22	0.83 (0.55–1.27)	0.89 (0.75–1.07)	0.70
ARISTOTLE[65]	Apixaban/Warfarin	1.46/2.08	1.20/1.43	0.70 (0.51–0.97)	0.84 (0.67–1.04)	0.378
RE-LY[59]	Dabi-150 mg/Warfarin	1.12/1.90	1.11/1.66	0.59 (0.37–0.93)	0.67 (0.52–0.86)	0.63
	Dabi-110 mg/Warfarin	1.84/1.90	1.45/1.66	0.97 (0.65–1.45)	0.88 (0.70–1.10)	0.65
ENGAGE-AF[28]	HDER/Warfarin	1.39/2.02	1.60/1.77	0.69 (0.44–1.07)	0.91 (0.77–1.07)	0.255
	LDER/Warfarin	1.94/2.02	2.04/1.77	0.97 (0.66–1.44)	1.15 (0.98–1.35)	0.440
ARISTOTLE[67] bioprosthetic valves (*n* = 82)	Apixaban/Warfarin	2.9/0.0	NA	NR	NA	—
ENGAGE-AF[26] bioprosthetic valves (*n* = 191)	HDER/Warfarin	1.19/1.66	NA	0.37 (0.10–1.42)	NA	0.15
	LDER/Warfarin	2.57/1.66	NA	0.53 (0.16–1.78)	NA	0.31
Major bleeding						
ROCKET-AF[64]	Rivaroxaban/Warfarin	6.14/4.20	3.22/3.33	1.56 (1.14–2.14)	0.98 (0.84–1.15)	0.01
ARISTOTLE[65]	Apixaban/Warfarin	2.49/3.14	2.01/3.07	0.79 (0.61–1.04)	0.65 (0.55–0.77)	0.23
RE-LY[59]	Dabi-150 mg/Warfarin	4.21/5.12	3.06/3.14	0.82 (0.64–1.06)	0.98 (0.83–1.15)	0.25
	Dabi-110 mg/Warfarin	3.77/5.12	2.63/3.14	0.73 (0.56–0.95)	0.84 (0.71–0.99)	0.38
ENGAGE-AF[28]	HDER/Warfarin	3.28/4.46	2.66/3.27	0.74 (0.53–1.02)	0.82 (0.71–0.94)	0.573
	LDER/Warfarin	1.82/4.46	1.59/3.27	0.41 (0.28–0.60)	0.49 (0.41–0.57)	0.439
ARISTOTLE bioprosthetic valves (*n* = 82)[68]	Apixaban/Warfarin	7.9/5.2	NA	NR	NA	0.61
ENGAGE-AF[29] bioprosthetic valves (*n* = 191)	HDER/Warfarin	NR	NA	0.50 (0.15–1.67)	NA	0.26
	LDER/Warfarin	0.76/6.27	NA	0.12 (0.01–0.95)	NA	0.045
ICH[b]						
ROCKET-AF[64]	Rivaroxaban/Warfarin	0.88/0.73	0.43/0.74	1.27 (0.58–2.79)	0.59 (0.40–0.86)	0.084
ARISTOTLE[65]	Apixaban/Warfarin	0.25/0.88	0.37/0.78	0.28 (0.14–0.57)	0.47 (0.33–0.68)	0.20
RE-LY[63]	Dabi-150 mg/Warfarin	0.34–0.93	0.31/0.72	0.36 (0.17–0.77)	0.43 (0.28–0.67)	0.68
	Dabi-110 mg/Warfarin	0.27/0.93	0.21/0.72	0.29 (0.13–0.68)	0.30 (0.18–0.49)	0.98
ENGAGE-AF[28]	HDER/Warfarin	0.32/0.82	0.41/0.85	0.39 (0.15–0.98)	0.48 (0.35–0.66)	0.657
	LDER/Warfarin	0.24/0.82	0.26/0.85	0.29 (0.11–0.79)	0.31 (0.21–0.45)	0.926
All-cause mortality						
ROCKET-AF[64]	Rivaroxaban/Warfarin	5.48/5.60	4.19/4.60	0.98 (0.75–1.29)	0.91 (0.80–1.03)	0.60
ARISTOTLE[65]	Apixaban/Warfarin	4.95/4.88	3.02/3.61	1.01 (0.84–1.22)	0.84 (0.73–0.96)	0.101
RE-LY[59]	Dabi-150 mg/Warfarin	4.28/4.73	3.46/3.96	0.91 (0.70–1.17)	0.87 (0.75–1.01)	0.79
	Dabi-110 mg/Warfarin	4.35/4.73	3.58/3.96	0.92 (0.71–1.19)	0.90 (0.78–1.04)	0.89
ENGAGE-AF[28]	HDER/Warfarin LDER/Warfarin	6.46/5.71	3.62/4.13	1.13 (0.90–1.41)	0.88 (0.78–0.98)	0.045
		5.81/5.71	3.46/4.13	1.03 (0.82–1.29)	0.83 (0.75–0.93)	0.100
ARISTOTLE bioprosthetic valves (*n* = 82)[69]	Apixaban/Warfarin	6.9/7.1	NA	NR	NA	0.88
ENGAGE-AF[26]b bioprosthetic valves (*n* = 191)	HDER/Warfarin	NR	NA	0.46 (0.23–0.91)	NA	0.03
	LDER/Warfarin	NR	NA	0.43 (0.21–0.88)	NA	0.02

ICH, intracranial haemorrhage; NA, not applicable; NOACS, non-vitamin K oral anticoagulants; NR, not reported; SE, systemic embolism; VHD, valvular heart disease.
[a]There was no effect modification of the presence or absence of VHD on relative outcomes with higher- or lower-dose edoxaban in comparison to warfarin (all interaction p were non-significant).
[b]In the subanalyses including only bioprosthetic valves, the rates of ICH were not specified; Composite outcome of stroke/SE, major bleeding or death.

A meta-analysis[70] of the VHD sub-groups from the RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48 trials broadly confirmed the findings shown in *Table 5*. Overall, AF patients with VHD had non-significantly higher rate of SSEE (RR 1.13; 95% CI, 0.99–1.28) and significantly higher rates of major bleeding (RR 1.34; 95% CI, 1.13–1.49) and all-cause death (RR 1.34; 95% CI, 1.13–1.59) than patients without VHD.

Compared with warfarin, the use of NOACs (i.e. rivaroxaban, apixaban or higher doses of dabigatran or edoxaban) was associated with consistently lower rates of SSEE regardless of the presence or absence of VHD (RR 0.70; 95% CI, 0.58–0.86 and 0.84; 95% CI, 0.75–0.95, respectively; interaction $P = 0.31$), similar major bleeding rates (VHD RR 0.93; 95% CI, 0.67–1.27 and no-VHD RR 0.85; 95% CI 0.70–1.02, interaction $P = 0.63$), consistently lower rates of ICH (VHD RR 0.47; 95% CI, 0.24–0.93 and no-VHD RR 0.49; 95% CI, 0.41–0.59, interaction $P = 0.91$) and higher all-cause death rate in VHD patients (RR 1.01; 95% CI, 0.90–1.14) than in those without VHD (RR 0.88; 95% CI, 0.82–0.94), interaction $P = 0.03$,[70] In the analysis that also included the lower doses of dabigatran and edoxaban, the magnitude of SSEE risk reduction with NOACs vs. warfarin was slightly reduced, as well as the rates of major bleeding and ICH, but there were no significant subgroup interactions by VHD status. Overall, the presence of VHD did not affect the relative protective effect of NOACs compared with warfarin in terms of SSEE and major bleeding. These findings were further supported by another meta-analysis of the four NOACs yielding identical results.[71] Of note, both meta-analyses reported significant treatment effect heterogeneity regarding the analysis of major bleeding.

With the exclusion of patients with moderate-to-severe mitral stenosis, prosthetic mechanical heart valve, TAVI or TMVI, who were not enrolled in the non-valvular AF trials, the aforementioned subgroup and meta-analyses may suggest that AF patients with VHD would experience at least the same benefit from NOACs as patients without VHD. However, due to limitations inherent to these types of analyses, further RCTs are required in AF patients with VHD before recommendations can be given (see *Tables 4* and *5*).

Prosthetic mechanical heart valves: Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement

Mechanical valve prosthesis trigger complex mechanisms of thrombogenesis and are associated with a very high cardioembolic risk requiring chronic OAC even in the absence of AF. Animal studies on mechanical valve implantation using first the direct FIIa inhibitors melagatran[72] and then dabigatran[73,74] as well as the phase III data from the RE-LY trial[61] informed the only study to date on a NOAC in patients with mechanical heart valves.

The Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN) trial was a phase-II, controlled, dose-finding, open-label study[75] randomizing (2:1) patients with aortic ($n = 172$; 68%) or mitral ($n = 71$; 28%) mechanical valve replacement, or both ($n = 9$; 4%) to dabigatran or adjusted-dose warfarin (target INR 2.0–3.0 or 2.5–3.5 in aortic or mitral position, respectively). The initial dabigatran dose of 150, 220, or 300 mg b.i.d. (selected according to renal function) was further adjusted over 12 weeks to achieve the primary study outcome—a trough plasma concentration ≥50 ng/mL, based on the pharmacokinetic model from the RE-LY trial. Most patients (79%) received study drug 5–7 days after surgery, and 23% of patients had AF. The RE-ALIGN study was prematurely terminated after randomizing 252 of 405 planned patients, due to an excess in stroke (5% vs. 0%), valve thrombosis (3% vs. 0%) and major bleeding events (4% vs. 2%) in the dabigatran arm, after a mean dabigatran exposure of ∼20 weeks. Different explanations have been proposed, including inadequate dabigatran plasma concentrations, different pharmacodynamics of dabigatran and warfarin, excessive activation of the contact coagulation pathway induced by the sewing ring in the early postoperative course, a higher inter-individual variability in the dabigatran arm and differences in predicted vs. observed drug concentrations in the RE-LY vs. RE-ALIGN.[75] A recent *in vitro* study suggested that the dabigatran trough plasma concentration required to reduce valve-induced FIIa generation should be much higher than 50 ng/mL (that is, 260 ng/mL) corresponding to a 620 mg b.i.d. dosing.[68] At present, all AF patients with a mechanical valve prosthesis should be treated with VKAs

Consensus statements

	Coloured heart	Supporting references
• The use of the NOACs in patients with AF and mechanical valve prosthesis is contraindicated.	♥	76
• Randomized clinical trials testing the efficacy and safety of direct oral FXa inhibitors in patients with AF and mechanical heart valved prosthesis are lacking. Until more data are available, rivaroxaban, apixaban, and edoxaban are contraindicated in such patients.	♥	. . .
• Until more data are available, AF patients with any degree of rheumatic mitral valve stenosis and those with moderate-to-severe non-rheumatic mitral stenosis should not be treated with NOACs.	♥	. . .
• The efficacy and safety of NOACs for stroke/SE prevention may be similar in AF patients with and without conservative valve surgery such as annuloplasty, commissurotomy or valvuloplasty, or bioprosthetic valves based on small numbers of patients in post hoc analyses of RCTs. More data	♥	9,66,72,77,78

Continued

Continued

	Coloured heart	Supporting references
are needed to define the role of NOACs in this setting.		
• The efficacy and safety of NOACs in patients with non-rheumatic mitral and/or aortic regurgitation or other native VHD may be similar to AF patients without VHD based on small numbers of patients in post hoc analyses of RCTs. More data are needed to define the role of NOACs in this setting.		9,66–72,77,78
• In patients with haemodynamically insignificant valve disease and in those who have had prior successful balloon mitral valvulotomy, NOACs can be considered as substitute for VKAs.		67,68,71–75,77

NB. Recommendations for TAVI are given in the specific section.

Antithrombotic therapy in patients with atrial fibrillation undergoing trans-aortic valve intervention or left atrial appendage occlusion

Trans-aortic valve intervention procedure

Most ischaemic events after TAVI are cerebrovascular, and for these AF is a strong contributor.[77] AF is common among high-risk patients with severe aortic stenosis undergoing TAVI, and is associated with a >2-fold increased risk of all-cause and cardiovascular death, irrespective of the type of AF.[78] In addition, the implanted valve adds a prothrombotic environment, which would accentuate the cardioembolic risk. Of importance, the gradient of risk directly correlates with the CHA_2DS_2-VASc score, which is usually used to aid decision-making as whether to initiate OAC.[77] At least 30% of the TAVI population requires OAC,[1] a strategy that seems underused and that has never been evaluated prospectively. Dual antiplatelet therapy (DAPT) remains the most widely used antithrombotic strategy after TAVI, being used in >60% of patients, while VKA is used in <20% of patients,[77] although AF is observed in >40% of TAVI patients. Current recommendations are expert-driven, rather than evidence-based (*Table 6*).

Up to 35% patients undergo coronary stenting prior to TAVI. In such patients, the risk of stent thrombosis and/or ischaemic cardiac events in addition to that of AF should be considered in the overall risk assessment.[82] Here triple therapy, a combination of a VKA, low-dose aspirin and clopidogrel, is used in high risk patients, and associated with an increased risk of death, stroke, TE, or major bleeding when compared to VKA alone.[78,82] Such combinations should be discussed in the context of recent (i.e. <6 months) acute coronary syndrome and/or stent implantation, especially in the presence of an unfavourable coronary anatomy (more than three stents, stent length ≥60 mm, multivessel disease, left main disease) but should be avoided whenever deemed possible given the established better safety and the possible preserved efficacy of a combination of warfarin and clopidogrel in patients with AF undergoing drug-eluting stent placement.[83–85]

Recent evidence suggests that VKA alone is much safer and provides a similar rate of ischaemic events as compared to VKA plus antiplatelet therapy (aspirin) in patients undergoing TAVI.[82] However this study was observational, not randomized with an unbalanced number of patients per treatment arm, and randomized confirmation is needed. Therefore, the association of OAC with SAPT in AF patients who underwent successful TAVI should be considered up to one year when there is a recent ACS or a recent coronary stenting[86] and when the bleeding risk is deemed low (*Figure 2*).

OAC alone as antithrombotic strategy is currently being tested in three trials (POPular-TAVI NCT02247128, GALILEO NCT02556203, ATLANTIS trial NCT02664649), while another trial is testing aspirin alone or in combination with clopidogrel (ARTE NCT02640794), although AF patients appear excluded. Indeed, the benefit of VKA over DAPT in AF depends on the quality of INR control,[76] and it has been modelled that a time in therapeutic range ≥58% would be needed to benefit from being on OAC rather than on DAPT,[76] which is probably not the case in the TAVI population.

Subclinical valve thrombosis is another challenging issue as it may may occur early after TAVI. Although the frequency of this potentially ominous phenomenon remains undefined, as this condition is difficult to detect, but it seems reversible with anticoagulation. Whether it is associated with cerebrovascular events remains to be established.[87] Given all these uncertainties, ongoing trials are also testing the anticoagulation hypothesis after successful TAVI irrespective of the need of OAC hypotheses using NOACs (NCT02556203, NCT02664649) which have been shown to be better tolerated. *Figure 2* shows all currently recommended treatment options.

Recent observational evidence suggest the safety of FXa inhibition in TAVI,[88] showing the feasibility of NOAC in the post-TAVI setting. However, results from randomized comparison of FXa inhibition vs. other antithrombotic strategies are lacking.

Left atrial appendage occlusion procedure

Following clinical trials,[89–91] percutaneous endovascular left atrial appendage occlusion (LAAO) has been increasingly developed and performed worldwide for patients with AF, especially those with contraindications to long-term OAC.[92,93] This is supported by guidelines from the ESC, which give a class IIB recommendation for LAAO in AF patients with high stroke risk and contraindications to long-term OAC.[4]

Antithrombotic therapy following LAAO has not been well evaluated, and it is not even known whether OAC or antiplatelet therapy or no therapy is preferable. When possible according to the patient bleeding risk profile, after LAAO most centres use a 6-week period of VKA (target INR 2.5) followed by once daily clopidogrel (75 mg)

Table 6 Recommendations for antithrombotic therapy during and after TAVI in the guidelines in patients with and without indication for OAC

	ACC/AHA/STS[79]	ESC[80]	ACCP[44]	CCS[44,80]
Procedural	Unfractionated Heparin (ACT> 300 s)	–	–	
Post-procedural	Aspirin 81 mg indefinitely and Clopidogrel 75 mg for 3 up to 6 months	Aspirin (or clopidogrel) indefinitely Aspirin and clopidogrel in first 3 months after TAVI	Aspirin (50–100 mg/day) and Clopidogrel (75 mg/day) in the first 3 months	Low-dose Aspirin indefinitely and 1–3 months of a thienopyridine (no evidence).
Patients with a clear indication for OAC (as in AF)	It is reasonable to continue low-dose Aspirin, but other antiplatelet therapy should be avoided	No antiplatelet therapy but OAC alone	No recommendation	Adjunctive antiplatelet agents is controversial and triple therapy should be avoided

ACC, American College of Cardiology; ACT, activated clotting time; ACCP, American College of Chest Physicians; AF, atrial fibrillation; AHA, American Heart Association; ASA, acetylsalicylic acid (aspirin); AVR, aortic valve replacement; CCS, Canadian Cardiovascular Society; ESC, European Society of Cardiology; INR, international normalized ratio; VKA, vitamin K antagonists.

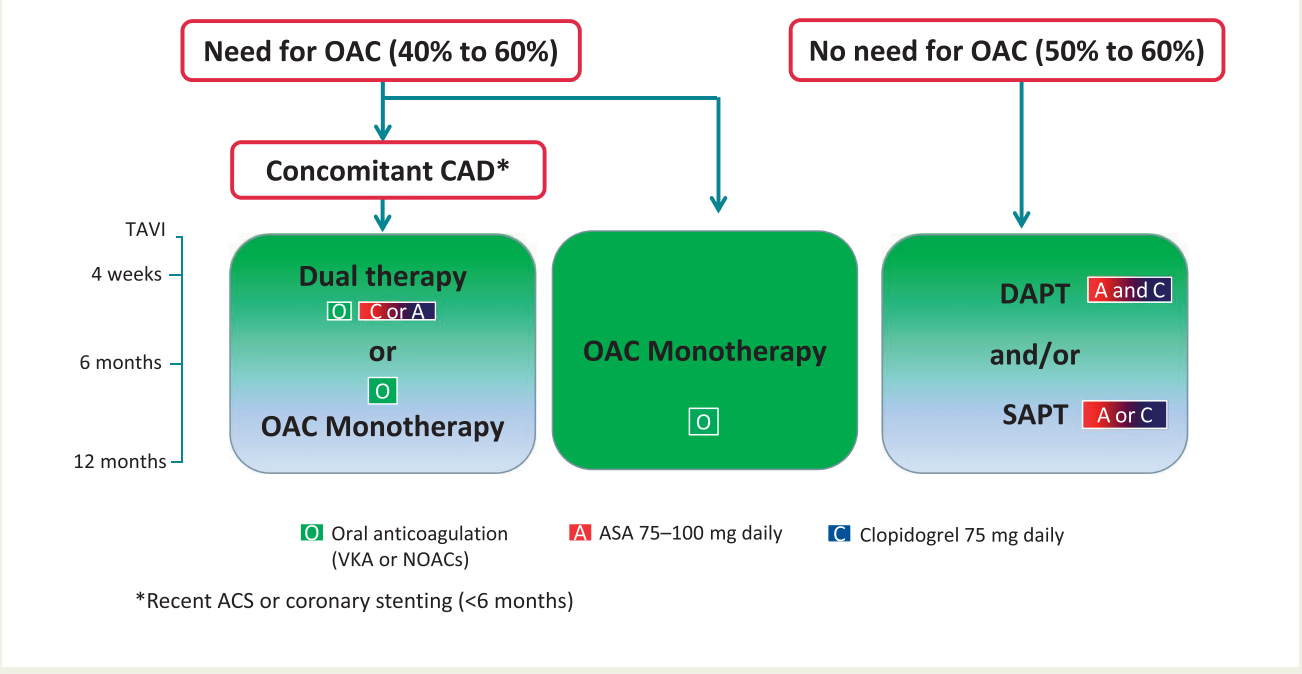

Figure 2 Proposed algorithm for AF patients undergoing a TAVI procedure (adapted from references 87). O refers to oral anticoagulation as VKA (or possibly NOAC). ASC, acute coronary syndrome; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; OAC, oral anticoagulant; SAPT, single antiplatelet therapy.

and aspirin (75–325 mg) until the 6-months visit. Some patients may also receive NOAC.[94] Subsequently, low-dose aspirin alone is continued indefinitely, as tested in the pivotal trials.[89,90,95] This antiplatelet regimen has never been compared with any long term NOAC-based anticoagulation regimen.[9,96] However, the ASAP study showed that LAAO with the Watchman device is feasible and could be safely performed without OAC cover (but with antiplatelet therapy).[95] Such strategy is being evaluated in the ongoing ADRIATIC study (Apixaban versus Dual or single antiplatelet therapy to Reduce Ischemic and bleeding events in Atrial fibrillation patients Treated with Invasive Closure of the left atrial appendage). The ASAP TOO randomized trial (NCT02928497) is currently establishing the safety

and effectiveness of the LAAO vs. SAPT in patients with non-valvular AF deemed not to be eligible for OAC to reduce the risk of stroke.

Consensus statements

	Coloured heart	Supporting references
• AF patients who underwent successful TAVI may be treated with FXa inhibitors; however data are limited.	♥	9
• AF patients with stable coronary artery disease who underwent TAVI may be treated with OAC only, including VKA and FXa inhibitors; however prospective data are limited.	♥	9,82,83
• Based on trial protocols, OAC and single antiplatelet therapy after successful LAAO may be used up to 6 weeks in low bleeding risk patients, followed by single antiplatelet therapy; however, long term data are limited, nor any comparison with NOACs.	♥	89,90,95
• Single antiplatelet therapy or no antithrombotic therapy may be used after LAAO in AF patients who are not eligible for VKA; however, long term data are limited, nor any comparison with NOACs.	♥	9,96

Antithrombotic therapy for valvular atrial fibrillation in pregnant women

Valvular AF in pregnancy is relatively rare and can be due to congenital heart disease, mitral valve prolapse with significant mitral regurgitation, or to rheumatic heart disease. Valves can be repaired or replaced with a mechanical valve prosthesis.[97] Pregnancy by itself is a prothrombotic state and the coalescence of venous stasis and hypercoagulability results in nearly a five-fold increase in the risk of venous thromboembolism during pregnancy.[86] The goal of anticoagulation during pregnancy should be to safely balance the maternal risk of TE and haemorrhage with the foetal risk of exposure to VKA. The continuously changing pharmacokinetics of LMWH during the various trimesters adds an additional challenge and requires monitoring by peak and trough anti-Xa levels,[86] which is often not feasible (*Figure 3*).

Women of child-bearing age with VHD need to be comprehensively counselled prior to valve replacement and pre-pregnancy to decide on the most appropriate type of valve and to be made aware of the teratogenicity and fetotoxicity of VKA, pregnancy-induced haemodynamic changes and the pre-existing hypercoagulable state which can compromise foetal development and significantly increase the risk of serious and/or fatal complications to both mother and child.[98] Women with mechanical prosthetic valves should ideally have preconception evaluation, including advice on risk prediction and contraception, by a joint cardiac-obstetric team seeking advice from other specialties.[97] Careful counselling on maternal and offspring risk should be done according the modified World Health Organization classification and should include information on complications such as heart failure, valve thrombosis, bleeding complications which can occur during, but also beyond the immediate delivery period. Also, the consequences of the medication that may be required (for example warfarin embryopathy) need to be discussed. However, often women in some countries may present after 20 weeks of gestation, which has implications for their functional assessment, harmful medication can't be terminated timeously and limits the option for pregnancy termination. Such cases are challenging and should be managed at tertiary centre where they can be appropriately assessed and guided/treated. Since anticoagulation is recommended in pregnant women with AF at risk of stroke, to minimise teratogenic risk and intrauterine bleeding, the ESC guidelines recommend that dose adjusted heparin should be used during the first trimester of pregnancy and in the 2–4 weeks before delivery.[4] VKA or heparin can be used in the remaining trimesters of the pregnancy.[4] In the absence of adequate safety data, NOACs should be avoided in pregnancy and in women planning a pregnancy[4].

Consensus statements

	Coloured heart	Supporting references
• There is no consensus on the optimal regimen for anticoagulation in peripartum women with mechanical valve prosthesis with AF.	♥	86,97,99
• As the optimal anticoagulation regimen for use in pregnancy and peripartum remains undetermined, all decisions should be made by a fully informed mother and partner in consultation with a multidisciplinary team.	♥	86,97,99

Patient values and preferences, and societal issues

Treatment decisions need to balance the benefits and risks of treatment and manage realistic patient expectations, particularly in association with co-morbidities and in pregnancy. These decisions are complex and require assimilation of life expectancy, ability and willingness to take anticoagulants, risk of bleeding, lifestyle, co-morbidities, risk of re-operation, and patient preference.[100–102]

Clinical guidelines on the management of VHD[100] advocate incorporating informed patient preferences into treatment decisions and technological advances (for VHD) must be employed 'responsibly within a framework of care which enables shared decision making and promotes patient goals and well-being'.[103] This requires candid discussions between the patient and physician to ensure that

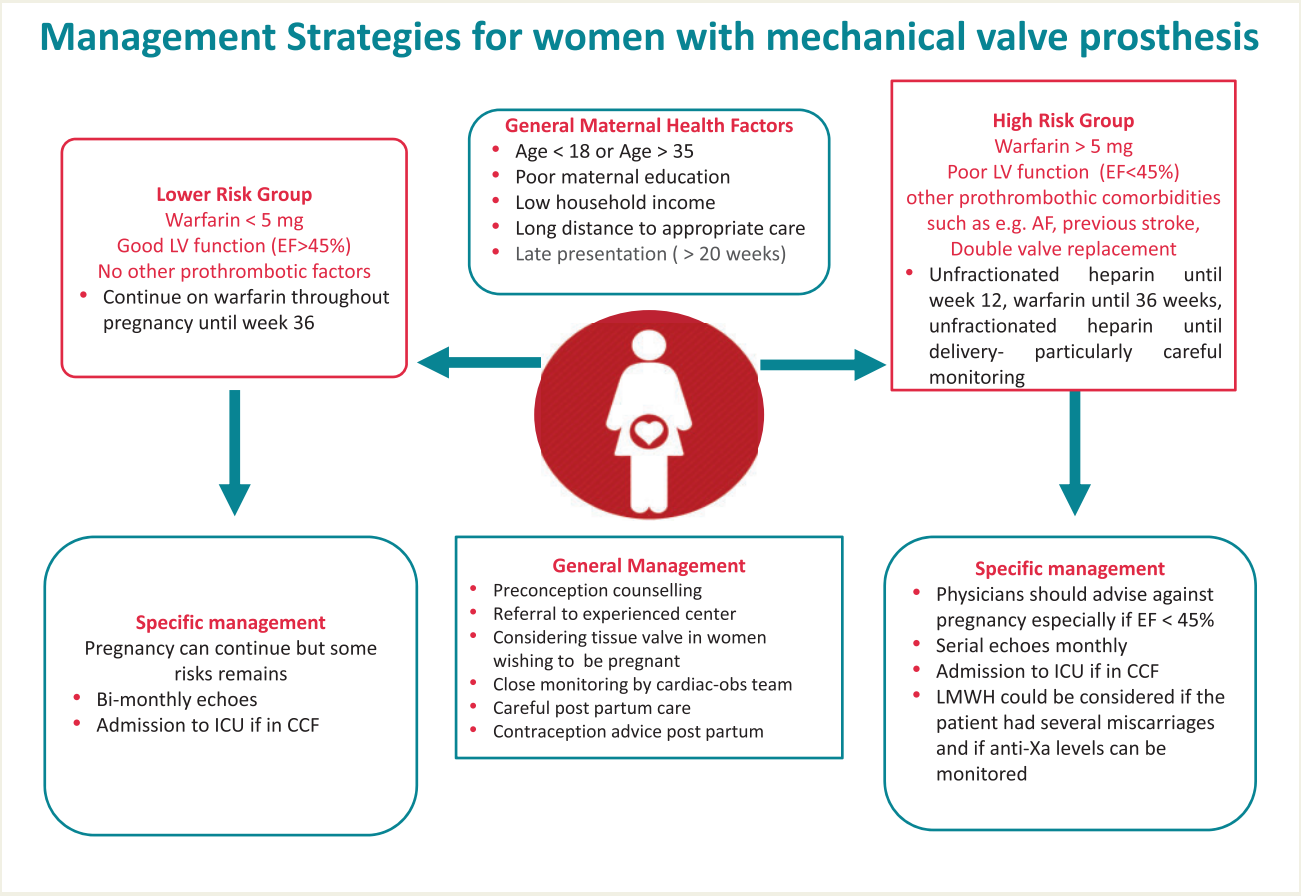

Figure 3 Management strategies for women with mechanical valve prosthesis. CCF, congestive heart failure; ICU, Intensive Care Unit.

treatment is not futile. Shared decision making[103,104] requires patients to be appropriately informed about treatment options and likely outcomes, to have the type of patient-physician relationship where patients feel able to ask questions and where physicians provide information and communicate risk effectively,[105,106] to enable patients to make an informed decision incorporating their values, goals and preferences.[103,107,108] Patient's treatment preferences are likely to vary markedly, with patients often willing to accept higher levels of risk.[108] Patient decision-aids including micro-simulation models are available for patients with VHD.[109,110]

Implications for low-to-middle income countries

Valvular AF is more common in the Asian and African population compared to their western counterparts mainly due to greater burden of rheumatic heart disease.[110,111,112] Stroke risk is higher among patients with valvular AF (17–18%/year) compared to those with non-valvular AF (4%/year).[113] Further, AF may further increase the risk of bioprosthetic valve thrombosis (see Supplementary material online, *Table S4*).[114] The burden of rheumatic valve disease is higher, but the quality of anticoagulation is suboptimal in low and middle income countries. Monitoring of the INR and follow-up remains poor and significant proportion of patients present with sub-therapeutic INR. The majority of these patients are young (median age 28 years),[118] unemployed (75.3%) and women (51–66%)[112,115] of reproductive age. On average, they tend to be nearly 10–12 years younger than their western counterparts. Many are unaware of the concept of therapeutic range INR (60%) and few (<4%) are on contraceptives despite treatment with warfarin. The NOACs are expensive and beyond the reach of the majority of patients requiring them in these countries. Suboptimal anticoagulation and consequent increased risk of stroke, may lead to significant disability adjusted life years lost and this is likely to pose a major economic burden. Strategies to improve awareness: (i) about the disease, (ii) medication side-effects, (iii) importance of medication adherence and INR monitoring, and 4) the danger of anticoagulation during pregnancy are scanty. Although point of care INR testing shows promise (see Supplementary material online, *Table S4*), its use among patients from the developing world needs to be determined. The impact of NOACs is less certain, although one recent Brazilian study evaluating NOACs in public health system context found that NOACs present a lower cumulative cost per patient when compared to VKAs.[116]

Health economic perspectives

AF is a disease that induces significant consumption of resources and costs, encompassing direct medical costs, associated with patient's

medical care (hospitalisations, medications, out-patient visits, etc.), and direct non-medical costs (i.e. costs related to residential or social care, as well as out of pocket expenses).[117,118]

Other costs that are usually taken into account in health-economic analyses are productivity losses caused by patients' inability to work, or absence from work of relatives in order to provide informal care.[119] In patients with AF direct costs, reported as per-patient annual costs, have been estimated $2000 to 14 200 in North America and 450 to 3000 Euros in Europe per patient.[119]

Patients with VHD who have AF require appropriate risk stratification for stroke/SE and, when indicated, the consequent prescription of OAC implies a difficult balance between the risk of stroke and systemic TE and the risk of bleeding.[120,121] Stroke and major bleeding have also an economic effect. Indeed, the main drivers of costs in AF patients are AF-related hospitalizations, stroke and haemorrhagic events. For strokes occurring in patients with AF, the direct costs per patient are approximately 33% greater than the costs of stroke not-related to AF[126] and are in the range of 30 000 Euros over a 2-year period for a severe ischaemic stroke.[123] The costs of intra-cerebral haemorrhage is 50% higher than the cost of ischaemic stroke over a 1 year time course.[124]

Underutilization of, and non-adherence to, warfarin is also quite common and is associated with increased costs,[125,126] resulting from TE and haemorrhagic complications. Improved adherence to OAC in AF patients at risk of stroke is important in order to attain the full clinical and economic benefit of thromboprophylaxis.

Non-vitamin K antagonist oral anticoagulants can be prescribed to some subgroups of patients with VHD[6,127,128] and a series of analyses focusing on the cost-effectiveness of these agents vs. warfarin has been published, although no study considered separately patients with VHD. In general, despite the higher cost of NOACs as compared to warfarin, the associated benefits make these agents cost-effective in the long-term, especially in settings with poor anticoagulation control associated with VKAs.[129,130]

Consensus statements

	Coloured heart	Supporting references
• Appropriate use of oral anticoagulants, when clinically indicated, has both a clinical and economic value since underutilization and/or non-adherence are associated with adverse outcomes and increased costs.		121–123

Summary and areas for future research

Mechanical valve prostheses

Currently, patients with AF and a mechanical prosthesis should only be treated with a VKA. Since the RE-ALIGN study, no other NOAC (factor Xa inhibitor drug class) has been tested in this patient group.[75] However, the thrombotic risk could be reduced once endothelial tissue is present around the ring.[17] A trial could potentially be designed after endothelialization: the first 3 months with VKA, followed by a randomized comparison between continuing VKA or switching to a NOAC.

One trial proposed or ongoing with NOACs in patients with and without AF, is the Comparison of Antithrombotic Treatments After Aortic Valve Replacement. Rivaroxaban: A New Antithrombotic Treatment for Patients With Mechanical Prosthetic Aortic Heart Valve: CATHAR trial(https://clinicaltrials.gov/ct2/show/NCT02128841?term=rivaroxaban+and+mechanical+valve&rank=2).

Bioprostheses, trans-aortic valve intervention, and transcatheter mitral valve interventions

Usually, patients with a bioprosthesis and AF receive a VKA. Pericardial valves are less thrombogenic than mechanical valve prostheses. Some physicians do not consider bioprostheses as a contra-indication of NOACs. Before recommending a NOAC rather than VKA for these patients, a randomized trial is needed. This is also the case for patients undergoing valve repair.

Trans-aortic valve intervention corresponds to transluminal implantation of a bioprosthesis and is being increasingly used. The antithrombotic treatment in patients with sinus rhythm and TAVI remains controversial and the optimal treatment in patients with AF requiring TAVI (as well as TMVI—see earlier section) is currently unknown.

A global study comparing a rivaroxaban-based anti-thrombotic strategy to an antiplatelet-based strategy after TAVI to optimize clinical outcomes (GALILEO) is currently ongoing.[131] The two arms consist of either rivaroxaban 10 mg once daily and aspirin 75–100 mg for the first 90 days, followed by rivaroxaban alone; or clopidogrel 75 mg and aspirin 75–100 mg for the first 90 days, followed by clopidogrel alone. Patients with current or previous AF are excluded. The investigators assume that 15% of patients in sinus rhythm at inclusion will develop AF during follow-up. Treatment after new onset AF will be, in patients randomized to rivaroxaban, a switch to rivaroxaban 20 mg OD or 15 mg OD for those with moderate renal impairment and in those randomized to clopidogrel, a switch to VKA (target INR 2–3).

Another ongoing study is the Anti-Thrombotic Strategy after Trans-Aortic Valve Implantation for Aortic Stenosis (ATLANTIS) study which is ongoing and plans to include 1509 patients after successful TAVI procedure. Randomization will be stratified according to the need for oral anticoagulant. Patients with an indication for OAC will be randomized 1:1 to VKA or apixaban 5 mg b.i.d. The primary endpoint after 1 year follow-up is a composite of death, myocardial infarction, stroke, systemic embolization, intracardiac or bioprosthesis thrombus, episode of deep vein thrombosis or pulmonary embolism, and major bleeding. Patients with no indication for oral anticoagulant therapy will be randomized 1:1 to either apixaban 5 mg bid or antiplatelet therapy. Other trials are also proposed or ongoing with NOACs in patients with and without AF, include the RIvaroxaban for bioprosthetic Valvular Heart diseasE and atRial Fibrillation Trial (Warfarin vs. Rivaroxaban): RIVER Trial.

Native valve diseases

The main phase III studies of NOACs have used variable criteria for excluding valvular patients. Some studies (ROCKET-AF and ARISTOTLE) only excluded patients with mechanical valve prostheses and significant (moderate to severe) mitral stenosis. The subanalyses did not show any differences in efficacy among patients with and without VHD. In the ROCKET-AF, there was more bleeding on rivaroxaban than on VKA in patients with VHD.

A report from the Loire Valley Atrial Fibrillation Project compared the outcome of patients without any valve disease and those with valve disease but did not include either valve prosthesis or mitral stenosis. Although patients with VHD had a higher risk of stroke and TE events on univariable analysis, the difference was no longer significant after adjustment, in line with an older age and a higher CHA_2DS_2-VASC score in patients with VHD.[128]

However, post hoc analyses are only hypothesis generating. Large RCTs are needed with NOACs in the setting of AS, non-rheumatic AR and MR before the role of NOACs can be fully defined in this setting.

Mitral stenosis

There has not yet been a randomized trial comparing VKA and NOACs in these patients. The prevalence of rheumatic mitral stenosis has become low in Western countries but remains high in Eastern Europe, India, Africa, South America, and south East Asia. In these regions, the time in therapeutic range is only 35–44%, according to a global AF registry.[7] Randomized clinical trials comparing VKA with a NOAC is highly welcomed and should preferably include patients from these affected countries.

Supplementary material

Supplementary material is available at *Europace* online.

References

1. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol* 2014;**11**:639–54.
2. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ *et al.* Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation* 2014;**129**:837–47.
3. 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**:1720–5.
4. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: the Task Force for the 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 ESCEndorsed by the European Stroke Organisation (ESO). *Europace* 2016;**18**:1609–78.
5. De Caterina R, John Camm A. Non-vitamin K antagonist oral anticoagulants in atrial fibrillation accompanying mitral stenosis: the concept for a trial. *Europace* 2016;**18**:6–11.
6. De Caterina R, Camm AJ. What is 'valvular' atrial fibrillation? A reappraisal. *Eur Heart J* 2014;**35**:3328–35.
7. Oldgren J, Healey JS, Ezekowitz M, Commerford P, Avezum A, Pais P *et al.* Investigators R-LAFR. Variations in cause and management of atrial fibrillation in a prospective registry of 15,400 emergency department patients in 46 countries: the RE-LY Atrial Fibrillation Registry. *Circulation* 2014;**129**:1568–76.
8. Fukuda N, Hirai T, Ohara K, Nakagawa K, Nozawa T, Inoue H. Relation of the severity of mitral regurgitation to thromboembolic risk in patients with atrial fibrillation. *Int J Cardiol* 2011;**146**:197–201.
9. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W *et al.* Advisors. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2015;**17**:1467–507.
10. Petronio AS, Capranzano P, Barbato E, Piazza N, Baumbach A, Haude M *et al.* Current status of transcatheter mitral valve therapy in Europe: results from an EAPCI survey (Part II). *EuroIntervention* 2017;**12**:1934–9.
11. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P *et al.* 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2733–79.
12. Benhorin J, Bodenheimer M, Brown M, Case R, Dwyer EM Jr, Eberly S *et al.* Improving clinical practice guidelines for practicing cardiologists. *Am J Cardiol* 2015;**115**:1773–6.
13. Piccini JP, Hammill BG, Sinner MF, Jensen PN, Hernandez AF, Heckbert SR *et al.* Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries: 1993–2007. *Circ Cardiovasc Qual Outcomes* 2012;**5**:85–93.
14. Friberg L, Bergfeldt L. Atrial fibrillation prevalence revisited. *J Intern Med* 2013;**274**:461–8.
15. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A *et al.* Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013;**34**:2746–51.
16. Lip GY, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. *Chest* 2012;**142**:1489–98.
17. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F *et al.* New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease position paper. *J Am Coll Cardiol* 2012;**59**:1413–25.
18. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet* 2009;**373**:155–66.
19. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA *et al.* EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace* 2016;**18**:1455–90.
20. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP *et al.*; American Society of Echocardiography; European Association of Echocardiography. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr* 2009;**22**:1–23. quiz 101-2.
21. Fauchier L, Philippart R, Clementy N, Bourguignon T, Angoulvant D, Ivanes F *et al.* How to define valvular atrial fibrillation? *Arch Cardiovasc Dis* 2015;**108**:530–9.
22. Dewanjee MK, Gross DR, Zhai P, Lanzo S, Shim H, Park K *et al.* Thrombogenicity of polyethylene oxide-bonded Dacron sewing ring in a mechanical heart valve. *J Heart Valve Dis* 1999;**8**:324–30.
23. Natorska J, Mazur P, Undas A. Increased bleeding risk in patients with aortic valvular stenosis: from new mechanisms to new therapies. *Thromb Res* 2016;**139**:85–9.
24. Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA *et al.* Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012;**33**:2451–96.
25. Torella M, Torella D, Chiodini P, Franciulli M, Romano G, De Santo L, De Feo M *et al.* LOWERing the INtensity of oral anticoaGulant Therapy in patients with bileaflet mechanical aortic valve replacement: results from the "LOWERING-IT" Trial. *Am Heart J* 2010;**160**:171–8.
26. Carnicelli AP, De Caterina R, Halperin JL, Renda G, Ruff CT, Trevisan M *et al.* Edoxaban for the prevention of thromboembolism in patients with atrial fibrillation and bioprosthetic valves. *Circulation* 2017;**135**:1273–5.
27. Renda R, De Caterina R, Carnicelli A, Nordio F, Mercuri M, Ruff C *et al.* Outcomes in 2824 patients with valvular heart disease treated with edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. *J Am Coll Cardiol* 2016;**67**:2194.
28. De Caterina R, Renda G, Carnicelli AP, Nordio F, Trevisan M, Mercuri MF *et al.* Valvular heart disease patients on edoxaban or warfarin in the ENGAGE AF-TIMI 48 Trial. *J Am Coll Cardiol* 2017;**69**:1372–82.
29. Salem DN, O'gara PT, Madias C, Pauker SG. Valvular and structural heart disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;**133**:593S–629S.
30. Heras M, Chesebro JH, Fuster V, Penny WJ, Grill DE, Bailey KR *et al.* High risk of thromboemboli early after bioprosthetic cardiac valve replacement. *J Am Coll Cardiol* 1995;**25**:1111–9.
31. Mérie C, Køber L, Skov Olsen P, Andersson C, Gislason G, Skov Jensen J *et al.* Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. *JAMA* 2012;**308**:2118–25.
32. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC *et al.*; American College of Cardiology/American Heart Association Task Force on

Practice Guidelines. 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**:e1–76.
33. Aramendi JI, Mestres C-A, Mestres C-A, Martinez-León J, Campos V, Muñoz G *et al.* Triflusal versus oral anticoagulation for primary prevention of thromboembolism after bioprosthetic valve replacement (trac): prospective, randomized, co-operative trial. *Eur J Cardio-Thorac Surg* 2005;**27**:854–60.
34. Brueck M, Kramer W, Vogt P, Steinert N, Roth P, Görlach G *et al.* Antiplatelet therapy early after bioprosthetic aortic valve replacement is unnecessary in patients without thromboembolic risk factors. *Eur J Cardiothorac Surg* 2007;**32**:108–12.
35. Philippart R, Brunet-Bernard A, Clementy N, Bourguignon T, Mirza A, Angoulvant D *et al.* Oral anticoagulation, stroke and thromboembolism in patients with atrial fibrillation and valve bioprosthesis. The Loire Valley Atrial Fibrillation Project. *Thromb Haemost* 2016;**115**:1056–63
36. Duraes AR, de Souza Roriz P, de Almeida Nunes B, Albuquerque FP, de Bulhoes FV, de Souza Fernandes AM *et al.* Dabigatran versus warfarin after bioprosthesis valve replacement for the management of atrial fibrillation postoperatively: dawa pilot study. *Drugs R D* 2016;**16**:149–54.
37. Yadlapati A, Groh C, Malaisrie SC, Gajjar M, Kruse J, Meyers S *et al.* Efficacy and safety of novel oral anticoagulants in patients with bioprosthetic valves. *Clin Res Cardiol* 2016;**105**:268–72.
38. Ende G, Sichting L, Pfluecke C, Quick S, Schoener L, Strasser RH *et al.* Anticoagulation therapy of patients with atrial fibrillation after TAVI–Dresdner DOAK Register-TAVI (DDRT). *Eur Heart J* 2015;**36**:343.
39. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW *et al.* A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on valvular heart disease. *Eur Heart J* 2003;**24**:1231–43.
40. Butchart EG, Gohlke-Bärwolf C, Antunes MJ, Tornos P, De Caterina R, Cormier B, *et al.*; Working Groups on Valvular Heart Disease Thrombosis, Cardiac Rehabilitation and Exercise Physiology, European Society of Cardiology. Recommendations for the management of patients after heart valve surgery. *Eur Heart J* 2005;**26**:2463–71.
41. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S *et al.* Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* 2010;**12**:1360–420.
42. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA *et al.* 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;**129**:2440–92.
43. Oxenham H, Bloomfield P, Wheatley DJ, Lee RJ, Cunningham J, Prescott RJ *et al.* Twenty year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. *Heart* 2003;**89**:715–21.
44. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. American College of Chest P. Antithrombotic and thrombolytic therapy for valvular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e576S–600S.
45. Turpie AG, Gent M, Laupacis A, Latour Y, Gunstensen J, Basile F *et al.* A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. *N Engl J Med* 1993;**329**:524–9.
46. Laffort P, Roudaut R, Roques X, Lafitte S, Deville C, Bonnet J *et al.* Early and long-term (one-year) effects of the association of aspirin and oral anticoagulant on thrombi and morbidity after replacement of the mitral valve with the St. Jude medical prosthesis: a clinical and transesophageal echocardiographic study. *J Am Coll Cardiol* 2000;**35**:739–46.
47. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH *et al.* 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. *Europace* 2012;**14**:1385–413.
48. Massel DR, Little SH. Antiplatelet and anticoagulation for patients with prosthetic heart valves. *Cochrane Database Syst Rev* 2013;**7**:Cd003464.
49. Larson RJ, Fisher ES. Should aspirin be continued in patients started on warfarin? *J Gen Intern Med* 2004;**19**:879–86.
50. Altman R, Rouvier J, Gurfinkel E, Scazziota A, Turpie AG. Comparison of high-dose with low-dose aspirin in patients with mechanical heart valve replacement treated with oral anticoagulant. *Circulation* 1996;**94**:2113–6.
51. Meschengieser SS, Fondevila CG, Frontroth J, Santarelli MT, Lazzari MA. Low-intensity oral anticoagulation plus low-dose aspirin versus high-intensity oral anticoagulation alone: a randomized trial in patients with mechanical prosthetic heart valves. *J Thorac Cardiovasc Surg* 1997;**113**:910–6.
52. Pengo V, Palareti G, Cucchini U, Molinatti M, Del Bono R, Baudo F *et al.* Low-intensity oral anticoagulant plus low-dose aspirin during the first six months versus standard-intensity oral anticoagulant therapy after mechanical heart valve replacement: a pilot study of low-intensity warfarin and aspirin in cardiac prostheses (LIWACAP). *Clin Appl Thromb Hemost* 2007;**13**:241–8.
53. Dong MF, Ma ZS, Ma SJ, Chai SD, Tang PZ, Yao DK *et al.* Anticoagulation therapy with combined low dose aspirin and warfarin following mechanical heart valve replacement. *Thromb Res* 2011;**128**:e91–4.
54. Dentali F, Douketis JD, Gianni M, Lim W, Crowther MA. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. *Ann Intern Med* 2007;**146**:278–88.
55. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S *et al.* Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;**45**:3754–832.
56. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA *et al.* 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Circulation* 2017;**135**:e1159–e1195.
57. Eikelboom JW, Hirsh J. Combined antiplatelet and anticoagulant therapy: clinical benefits and risks. *J Thromb Haemost* 2007;**5**:255–63.
58. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–91.
59. Ezekowitz MD, Nagarakanti R, Noack H, Brueckmann M, Litherland C, Jacobs M *et al.* Comparison of dabigatran and warfarin in patients with atrial fibrillation and valvular heart disease: the RE-LY Trial (randomized evaluation of long-term anticoagulant therapy). *Circulation* 2016;**134**:589–98.
60. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M *et al.*; Committees A, Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–92.
61. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Committee R-LS, Investigators *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–51.
62. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL *et al.* ENGAGE-AF TIMI48; Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–104.
63. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S *et al.* Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;**364**:806–17.
64. Breithardt G, Baumgartner H, Berkowitz SD, Hellkamp AS, Piccini JP, Stevens SR *et al.*; Committee RAS, 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**:3377–85.
65. Avezum A, Lopes RD, Schulte PJ, Lanas F, Gersh BJ, Hanna M *et al.* Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease: findings from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. *Circulation* 2015;**132**:624–32.
66. Lip GY, Laroche C, Dan GA, Santini M, Kalarus Z, Rasmussen LH *et al.* A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) pilot general registry. *Europace* 2014;**16**:308–19.
67. Pokorney SDRM, Wojdyla DM, Gersh BJ, Lopes RD, Lewis BS, Hanna M *et al.* Apixaban use in patients with atrial fibrillation with bioprosthetic valves: insights from ARISTOTLE. *Circulation* 2015;**132**:A17277.
68. 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.
69. Breithardt G, Baumgartner H, Berkowitz SD, Hellkamp AS, Piccini JP, Lokhnygina Y, Committee RAS, Investigators *et al.* Native valve disease in patients with non-valvular atrial fibrillation on warfarin or rivaroxaban. *Heart* 2016;**102**:1036–43.
70. Renda G, Ricci F, Giugliano RP, De Caterina R. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. *J Am Coll Cardiol* 2017;**69**:1363–71.
71. Siontis KC, Yao X, Gersh BJ, Noseworthy PA. Direct oral anticoagulants in patients with atrial fibrillation and valvular heart disease other than significant mitral stenosis and mechanical valves: a meta-analysis. *Circulation* 2017;**135**:714–6.
72. Thompson JL, Hamner CE, Potter DD, Lewin M, Sundt TM, Schaff HV. Melagatran for thromboprophylaxis after mechanical valve implantation: results in a heterotopic porcine model. *J Thorac Cardiovasc Surg* 2007;**134**:359–65.
73. 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**:1410–6.
74. 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**:150–5.

75. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ *et al.*; Investigators R-A. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013;**369**:1206–14.
76. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG *et al.*; AW Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation* 2008;**118**:2029–37.
77. Nombela-Franco L, Webb JG, de Jaegere PP, Toggweiler S, Nuis RJ, Dager AE *et al.* Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. *Circulation* 2012;**126**:3041–53.
78. Stortecky S, Buellesfeld L, Wenaweser P, Heg D, Pilgrim T, Khattab AA *et al.* Atrial fibrillation and aortic stenosis: impact on clinical outcomes among patients undergoing transcatheter aortic valve implantation. *Circ Cardiovasc Interv* 2013;**6**:77–84.
79. Holmes DR Jr, Mack MJ, Kaul S, Agnihotri A, Alexander KP, Bailey SR *et al.*; American Heart A, American Society of E, European Association for Cardio-Thoracic S, Heart Failure Society of A, Mended H, Society of Cardiovascular A, Society of Cardiovascular Computed T, Society for Cardiovascular Magnetic Researcher. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement: developed in collaboration with the American Heart Association, American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Failure Society of America, Mended Hearts, Society of Cardiovascular Anesthesiologists, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *J Thorac Cardiovasc Surg* 2012;**144**:e29–84.
80. Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, Ten Berg JM *et al.* Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). *Eur Heart J* 2014;**35**:3155–79.
81. Webb J, Rodes-Cabau J, Fremes S, Pibarot P, Ruel M, Ibrahim R *et al.* Transcatheter aortic valve implantation: a Canadian Cardiovascular Society position statement. *Can J Cardiol* 2012;**28**:520–8.
82. Cayla G, Hulot JS, O'connor SA, Pathak A, Scott SA, Gruel Y *et al.* Clinical, angiographic, and genetic factors associated with early coronary stent thrombosis. *JAMA* 2011;**306**:1765–74.
83. Abdul-Jawad Altisent O, Durand E, Munoz-Garcia AJ, Nombela-Franco L, Cheema A, Kefer J *et al.* Warfarin and antiplatelet therapy versus warfarin alone for treating patients with atrial fibrillation undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2016;**9**:1706–17.
84. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP *et al.*; WOEST study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;**381**:1107–15.
85. Schulz-Schupke S, Byrne RA, Ten Berg JM, Neumann FJ, Han Y, Adriaenssens T *et al.* EFoMDATAD-EST Investigators. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J* 2015;**36**:1252–63.
86. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrie D, Naber C *et al.* Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med* 2015;**373**:2038–47.
87. Gargiulo G, Collet JP, Valgimigli M. Antithrombotic therapy in TAVI patients: changing concepts. *EuroIntervention* 2015;**11**:W92–5.
88. Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofoed KF, de Backer O *et al.* Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med* 2015;**373**:2015–24.
89. Seeger J, Gonska B, Rodewald C, Rottbauer W, Wohrle J. Apixaban in patients with atrial fibrillation after transfemoral aortic valve replacement. *JACC Cardiovasc Interv* 2017;**10**:66–74.
90. Holmes DR Jr, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK *et al.* Prospective randomized evaluation of the watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014;**64**:1–12.
91. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, PA Investigators *et al.* Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;**374**:534–42.
92. Price MJ, Reddy VY, Valderrabano M, Halperin JL, Gibson DN, Gordon N *et al.* Bleeding outcomes after left atrial appendage closure compared with long-term warfarin: a pooled, patient-level analysis of the WATCHMAN Randomized Trial Experience. *JACC Cardiovasc Interv* 2015;**8**:1925–32.
93. Meier B, Blaauw Y, Khattab AA, Lewalter T, Sievert H, Tondo C *et al.* EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. *Europace* 2014;**16**:1397–416.
94. Bosche LI, Afshari F, Schone D, Ewers A, Mugge A, Gotzmann M. Initial experience with novel oral anticoagulants during the first 45 days after left atrial appendage closure with the watchman device. *Clin Cardiol* 2015;**38**:720–4.
95. Reddy VY, Mobius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J *et al.* Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol* 2013;**61**:2551–6.
96. Bax JJ, Delgado V, Bapat V, Baumgartner H, Collet JP, Erbel R *et al.* Open issues in transcatheter aortic valve implantation. Part 2: Procedural issues and outcomes after transcatheter aortic valve implantation. *Eur Heart J* 2014;**35**:2639–54.
97. Sliwa K, Johnson MR, Zilla P, Roos-Hesselink JW. Management of valvular disease in pregnancy: a global perspective. *Eur Heart J* 2015;**36**:1078–89.
98. van Hagen IM, Roos-Hesselink JW, Ruys TP, Merz WM, Goland S, Gabriel H *et al.* Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation* 2015;**132**:132–42.
99. Xu Z, Fan J, Luo X, Zhang WB, Ma J, Lin YB *et al.* Anticoagulation regimens during pregnancy in patients with mechanical heart valves: a systematic review and meta-analysis. *Can J Cardiol* 2016;**32**:1248 e1–e9.
100. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H *et al.* Guidelines ESCCfP, Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg* 2012;**42**:S1–44.
101. Desai CS, Bonow RO. Transcatheter valve replacement for aortic stenosis: balancing benefits, risks, and expectations. *JAMA* 2012;**308**:573–4.
102. Tillquist MN, Maddox TM. Cardiac crossroads: deciding between mechanical or bioprosthetic heart valve replacement. *Patient Prefer Adherence* 2011;**5**:91–9.
103. Lindman BR, Alexander KP, O'gara PT, Afilalo J. Futility, benefit, and transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2014;**7**:707–16.
104. Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango). *Soc Sci Med* 1997;**44**:681–92.
105. Charles C, Gafni A, Whelan T. How to improve communication between doctors and patients. Learning more about the decision making context is important. *BMJ* 2000;**320**:1220–1.
106. Malloy-Weir LJ, Charles C, Gafni A, Entwistle VA. Empirical relationships between health literacy and treatment decision making: a scoping review of the literature. *Patient Educ Couns* 2015;**98**:296–309.
107. Coylewright M, Palmer R, O'neill ES, Robb JF, Fried TR. Patient-defined goals for the treatment of severe aortic stenosis: a qualitative analysis. *Health Expect* 2015.
108. Hussain AI, Garratt AM, Brunborg C, Aakhus S, Gullestad L, Pettersen KI. Eliciting patient risk willingness in clinical consultations as a means of improving decision-making of aortic valve replacement. *J Am Heart Assoc* 2016;**4**:e002828.
109. Birkmeyer NJ, Birkmeyer JD, Tosteson AN, Grunkemeier GL, Marrin CA, O'Connor GT. Prosthetic valve type for patients undergoing aortic valve replacement: a decision analysis. *Ann Thorac Surg* 2000;**70**:1946–52.
110. Takkenberg JJ, Puvimanasinghe JP, van Herwerden LA, Eijkemans MJ, Steyerberg EW, Habbema JD *et al.* Decision-making in aortic valve replacement: bileaflet mechanical valves versus stented bioprostheses. *Neth Heart J* 2003;**11**:5–10.
111. Narasimhan CVJ, Kishore AGR, Singh B, Dani S, Chawala K *et al.* The REALIZE AF study. An International, observational cross sectional survey evaluating AF Management and Cardiovascular Risk profile of AF patients, Indian subset data presented at the ISE Meeting Jaipur. 2012.
112. Zühlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B *et al.* 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**:1115–22a.
113. Narasimhan C, Verma JS, Ravi Kishore AG, Singh B, Dani S, Chawala K *et al.* Cardiovascular risk profile and management of atrial fibrillation in India: real world data from RealiseAF survey. *Indian Heart J* 2016;**68**:663–70.
114. Egbe AC, Pislaru SV, Pellikka PA, Poterucha JT, Schaff HV, Maleszewski JJ, Connolly HM. Bioprosthetic valve thrombosis versus structural failure: clinical and echocardiographic predictors. 2015;**66**:2285–94.
115. Vora A, Kapoor A, Nair M, Lokhandwala Y, Narsimhan C, Ravikishore AG *et al.* Clinical presentation, management, and outcomes in the Indian Heart Rhythm Society-Atrial Fibrillation (IHRS-AF) registry. *Indian Heart J* 2017;**69**:43–7.
116. Marcolino MS, Polanczyk CA, Bovendorp AC, Marques NS, Silva LA, Turquia CP *et al.* Economic evaluation of the new oral anticoagulants for the prevention of thromboembolic events: a cost-minimization analysis. *Sao Paulo Med J* 2016;**134**:322–9.

117. Maniadakis N, Vardas P, Mantovani LG, Fattore G, Boriani G. Economic evaluation in cardiology. *Europace* 2011;**13**:ii3–8.
118. Boriani G, Maniadakis N, Auricchio A, Muller-Riemenschneider F, Fattore G, Leyva F *et al*. Health technology assessment in interventional electrophysiology and device therapy: a position paper of the European Heart Rhythm Association. *Eur Heart J* 2013;**34**:1869–74.
119. Wolowacz SE, Samuel M, Brennan VK, Jasso-Mosqueda JG, Van Gelder IC. The cost of illness of atrial fibrillation: a systematic review of the recent literature. *Europace* 2011;**13**:1375–85.
120. Boriani G, Diemberger I, Biffi M, Martignani C. Balancing the risk of hemorrhage vs thromboembolism in patients with atrial fibrillation: how to navigate between Scylla and Charybdis? *Chest* 2010;**138**:1032–3.
121. Kirchhof P, Breithardt G, Bax J, Benninger G, Blomstrom-Lundqvist C, Boriani G *et al*. A roadmap to improve the quality of atrial fibrillation management: proceedings from the fifth Atrial Fibrillation Network/European Heart Rhythm Association consensus conference. *Europace* 2016;**18**:37–50.
122. Bruggenjurgen B, Rossnagel K, Roll S, Andersson FL, Selim D, Muller-Nordhorn J *et al*. The impact of atrial fibrillation on the cost of stroke: the berlin acute stroke study. *Value Health* 2007;**10**:137–43.
123. Cotte FE, Chaize G, Kachaner I, Gaudin AF, Vainchtock A, Durand-Zaleski I. Incidence and cost of stroke and hemorrhage in patients diagnosed with atrial fibrillation in France. *J Stroke Cerebrovasc Dis* 2014;**23**:e73–83.
124. Mercaldi CJ, Siu K, Sander SD, Walker DR, Wu Y, Li Q *et al*. Long-term costs of ischemic stroke and major bleeding events among medicare patients with nonvalvular atrial fibrillation. *Cardiol Res Pract* 2012;**2012**:645469.
125. Casciano JP, Dotiwala ZJ, Martin BC, Kwong WJ. The costs of warfarin underuse and nonadherence in patients with atrial fibrillation: a commercial insurer perspective. *JMCP* 2013;**19**:302–16.
126. Beyer-Westendorf J, Ehlken B, Evers T. Real-world persistence and adherence to oral anticoagulation for stroke risk reduction in patients with atrial fibrillation. *Europace* 2016;**18**:1150–7.
127. Boriani G, Cimaglia P, Fantecchi E, Mantovani V, Ziacchi M, Valzania C *et al*. Non-valvular atrial fibrillation: potential clinical implications of the heterogeneous definitions used in trials on new oral anticoagulants. *J Cardiovasc Med* 2015;**16**:491–6.
128. Philippart R, Brunet-Bernard A, Clementy N, Bourguignon T, Mirza A, Babuty D *et al*. Prognostic value of CHA2DS2-VASc score in patients with 'non-valvular atrial fibrillation' and valvular heart disease: the Loire Valley Atrial Fibrillation Project. *Eur Heart J* 2015;**36**:1822–30.
129. Kasmeridis C, Apostolakis S, Ehlers L, Rasmussen LH, Boriani G, Lip GY. Cost effectiveness of treatments for stroke prevention in atrial fibrillation: focus on the novel oral anticoagulants. *Pharmacoeconomics* 2013;**31**:971–80.
130. Janzic A, Kos M. Cost effectiveness of novel oral anticoagulants for stroke prevention in atrial fibrillation depending on the quality of warfarin anticoagulation control. *Pharmacoeconomics* 2015;**33**:395–408.
131. Hemmrich M, Peterson ED, Thomitzek K, Weitz JI. Spotlight on unmet needs in stroke prevention: the PIONEER AF-PCI, NAVIGATE ESUS and GALILEO trials. *Thromb Haemost* 2016;**116**:S33–40.