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DOACs and rheumatic valvulopathy: always a red light?

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Despite the sharp decline in most high-income industrialized countries, rheumatic heart disease (RHD) continues to be highly prevalent in many rural, low- and middle-income countries. RHD most frequently involves the mitral valve, both in the form of isolated regurgitation and in the form of regurgitation associated with mitral stenosis (mitral stenosis, MS). Atrial fibrillation (AF) is a common complication of RHD that is independently associated with an increased risk of death, heart failure, and systemic thromboembolism. Few studies have focused on the issue of the best oral anticoagulation strategy for patients with RHD and AF. Randomized trials establishing the non-inferiority of new direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) in the prevention of stroke and systemic embolism excluded AF patients with mechanical valves or with moderate-to-severe MS. Nevertheless, variable proportions of patients with other VHD types were included. Recently, the INVICTUS trial demonstrated that in patients with RHD-related AF, direct oral anticoagulant rivaroxaban is inferior to VKAs in preventing stroke, systemic embolism, myocardial infarction, or death and is similar in bleeding risk. These results confirm and reinforce the recommendations of current international guidelines supporting the use of VKAs in patients with RHD-related AF.

Abbreviations

AF =	atrial fibrillation
DOACs =	direct oral anticoagulants
INR =	international normalized ratio
MR =	mitral regurgitation
MS =	mitral stenosis
RCTs =	randomized controlled trials
RHD =	rheumatic heart disease
VHD =	valvular heart disease
VKAs =	vitamin K antagonists

Introduction

Rheumatic heart disease (RHD) has rapidly declined in most high-income industrialized countries due to improved socioeconomic conditions and the spread of penicillins, but it continues to be highly prevalent and even endemic in many rural and low- and middle-income countries. In 2015, 33.4 million cases and 319 400 deaths were attributed to RHD, with higher prevalence, disability, and mortality rates in Oceania, South Asia, and sub-Saharan Africa.[1] All heart valves can be affected by RHD, although mitral valve involvement is the most frequent, either in the form of isolated mitral regurgitation (MR) or in the form of MR associated with mitral stenosis (MS) or aortic dysfunction.[2]

Atrial fibrillation (AF) is a common complication of RHD and is independently associated with mortality, heart failure, and systemic thromboembolism. The main determinants of AF risk are age, moderate and severe MS, tricuspid regurgitation, left atrial size, and heart failure class.[3] The Framingham Heart Study demonstrated that MS in patients with AF increases the risk of stroke more than 20-fold.[4] In MS, the increase in upstream pressure leads to the progressive enlargement and remodelling of the left atrium, promoting fibrosis and electrical dysfunction. At the same time, blood stasis increases the risk of thrombus formation not only in the left appendage but also in the left atrium. The onset of AF therefore requires the initiation of oral anticoagulant therapy for stroke prevention.[5,6]

Current recommendations

Vitamin K antagonists (VKAs) were the only oral anticoagulants available until 2009. Warfarin, in particular, is a

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cheap and effective VKA, but its use is complicated by a slow onset of action and a narrow therapeutic index which requires continuous monitoring of the international normalized ratio (INR) and dose adjustments. Furthermore, warfarin is associated with multiple dietary and drug interactions and is susceptible to numerous genetic polymorphisms. The new direct oral anticoagulants (DOACs) were introduced to overcome these limitations: they have a predictable effect that does not require continuous monitoring of coagulation indices and have no food interactions and few drug interactions. The short half-life and the availability of antidotes make them a convenient alternative to VKAs in the prevention of stroke and systemic embolism in patients with AF. The current European and American guidelines recommend the use of DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) in eligible patients with AF, with the exception of patients with mechanical heart valves or moderate-to-severe MS [class of recommendation (COR) I, level of evidence (LOE) A], for which DOACs are specifically contraindicated by European guidelines (COR III, LOE C).[5,6]

The exclusion of these categories of patients has historical and methodological bases. Namely, the main randomized controlled trials (RCTs) of DOACs in patients with AF[7-11] were designed to demonstrate the non-inferiority of the new agents to warfarin. Having the first studies of warfarin for the prevention of stroke in patients with AF excluded patients with moderate or severe MS and prosthetic heart valves, and the most recent trials on DOACs also adopted this approach to maintain the validity of the comparison. Over time, the distinction between 'valvular AF', to indicate AF in the setting of moderate-to-severe MS or in the presence of mechanical valves (a condition that requires long-term anticoagulation with VKAs), and 'non-valvular AF' in the absence of moderate-to-severe MS or mechanical valves, but in the presence of any other valvular heart disease (VHD), has become a matter of fact. However, this dichotomy has led to a certain degree of confusion, due to frequent changes of definition in the literature, guidelines, and consensus documents, and to a consequent arbitrary application of the term 'valvular AF' (e.g. AF associated with any VHD). The most recent European guidelines on AF advocate that the aforementioned terminology should be abandoned, while a 2017 European consensus document considered this distinction outdated and proposed a new functional classification system based on the type of anticoagulant therapy needed, called 'Evaluated Heartvalves, Rheumatic or Artificial (EHRA)' (*Table 1*).[12]

Table 1 EHRA (Evaluated Heartvalves, Rheumatic or Artificial) functional classification

Definition	Categories
EHRA type 1 Patients with AF and VHD who require anticoagulant therapy with a VKA	• Mitral stenosis (moderate-severe, of rheumatic origin) • Mechanical valve prostheses
EHRA type 2 Patients with AF and VHD who require anticoagulant therapy with a VKA or DOAC, also considering the CHA_2DS_2-VASc score	• Mitral regurgitation • Mitral valve repair • Aortic stenosis • Aortic regurgitation • Tricuspid regurgitation • Tricuspid stenosis • Pulmonary insufficiency • Pulmonary stenosis • Biological valve prostheses • TAVI

Abbreviations: AF, atrial fibrillation; DOAC, direct oral anticoagulant; TAVI, trans-aortic valve intervention; VHD, valvular heart disease; VKA, vitamin K antagonist

Current evidence

Oral anticoagulation in patients with atrial fibrillation and non-rheumatic valve disease

In the major randomized trials of DOACs, common characteristics of enrolled patients were the presence of 'non-valvular AF' documented on the electrocardiogram and the high risk of cardioembolic stroke defined by the following variables: age ≥75 years, history of systemic embolism or transient ischemic attack (TIA), and mean $CHADS_2$ score ≥2. Despite the exclusion of patients with moderate-to-severe MS and those with prosthetic heart valves, these studies still included variable proportions of patients with other types of VHD, allowing for targeted sub-analyses (*Table 2*). The primary efficacy endpoints were a composite of stroke and systemic embolism. Overall, these studies established the non-inferiority of DOACs compared to VKAs in the prevention of stroke and systemic embolism in patients with AF not related to RHD. Of note, DOACs were associated with a large reduction in the risk of haemorrhagic stroke, regardless of the presence of VHD.[13,14]

RE-LY—The RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy With Dabigatran Etexilate) trial demonstrated the non-inferiority of dabigatran 110 mg and the superiority of dabigatran 150 mg over warfarin at 2 years. Subjects with prosthetic valves and haemodynamically relevant VHD or those who would likely have required surgery before the end of the study were excluded.[7] A *post hoc* analysis showed that 3950 (21.8%) out of all the enrolled patients had VHD and that compared with those without VHD, these patients were typically older, with a higher $CHADS_2$ score, and more frequently were female and suffering from heart failure, coronary artery disease, and renal insufficiency. They also had similar risks of stroke and systemic embolism, death and intracranial haemorrhage, and a higher risk of major bleeding [hazard ratio (HR), 1.32; 95% CI, 1.16–1.50; $P < 0.001$]. Compared with patients assigned to warfarin, those randomized to dabigatran 150 mg had a lower risk of stroke and systemic embolism, both with VHD (HR, 0.59; 95% CI, 0.37–0.93; $P = 0.021$) and without any VHD (HR, 0.67; 95% CI, 0.52–0.86; $P = 0.001$; interaction $P = 0.63$). The risk of major bleeding was also similar in patients either with VHD or without VHD (interaction $P = 0.25$). In contrast, patients randomized to dabigatran 110 mg had comparable risks of stroke and systemic embolism, both with VHD and without VHD (interaction $P = 0.65$), and the risk of major bleeding was lower than warfarin both with VHD (HR, 0.73; 95%

Table 2 Types of valvular disorders in patients randomized to RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF
Patients with VHD, *n* (%)	3950 (21.8)	2003 (14.1)	4808 (26.4)	2824 (13.4)
Moderate/severe MR, *n* (%)	3101 (78.5)	1756 (87.7)	3526 (73.3)	2250 (79.7)
Mild MS, *n* (%)	193 (4.9)	NR	131 (2.7)	NR
Moderate/severe AR *n* (%)	817 (20.7)	486 (24.3)	887 (18.4)	369 (13)
Moderate/severe AS, *n* (%)	471 (12)	215 (10.7)	384 (8)	165 (5.8)
Moderate/severe TR, *n* (%)	1179 (29.8)	NR	2124 (44.2)	NR
Valve surgery (excluding mechanical prostheses), *n* (%)	NR	106 (5.3)	251 (5.2)	325 (11.5)

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; NR, not reported; MR, mitral regurgitation; MS, mitral stenosis; VHD, valvular heart disease; TR, tricuspid regurgitation

CI, 0.56-0.95; $P = 0.017$) and without VHD (HR, 0.84; 95% CI, 0.71-0.99; $P = 0.042$; interaction $P = 0.38$).[15]

ROCKET AF—In ROCKET AF (Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation), rivaroxaban was non-inferior to warfarin at 1.9 years. Subjects with haemodynamically significant MS, prosthetic valves, and planned invasive procedures at risk of uncontrolled bleeding (e.g. major surgery) were excluded from the study; instead, all other VHDs were included, as well as annuloplasty (with or without prosthetic ring), commissurotomy, and/or valvuloplasty.[8] A retrospective analysis showed that out of 14 171 patients, 2003 (14.1%) had significant VHD, specifically MR in 89.6% of cases, and were typically older and with more comorbidities. Compared with patients without VHD, those with significant VHD had higher rates of systemic embolism (HR, 2.02; 95% CI, 1.00-4.08; $P = 0.049$), major or non-major clinically relevant bleeding (HR, 1.14; 95% CI, 1.03-1.25; $P = 0.011$), and major bleeding (HR, 1.32; 95% CI, 1.10-1.57; $P = 0.0027$). The composite endpoint of stroke and major bleeding was also significantly more frequent (HR, 1.22; 95% CI, 1.05-1.42; $P = 0.0099$). Compared with warfarin, patients randomized to rivaroxaban had lower but similar rates of stroke or systemic embolism (interaction $P = 0.76$) and all-cause death (interaction $P = 0.60$), both with significant VHD and without significant VHD. Conversely, rates of major or non-major clinically relevant bleeding were significantly more frequent with rivaroxaban in patients without significant VHD (HR, 1.25; 95% CI, 1.05-1.49), but not in those with significant VHD (HR, 1.01; 95% CI, 0.94-1.10; interaction $P = 0.034$). There was no statistical interaction with regards to intracranial haemorrhages (interaction $P = 0.084$).[16]

ARISTOTLE—The ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) study demonstrated the superiority of apixaban over warfarin at 1.8 years. The study excluded patients with moderate or severe clinically significant MS and those with prosthetic valves, including all other VHD conditions and valve surgery.[9] A secondary analysis showed that 4808 patients, equal to 26.4% of the total, had a history of moderate or severe VHD. At baseline, the presence of VHD was associated with older age, more comorbidities (heart failure, history of bleeding, myocardial infarction, renal failure), and a higher mean CHADS2 score but less hypertension and diabetes mellitus than patients without VHD. Overall, compared with patients without VHD, those with VHD had higher rates of stroke or systemic embolism (HR, 1.34; 95% CI, 1.10-1.62; $P = 0.003$), death (HR, 1.48; 95% CI, 1.32-1.67; $P < 0.001$), and major bleeding, the latter not significant ($P = 0.21$). Compared with warfarin, in both patients with and without VHD, apixaban resulted in a similar benefit in terms of reduction of stroke or systemic embolism (interaction $P = 0.38$), major bleeding (interaction $P = 0.23$), and of all-cause mortality (interaction $P = 0.10$).[17]

ENGAGE AF TIMI 48—The ENGAGE (Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs. Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation) study showed that both doses of edoxaban (60 mg or 30 mg) were non-inferior to warfarin at 2.8 years. Patients with moderate or severe MS and mechanical heart valves were excluded from the study; however, all the other VHD conditions were included.[11] A sub-analysis found that out of the 21 105 patients enrolled in the trial, 2824 (13%) had a history of moderate or severe VHD or had undergone prior valve surgery. On average, patients with VHD were older, more often female, with a history of heart failure, and had higher CHA_2DS_2VASCs. Compared with patients without VHD, patients with VHD had similar rates of stroke or systemic embolism ($P = 0.56$) but significantly higher rates of death (HR, 1.40; 95% CI, 1.26-1.56; $P < 0.001$), major adverse cardiovascular events (MACEs), (HR, 1.29; 95% CI, 1.16-1.43; $P < 0.001$), and major bleeding (HR, 1.21; 95% CI, 1.03-1.42; $P = 0.02$). Treatment with edoxaban 60 mg showed efficacy similar to warfarin regardless of the presence of VHD, in terms of stroke and systemic embolism (interaction $P = 0.26$) and major bleeding (interaction $P = 0.57$).[18]

RIVER—The RIVER (Rivaroxaban for Valvular Heart diseasE and atRial Fibrillation) trial enrolled 1005 patients with AF and a bioprosthetic mitral valve, who had an indication for oral anticoagulation for the prevention of thromboembolism. Patients were randomized to rivaroxaban or warfarin in a 1:1 ratio and followed-up for 1 year. RIVER is currently the only study comparing direct oral anticoagulants and warfarin in a population thoroughly consisting of patients with VHD. Rivaroxaban was non-inferior to warfarin with respect to the primary endpoint of death, MACEs, and major bleeding (difference in mean time to event, 7.4 days; 95% CI, −1.4 to 16.3; $P < 0.001$ for non-inferiority).[19]

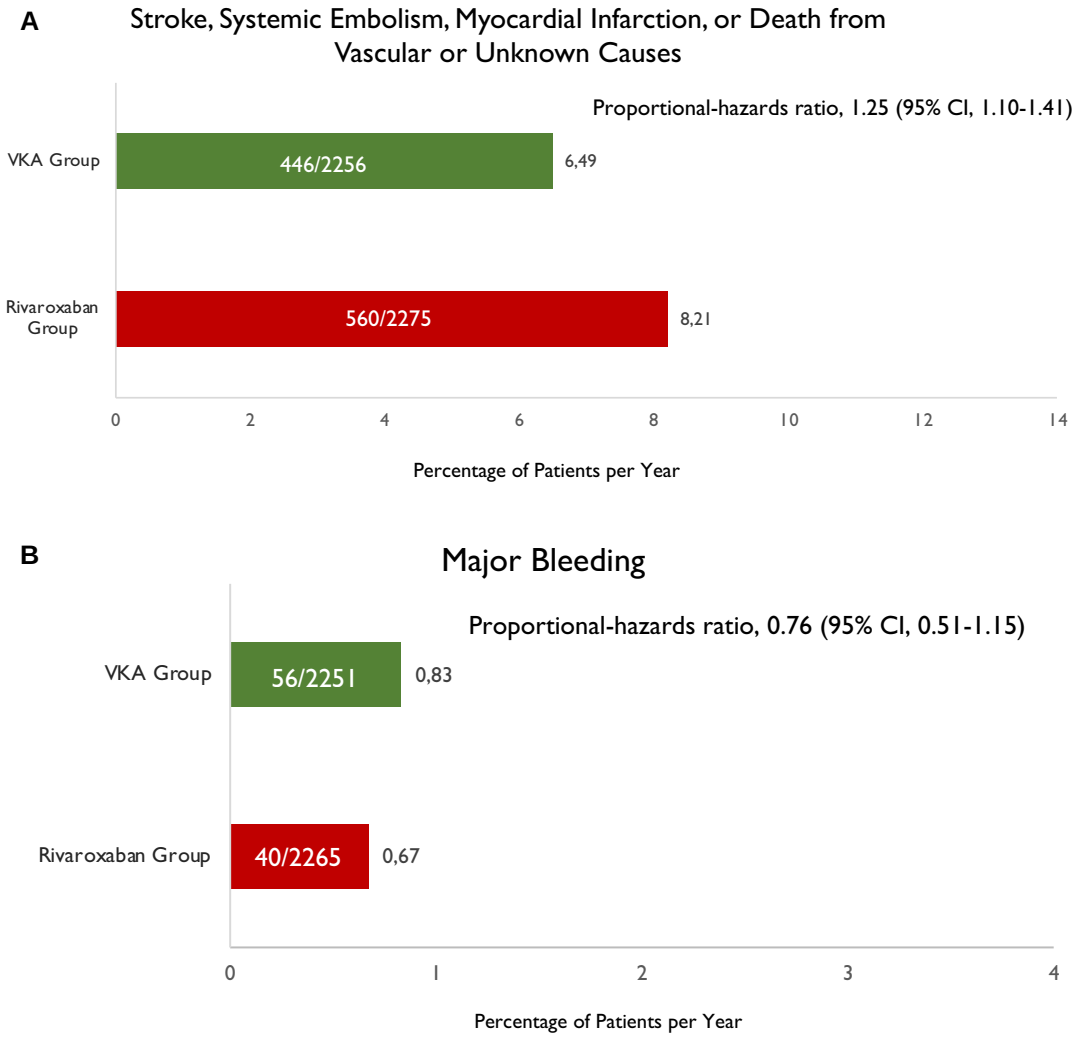

Figure 1 (*A*) Thromboembolic outcomes in the INVICTUS study. (*B*) Major bleeding in the INVICTUS study.

Oral anticoagulation in patients with atrial fibrillation and rheumatic valvulopathy: INVICTUS

The INVICTUS (INVestIgation of rheumatiC AF Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies, Non-Inferiority) trial investigated whether rivaroxaban could represent an alternative to VKAs also in patients with AF associated with RHD. Indeed, the use of a DOAC would come in handy in middle- and low-income countries, where the incidence of RHD is still high and INR monitoring can be challenging.[20]

In this open-label, event-driven trial, 4565 patients with AF or atrial flutter, echocardiographically documented RHD, and at least one criterion among $CHA_2DS_2VASCs \geq 2$, mitral valve area $\leq 2\ cm^2$, spontaneous left atrial echo contrast, or left atrial thrombus were randomized to receive either rivaroxaban (20 mg or 15 mg depending on renal function) or a VKA (to achieve a INR of 2:3). The primary efficacy endpoint was a composite of stroke, systemic embolism, myocardial infarction, and death from vascular (cardiac or non-cardiac) or unknown causes. The primary safety endpoint was major bleeding. The mean duration of follow-up was 3.1 ± 1.2 years. Overall, a total of 85% of patients had moderate-to-severe MS, and, compared to previous trials on DOACs, patients were younger (mean age 50.5 years) and more often female (72.3%).

In the initial trial design, the primary efficacy endpoint was a composite of total stroke and systemic embolism events, and the primary analysis was planned for non-inferiority with a margin of 1.46, with potential testing for superiority if the first hypothesis was confirmed. During the course of the trial, however, the occurrence of a substantially lower-than-expected stroke event rate and a higher-than-expected death rate quickly made it clear that it would take too long to reach the number of stroke events needed to provide the expected statistical power. Therefore, the primary outcome and the non-inferiority margin were modified in the course of work, adopting those of the ACTIVE W study (NCT00243178).

The primary endpoint occurred in 560 patients (8.21%) of the intervention group and 446 patients (6.5%) of the control group (HR, 1.25; 95% CI, 1.1-1.4; $P < 0.001$).

Higher rates of stroke (HR, 1.37; 95% CI, 1.0–1.89), mostly ischemic (HR, 1.53; 95% CI, 1.06–2.2) and death (HR, 1.23; 95% CI, 1.09–1.4; $P < 0.001$), were found in the intervention group, mainly death from vascular causes (HR, 1.29; 95% CI, 1.12–1.49), sudden cardiac death (HR, 1.51; 95% CI, 1.16–1.96), and death from mechanical causes or pump failure (HR, 1.35; 95% CI, 1.11–1.64). The median survival time was 1599 days in the intervention group and 1675 days in the control group, with a difference of −76 days (95% CI, −121 to −31 days; $P < 0.001$ for superiority). No significant differences were observed either in terms of hospitalizations (HR, 1.08; 95% CI, 0.97–1.21) or in terms of major bleeding between the two groups (HR, 0.76; 95% CI, 0.51–1.15; $P = 0.18$) (*Figures 1A* and *B*).

One may wonder whether the trial had sufficient statistical power for stroke outcome, because the events that occurred in the two groups were fewer than expected. Furthermore, while it is likely to attribute to chance the modest difference in stroke rates between the two groups, the same cannot be said for the considerable difference in mortality rates. Considering the significant prognostic impact of adherence to therapy, a higher rate of drug discontinuation was observed in the intervention group (which however does not explain the advantage of VKAs in light of the on-treatment analysis). It could be argued that the better adherence of the control group derives from the greater number of medical interactions (necessary for INR monitoring) or that the difference in outcome became evident after 3 years of follow-up because of a late achievement of better control of INR or even that the reduction in mortality associated with VKAs is the indicator of a class effect on the natural history of RHD.

Regardless of these questions, INVICTUS demonstrated that rivaroxaban was inferior to VKAs in preventing stroke, systemic embolism, myocardial infarction, or death in patients with RHD-related AF and was similar in bleeding risk. At present, therefore, international guidelines should even be strengthened to support the use of VKAs in patients with RHD-related AF. The use of long-term anticoagulation in the presence of rheumatic MS and sinus rhythm remains controversial, with indications based solely on the enlargement of the left atrium and the presence of spontaneous echo contrast.[21]

Conclusions

In patients with AF, anticoagulation (for stroke prevention) is only the first of the three pillars of the integrated Atrial Fibrillation Better Care (ABC) pathway, according to which it is also necessary to achieve a better control of symptoms (rate and rhythm) and a careful management of cardiovascular risk factors and comorbidities.

As regards to the prevention of thromboembolic risk in patients with AF and VHD, the literature data leave some room for DOACs in patients with non-rheumatic valvulopathy, including patients with valve bioprostheses, but the INVICTUS study clarifies that anticoagulation with VKAs should be preferred in patients with AF and RHD.

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Data availability

No new data were generated or analysed in support of this research.

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