

Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease: systematic review and meta-analysis

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The non-vitamin K antagonist oral anticoagulants (NOACs) were approved for non-valvular atrial fibrillation (AF) but this term may be misnomer. Thus, the term non-mechanical and rheumatic mitral valvular (non-MARM) AF was proposed to exclude patients with valvular heart disease (VHD) without contraindications for NOACs. We aimed to review the efficacy and safety of NOACs in patients with AF and VHD compared to Vitamin K Antagonists (VKA). We performed a systematic review with meta-analysis (PROSPERO CRD42015024837) including data from randomized controlled trials (RCTs) retrieved in November 2016. The efficacy and safety data were pooled using random-effects meta-analyses using the hazard ratio (HR) with the 95% confidence interval (95%CI). Trial sequential analysis (TSA) was performed in statistical significant results to evaluate whether cumulative sample size was powered for the obtained effect. In 5 RCTs (with 12 653 VHD AF patients), NOACs significantly reduced the risk of stroke and systemic embolism (HR 0.73, 95%CI:0.60–0.90; TSA showed estimate was robust — O'Brien-Fleming α -spending boundary crossed before reaching the estimated information size) and intracranial hemorrhage (HR 0.45, 95%CI:0.24–0.87) compared with VKA. Major bleeding risk was not significantly different. In patients with bioprosthesis (3 trials-280 patients) the risks of thromboembolism (HR 0.65, 95%CI:0.20–2.08) and major bleeding (HR 0.94, 95%CI:0.28–3.18) with NOACs were similar to VKA. NOACs are efficacious and safe in patients with non-MARM VHD AF, showing significant reduction in the risk of stroke and systemic embolism and intracranial hemorrhage compared with VKA.

Keywords

Apixaban • Dabigatran • Edoxaban • Rivaroxaban • Valve • Bioprosthesis

Introduction

The novel oral anticoagulants, also called non-vitamin K antagonist oral anticoagulants (NOACs), have shown to be safe,^{1–5} are at least as efficacious as Vitamin K antagonists (VKA) in patients with non-valvular atrial fibrillation (AF),^{6,7} and do not require regular evaluations of haemostasis parameters.^{7,8} However each of the pivotal trials

that led to the approval of NOACs had different definitions for the 'non-valvular' term,⁹ which may lead to doubts in the prescription of these drugs in patients with valvular heart disease (VHD) who were eligible for these trials.

Patients with VHD are associated with an increased risk of stroke, irrespective of the cardiac rhythm.¹⁰ Furthermore, differently from non-MARM AF, where 90% of the thrombi are likely to arise from

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the left atrial appendage, VHD patients, particularly those with rheumatic VHD, thrombi are deemed to be formed outside from the left atrial appendage in 40% of the cases.¹¹ Therefore, it is not clear whether NOACs behave similarly in VHD patients. Additionally, patients with mechanical heart valves (MHV) should be anticoagulated with VKA instead of NOACs due to the harmful effect of dabigatran in a phase II trial (RE-ALIGN).¹²

Acknowledging the gap in the evidence and uncertainty about the topic, we performed a systematic review with meta-analysis in order to appraise the impact of NOACs compared with VKA in patients with AF and VHD.

Methods

This systematic review was registered in the International prospective register of systematic reviews—PROSPERO (<https://www.crd.york.ac.uk/PROSPERO/>) with the registration reference CRD42015024837 (DOI 10.15124/CRD42015024837). Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were used for reporting.¹³

Search strategy

We performed an electronic search through the databases MEDLINE (Ovid), Cochrane Collaboration's Database (Ovid), Health Technology Assessment, Database of Abstracts of Reviews of Effects, NHS Economic Evaluation, Cochrane Database of Systematic Reviews, PsycINFO, Web of Science Collection, KCI Korean Journal Database and SciELO Citation Index, all until November 2016,¹⁴ and is detailed in [Supplementary material online](#). Food and Drug Administration (FDA) and European Medicines Agency (EMA) reports were also consulted for additional unpublished data. Reference lists of retrieved studies and review papers were also cross-checked.

Study selection (eligibility criteria) and data collection

We searched for randomized controlled trials (RCTs) comparing NOACs with VKA. Studies were required to include patients with AF or atrial flutter with indication for anticoagulation, and reporting data of patients with VHD (including native valvular disease, bioprosthesis, and valve repair). For the purpose of this review, the VHD definition excluded patients with mechanical and rheumatic mitral valvular (moderate to severe mitral stenosis,¹⁵ i.e. with a valve area ≤ 1.5 cm²) AF (MARM-AF).^{9,16}

Titles and abstracts of obtained records were screened independently by two authors. Potentially relevant studies were assessed in full-text to determine its appropriateness for inclusion. Doubts and disagreements were solved by a third person. Data about the included studies, namely design, characteristics of the patients, interventions' data outcomes were retrieved.

Quality of reporting was independently analysed by two investigators using the Cochrane Collaboration's Tool.¹⁷ The pre-specification of a VHD subgroup analysis and the adjustment of outcome estimates to confounding factors were also considered in the risk of bias assessment of trials.

Outcomes

The primary efficacy outcome was the composite of stroke (ischaemic, haemorrhagic, and undetermined stroke) and systemic embolism, and the primary safety outcome was major bleeding according to the

definition of International Society of Thrombosis and Haemostasis.¹⁸ Intracranial haemorrhage (ICH) was the secondary outcome.

Whenever possible and adequate, valvular, or intracardiac thrombosis were included in the primary efficacy outcome.^{12,19}

Statistical analysis

Statistical analyses were performed using RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Individual studies and meta-analysis estimates were derived and presented in forest plots.

For the meta-analysis, we used by default the random-effects model (irrespective of the heterogeneity) to estimate pooled risk ratios and 95% confidence intervals (CIs).²⁰ Hazard ratio (HR) was chosen as the measure to report the results.²¹ Overall results were statistically significant if $P < 0.05$. Data from VHD and non-VHD random effects meta-analysis were presented and the interaction between these subgroups was evaluated.

Whenever a trial presented estimates for two different dosages, a conservative approach was adopted by pooling the different dose estimates into a single estimate using random effects meta-analysis, and then pooled together with other RCTs. In a secondary analysis, the estimates from different dosages were pooled independently with the other trials.²²

We also performed a sub-analysis of patients with bioprosthesis or valve repair in order to assess the risk of NOACs in this subgroup.

Heterogeneity was measured through the I^2 test that estimates the percentage of total variation between studies.²³

When results were statistically significant, we calculated the number of patients needed to treat (NNT) to expect the avoidance of one event.²⁴ Number of events avoided per 1000 treated-patients was also derived.

Publication bias was tested if more than 10 studies were included in the analyses.²⁵

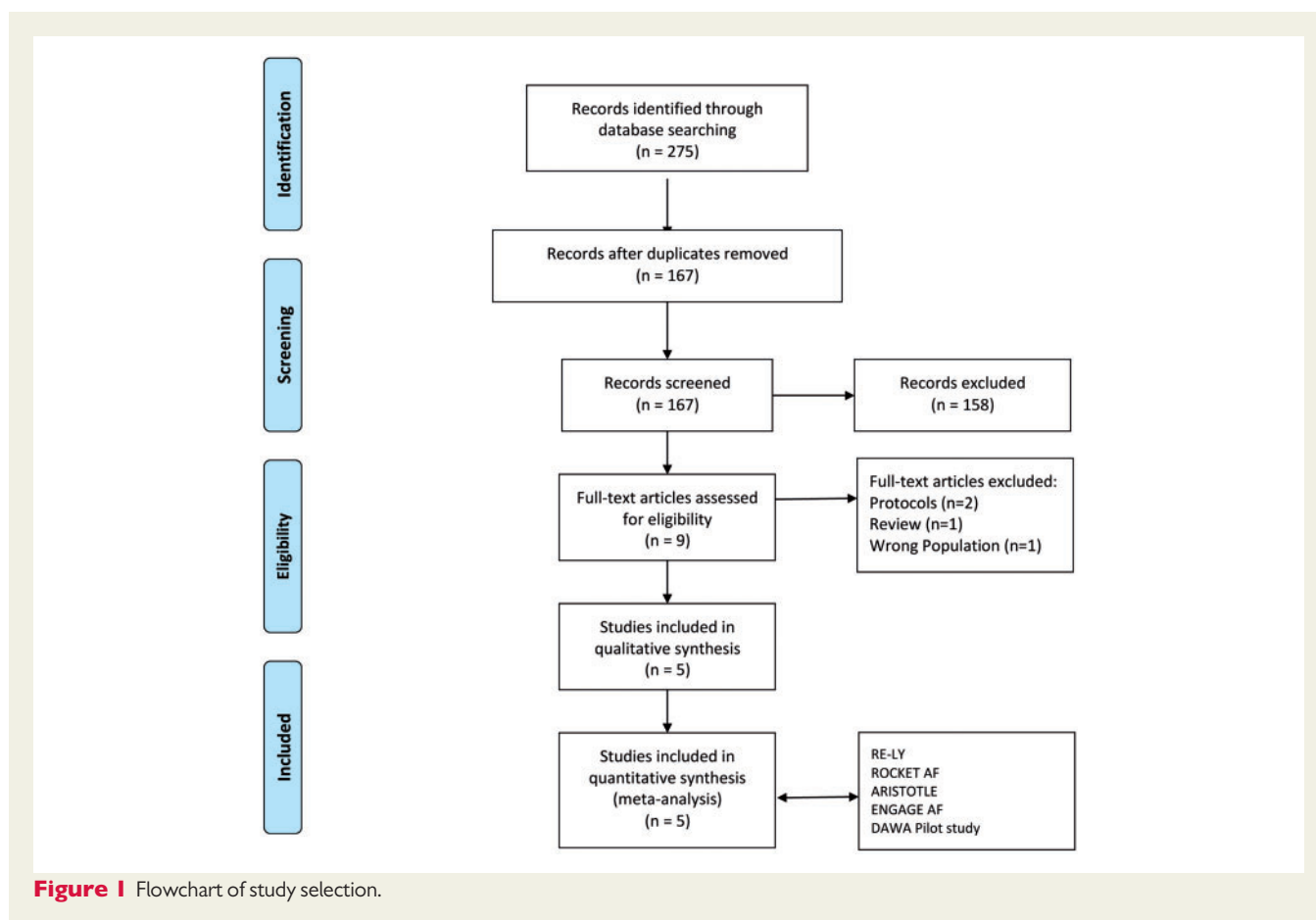
Trial sequential analyses (TSAs) were performed for primary outcomes using TSA version 0.9 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark, 2011) to explore whether cumulative data were adequately powered to evaluate the outcomes in the subgroups of interest, patients with VHD in this case.^{26–28} The required information size and the O'Brien-Fleming adjacent trial sequential alpha spending monitoring boundaries were calculated based on a two-sided 5% risk of a type I error, 20% risk of a type II error (power of 80%), risk reduction based on pooled analysis, the weighted incidence of events in the control group, and heterogeneity.^{27,28} Power of the outcomes was interpreted if significance was reached with either a minimum sample size, or crossing trial sequential alpha spending monitoring boundary.

Results

Studies included

Five studies with VHD AF patients were encompassed in the review,^{29–33} including one study exclusively with patients having bioprosthetic heart valves (aortic or mitral) and post-operative AF.³² *Figure 1* details the study selection process and *Table 1* shows the types of VHD evaluated in each trial. Risk of bias assessment is provided in [Supplementary material online](#) (see [Supplementary material online, Figure S1](#)).

These studies included 12 653 AF patients with VHD. Details about events and characteristics of VHD are detailed in [Supplementary material online, Tables S1 and S2](#). Mitral regurgitation was the most common type of native VHD. About 5.3% of the

**Table 1** The different types of VHD included in the different trials

Trial	Design	NOAC	Control	No VHD	VHD			Data in the meta-analysis
					Non MARM-AF	Native valvular heart disease ^a	Bioprosthetic heart valves	
RE-LY	Open-label RCT	Dabigatran 110/150 mg bid	VKA	✓	✓			Post hoc retrospective RCT subgroups' data
ROCKET AF	DB RCT	Rivaroxaban 20/15 mg od	VKA	✓	✓		✓	Post hoc retrospective RCT subgroups' data
ARISTOTLE	DB RCT	Apixaban 5/2.5 mg bid	VKA	✓	✓	✓	✓	Post hoc retrospective RCT subgroups' data
ENGAGE AF	DB RCT	Edoxaban 60/30 mg od	VKA	✓	✓	✓	✓	Post hoc retrospective RCT subgroups' data
DAWA Pilot trial	Open-label RCT	Dabigatran 110 mg bid	VKA			✓		RCT data
						Post-operative AF		

AF, atrial fibrillation; bid, twice daily; DB, double-blinded; INR, International Normalised Ratio; MARM, mechanical and rheumatic mitral valve disease⁶; N/A, not applicable; NOACs, non-vitamin K antagonist oral anticoagulants; od, once daily; RCT, randomized controlled trial; VKA, INR-adjusted vitamin K antagonist.

^aExcluding significant mitral stenosis.

^bIncludes valvuloplasty (percutaneous or surgical), annuloplasty.

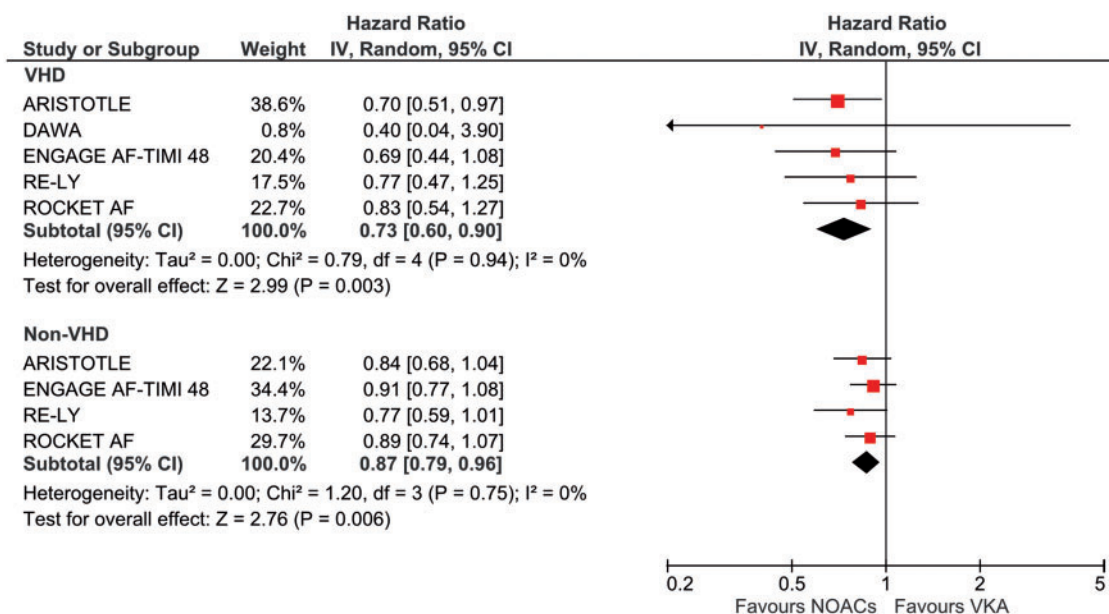


Figure 2 Forest plot with pooled estimates regarding stroke and systemic embolism risk. CI, confidence interval; IV, inverse variance; NOACs, non-vitamin K antagonist oral anticoagulants; VHD, valvular heart disease, VKA, vitamin K antagonist.

patients with VHD had history of valvular interventions in ARISTOTLE and ROCKET AF. VHD patients were older, had more frequently history of coronary artery disease (or myocardial infarction), heart failure, and renal dysfunction than patients without VHD.^{29–31, 33}

Stroke and systemic embolism

Considering stroke and systemic embolism, NOACs were more efficacious compared with VKA in patients with and without VHD. NOACs significantly reduced the risk of stroke and systemic embolism in both VHD (HR 0.73, 95% CI: 0.60–0.90) and non-VHD subgroups (HR 0.87, 95% CI: 0.79–0.96) (Figure 2).

None of the analyses showed heterogeneity and no significant differences were observed between groups ($P_{\text{interaction}} = 0.15$).

The cumulative evidence for the VHD subgroup reached 84.4% of minimum information size required (14 998 patients) adjusted for the obtained relative risk reduction (RRR) and heterogeneity (see [Supplementary material online, Figure S2](#)). As statistical significance was obtained for the VHD subgroup before the information size has been reached it was important to evaluate whether an adjustment of significance boundaries (O'Brien-Fleming boundaries) to the sample size still results in statistical significant estimates. The TSA graph shows that cumulative estimates were robust to determine a premature statistically significant result (see [Supplementary material online, Figure S2](#)).

Major bleeding

Major bleeding analysis did not show significantly different risk associated with NOACs compared with VKA in VHD patients compared with VKA (HR 0.91, 95% CI 0.68–1.23) (Figure 3).

In non-VHD population, NOACs were associated with a significant major bleeding risk reduction (HR 0.76, 95% CI 0.63–0.91)

(Figure 3). There was significant statistical heterogeneity in both major bleeding risk analyses (Figure 3).

In VHD subgroup, the heterogeneity was driven by the negative result ROCKET AF trial. Excluding this study there was no heterogeneity ($P_{\chi^2} = 0.90$, $I^2 = 0\%$) and a significant major bleeding risk reduction was observed (HR 0.79, 95% CI 0.68–0.91).

Overall no significant differences were found between VHD and non-VHD regarding major bleeding ($P_{\text{interaction}} = 0.31$).

Intracranial haemorrhage

NOACs showed a significant risk reduction of ICH in VHD patients (HR 0.45, 95% CI 0.24–0.87) and non-VHD patients (HR 0.47, 95% CI 0.39–0.56) (Figure 4) compared with VKA.

Significant statistical heterogeneity was present in the VHD analysis due to the neutral results of the ROCKET AF trial ($P_{\chi^2} = 0.02$ and $I^2 = 69\%$).

The risk reduction of ICH with NOACs was not different among VHD and non-VHD patients ($P_{\text{interaction}} = 0.94$).

The cumulative evidence for ICH risk in the VHD subgroup reached 30.7% of minimum information size required (41 118 patients) adjusted for the obtained RRR and heterogeneity, and the significance of the outcome was not robust enough to determine a premature statistically significant result (see [Supplementary material online, Figure S3](#)). The results of the TSA of intracranial haemorrhage were largely influenced by the heterogeneity ($I^2 = 69\%$). An exploratory TSA was performed assuming no heterogeneity due to the absence of differences among the VHD and non-VHD subgroups, and the cumulative evidence (with 87.9% of minimum information size required without heterogeneity) was robust to determine the significance of the risk reduction (see [Supplementary material online, Figure S4](#)).

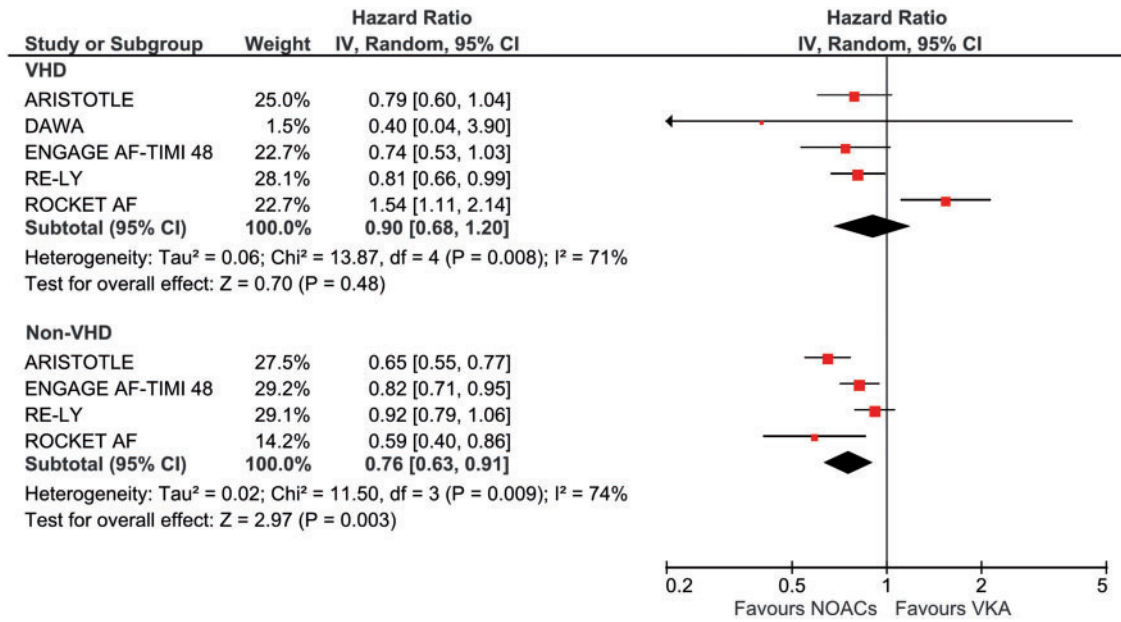


Figure 3 Forest plot with pooled estimates regarding major bleeding. CI, confidence interval; IV, inverse variance; NOACs, non-vitamin K antagonist oral anticoagulants; VHD, valvular heart disease, VKA, vitamin K Antagonist.

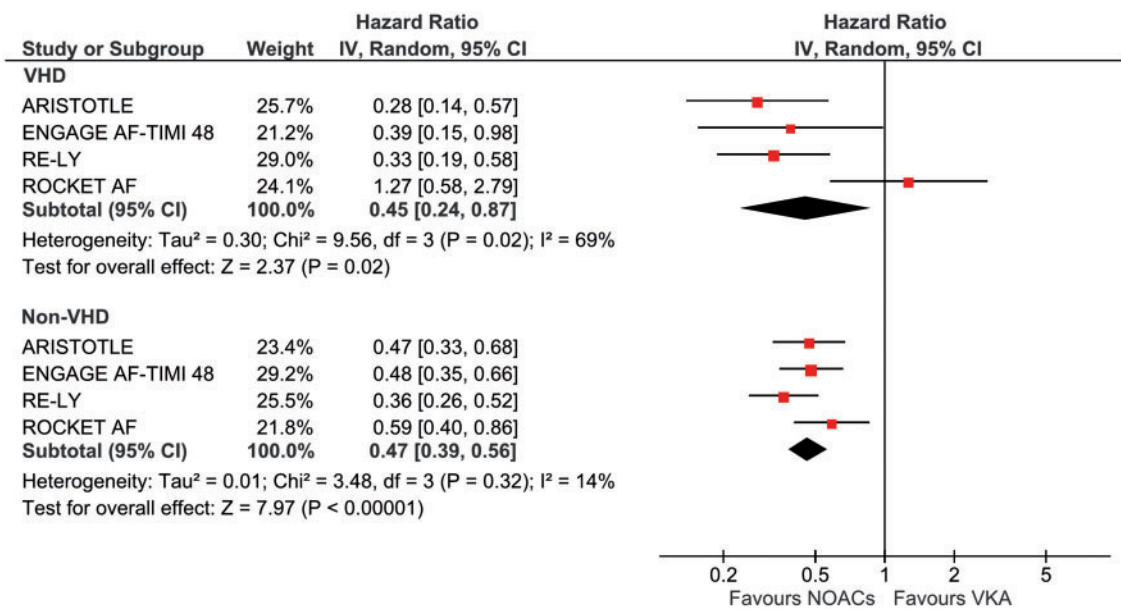


Figure 4 Forest plot with pooled estimates regarding intracranial haemorrhage. CI, confidence interval; IV, inverse variance; NOACs, non-vitamin K antagonist oral anticoagulants; VHD, valvular heart disease, VKA, vitamin K antagonist.

Bioprosthetic heart valves and secondary analyses

Regarding patients with bioprosthetic heart valves, there were three studies with detailed data about this subgroup: an interim report of 82 ARISTOTLE patients (41 in the apixaban arm vs. 41 in the warfarin

arm),³⁴ the results of ENGAGE AF high dose edoxaban vs. warfarin from a conference paper,³⁵ and a pilot study of dabigatran 110 mg twice daily vs. warfarin in patients with bioprosthesis and post-operative AF (the DAWA Pilot study). Pooling the available data (3 studies with overall 280 patients), both thromboembolic

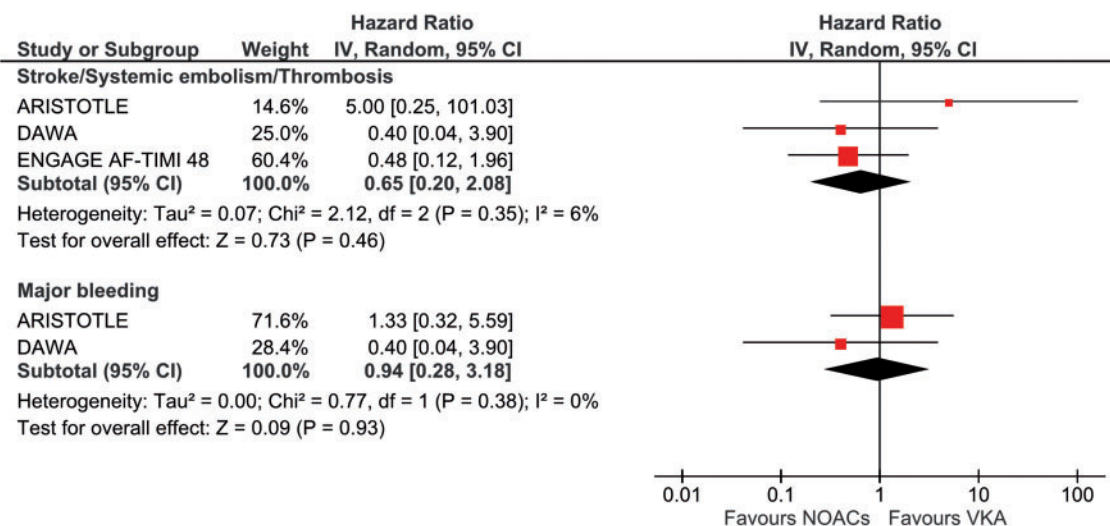


Figure 5 Forest plot with pooled estimates of thromboembolic complications and major bleeding risks with NOACs in patients with AF and bio-prosthesis. CI, confidence interval; IV, inverse variance; NOACs, non-vitamin K antagonist oral anticoagulants; VHD, valvular heart disease, VKA, vitamin K antagonist.

complications (HR 0.65, 95% CI 0.20–2.08) and major bleeding risks (HR 0.94, 95% CI 0.28–3.18) with NOACs were similar to VKA (Figure 5).

The absolute estimates expressed as NNT or events avoided per 1000 patients treated are depicted in [Supplementary material online, Table S3](#). Secondary analyses overlap the results of the primary analyses (see [Supplementary material online, Table S4 and Figure S5](#)).

Discussion

The main findings of this systematic review were: (i) NOACs reduced the risk of stroke and systemic embolism in AF patients with VHD (non-MARM) compared with VKA. TSA confirmed the robustness of NOACs efficacy in VHD patients; (ii) In comparison to VKA, the ICH risk (but not major bleeding) was significantly reduced by NOACs in AF patients with VHD similarly to AF patients without VHD; and (iii) There were not any concerning signs regarding the thromboembolic and major bleeding risks in patients with bioprosthetic valves.

The efficacy outcome analysis showed a ‘class effect’ in NOACs prevention of stroke and systemic embolism in patients with non-MARM AF (both in patients with or without VHD). Major bleeding risk was not significantly reduced with patients with VHD as occurred with non-VHD. Intracranial haemorrhage risk was significantly halved in both patients with VHD and non-VHD. However significant statistical heterogeneity was noticed, mostly due to the results of the VHD subgroup of the ROCKET AF trial. Rivaroxaban was associated to increased risk of major bleeding and a non-significant ICH risk increase in patients VHD but not in those without VHD. The reasons for such treatment–disease interaction are not clear. However, play of chance or unidentified residual confounding effects may have had a role, despite the adjustments in the estimates.²⁹ For example, ROCKET AF was the trial with the larger proportion of elderly

patients and the median age was 65 years, which is the threshold of HAS-BLED score to be considered at higher bleeding risk. The HAS-BLED score was similar in both VHD and non-VHD (2.8 vs. 2.8) but does not consider age as a continuous risk factor and patients with VHD were older (median 75 vs. 72 years old) and this feature could have influenced the clinical impact of rivaroxaban. Yet it seems likely that NOACs, particularly apixaban, dabigatran and edoxaban, may offer advantage in terms of ICH risk reduction compared with warfarin showing a dimension of effect similar to non-VHD patients. It is important to stress that VHD patients included in the trials were older, had more frequently history of coronary artery disease, heart failure and renal dysfunction. Despite the peculiarities of this subgroup the cumulative evidence evaluated through TSA confirm the strength of the pooled data regarding stroke prevention and suggest that ICH risk reduction compared with VKA is robust.

The topic here explored is of paramount importance for all stakeholders. About 20% of the patients with AF have VHD and most these patients do not have significant mitral stenosis or MHV.³⁶ NOACs are not recommended in patients with AF and MHV based on the data of the RE-ALIGN trial. The RE-ALIGN study was a phase II RCT that randomized 252 patients with MHV to dabigatran or warfarin.¹⁶ About 28% of these patients (71 patients) had atrial fibrillation or atrial flutter, and 44 of them were treated with dabigatran. The trial was prematurely halted due to the higher risk of thrombotic and bleeding events in the dabigatran arms.¹⁶ There were no data available regarding the subgroup of patients with AF or atrial flutter.

The thromboembolic risk of patients with AF and concomitant valvular bioprosthesis or valve repair does not seem to be extremely different from the common ‘non-valvular’ AF.⁹ Our analysis about this topic pooled the data of 3 studies with 280 patients, which included an interim analysis of bioprosthesis in ARISTOTLE, the data of a prematurely halted phase II DAWA Pilot study (stopped due to low enrolment rate), and the data about bioprosthesis of the

ENGAGE trial. Despite the limitations in terms of sample size and events which precludes a definite and robust conclusion, the current evidence does not suggest harm with NOACs in these patients.

The recognition that NOACs are overall more effective than VKA, with the additional advantages related to the convenience of NOACs is especially relevant. Physicians should acknowledge that other forms of VHD, rather than significant mitral stenosis (mitral valve area $\leq 1.5 \text{ cm}^2$)¹⁵ or MHV, should not be detrimental for NOACs consideration in these patients. NOACs already have a substantial share of the anticoagulants' prescription,^{37–39} but the 'non-valvular' AF label can be misinterpreted and exclude patients that could benefit from these drugs. Considering that NOACs are cost-effective, the dissemination of our results is also of interest to policymakers.^{40–42} The European Society of Cardiology guidelines of atrial fibrillation support that valvular diseases (other than MARM) are bystanders in the stroke risk estimation and in the decision of the type anticoagulant treatment, which means that clinical decisions regarding anticoagulation in this subgroup are similar to the population without VHD.¹⁹

Limitations

Our results are limited by methodological issues associated to the individual studies and meta-analysis. The results of our meta-analysis are based on study-level data and not on individual patients' data. Furthermore, the meta-analysis is majorly composed by specific subgroups (VHD and non-VHD) derived from *post hoc* analyses of RCTs which downgrades the robustness of the data.

We pooled together the different NOACs under the assumption of a class effect of these drugs, which may be assumed for efficacy purposes, but not for safety purposes as detailed previously, considering the significant heterogeneity between the trials.

Whenever possible we used adjusted data, and a TSA was performed which represents an addition to previously published review.⁴³ Pooled estimates regarding stroke or systemic embolism and ICH (without considering the heterogeneity) were strong enough to determine robustness in the significance of the results through this method.

Conclusions

In patients with AF and VHD, without MHV or significant mitral stenosis (mitral valve area $\leq 1.5 \text{ cm}^2$), NOACs reduced significantly the risk of stroke or systemic embolism and intracranial haemorrhage compared with VKA. The global major bleeding risk was not increased but bleeding results were heterogeneous between the trials. There was not any risk increase among patients with bioprostheses treated with NOACs but data are limited.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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