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Efficacy and Safety of Anticoagulants in Patients with Atrial Fibrillation and History of Falls or Risk of Falls: A Systematic Review and Multilevel Meta-Analysis

Efficacy and safety of anticoagulants in patients with atrial fibrillation and history of falls or risk of falls. A systematic review and multilevel meta-analysis

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Running head: Multilevel meta-analysis of anticoagulants in patients with atrial fibrillation and falls.

Declarations

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Competing interests

TG is an employee of Johnson and Johnson Medical. RH declares a financial - non-personal, non-specific interest, having delivered educational workshops on health economics, medicines management and HTA for cancer specialists supported by unrestricted sponsorship by the pharmaceutical industry and an industry association (March 2019). No fees received personally. Not specific to the topic of the review. GYHL has served as a consultant for Bayer/Janssen, Bristol Myers Squibb (BMS)/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo and as a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. The other authors report no competing interests (SD, PL and GC).

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Not applicable.

Consent to participate

Not applicable.

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Not applicable.

Availability of data and materials

Template data collection form, data extracted, analytical code and any other study documents will be available from the corresponding author on reasonable request.

Code availability

Analytical code will be available from the corresponding author on reasonable request.

Authors' contributions

Conceptualization: GYHL, PL, GC, SD, RH and TG; methodology: GYHL, PL, GC, SD, RH and TG; formal analysis: GC and TG; investigation: GYHL, PL, GC, SD, RH and TG; data curation: GC and TG; writing

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Abstract

Introduction: Atrial fibrillation (AF) is a major cause of stroke. Anticoagulants substantially reduce risk of stroke but are also associated with an increased risk of bleeding. Because of that many patients do not receive anticoagulants; particularly patients at risk of falls. This systematic review and meta-analysis aims to compare anticoagulant treatment options for the management of atrial fibrillation patients at risk of falls or with a history of falls.

Methods: We conducted a PRISMA systematic review (until March 2022), including studies evaluating safety and efficacy of different anticoagulants (Vitamin K antagonist [VKA] versus non-vitamin K antagonist oral anticoagulant [NOAC]). Outcomes were ischemic stroke, major bleeding, intracranial hemorrhage, hemorrhagic stroke, myocardial infarction, gastro-intestinal bleeding, cardiovascular and all-cause mortality. A multilevel meta-analysis was conducted adjusting for clustering effects within studies examining more than one effect size.

Results: 919 articles were identified, 848 after removing duplicates. 155 were screened for full text and 10 articles were retained for final quantitative synthesis. Risk of bias was moderate to serious for the included studies. In meta-analysis, NOACs were associated with superior effectiveness compared to VKA for ischemic stroke/systemic embolism (HR 0.82, 95%CI [0.69–0.98]; p<0,05) and safety (hazard ratio (HR) 0.53, 95% confidence interval (CI) [0.40–0.71]; p<0,05) for intracranial hemorrhage. There were no differences in other outcomes.

Conclusion: NOACs were associated with less intracranial hemorrhages and ischemic strokes/systemic embolisms than VKAs in AF patients at risk of falls. These findings suggesting preferred use of NOACs over VKAs would have clinical implications for physicians, patients and policy makers.

Key points:

- AF patients at risk or with history of falls often do not receive anticoagulants. Anticoagulation treatments for AF patients at risk or with history of falls is an under-researched area and clinical guidelines are missing.
- This systematic review and multilevel meta-analysis evaluated safety and efficacy of NOACs compared to VKA in patients with atrial fibrillation and at risk of falls or with history of falls.
- NOACs were associated with less intracranial hemorrhages and ischemic strokes/systemic embolisms than VKAs in AF patients at risk of falls. These findings suggesting preferred use of NOACs over VKAs would have clinical implications for physicians, patients and policy makers.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia [1] and is a major cause of stroke, heart failure, and death [2], as well as healthcare costs [3]. Stroke is the second most common cause of death in the general population and it is a major cause of disability [4,5]. AF patients have a yearly risk of stroke of 5%, and this risk is increased in the presence of certain risk factors, including left ventricular dysfunction, hypertension, a history of stroke, and increasing age [6].

Treatment with oral anticoagulants (OACs) substantially reduces risk of stroke but is also associated with an increased risk of bleeding and especially intracranial hemorrhage which is the most feared complication [7,8]. Because of that, many patients do not receive anticoagulants, and particularly patients at risk of falls or with history of falls [9,10]. In eligible patients with elevated stroke risk overall, the median rate of non-treatment is 23.3% (from 7.9% to 51.1%) [11]. In patients at risk of falls, this rate was estimated at 50% in the era pre-NOAC [12]. AF patients at high risk of falls and on oral anticoagulation do not have a significantly increased risk of major bleeding, suggesting that being at risk of falls should not prevent OAC prescribing [13,14]. Additionally, the HAS-BLED risk stratification tool for bleeding assessment in anticoagulated patients with atrial fibrillation does not consider falls (risk or history) as an independent predictor of major bleeding [15,16].

The non-vitamin K antagonist oral anticoagulants (NOACs) were shown in a number of systematic reviews and meta-analyses to reduce the risk for intracranial hemorrhage by approximately 50% compared to vitamin K antagonists (VKAs) in the general AF population at risk of stroke [17,18], and are therefore the preferred option in guidelines [19,20]. NOACs might be the most appropriate anticoagulant in patients with an increased risk of falls and help to alleviate fears of bleeding complications.

To our knowledge there is limited evidence and there are no recommendations and guidelines for the use of NOACs specifically for the patients at risk of falls or with history of falls. To date, efforts

have been focusing on elderly patients only. In a recent meta-analysis in older AF patients, NOACs were associated with superior efficacy in preventing stroke/systemic embolism (hazard ratio [HR] 0.83, 95% CI: 0.74-0.94), superior safety for intracranial bleeding (HR 0.58, 95% CI: 0.50-0.67) and non-inferiority safety for major bleeding (HR 0.93, 95% CI: 0.86-1.01) and gastrointestinal bleeding (HR 1.17, 95% CI: 0.99-1.38) compared to VKAs [21]. Whether NOACs are the most appropriate anticoagulant treatment option for AF patients at risk of falls or with history of falls remain uncertain.

In the first contemporary study of its kind, the Liverpool AF-Falls project aims to determine the safety and efficacy of NOACs compared to vitamin K antagonists (VKAs) for the management of AF patients at risk of falls or with a history of falls. Results from the project could provide clinicians and policy makers with information on which to make evidence-based recommendations.

2. Methods

The protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020201086) [22]. The methodology used for this systematic review follows the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [23]. This review is reported according to PRISMA 2020 and the checklist is available as an additional file (electronic supplementary material [ESM] Table S1) [24].

2.1. Eligibility criteria

Randomized controlled trials (RCT) (including *post hoc* and ancillary analysis), quasi-randomized studies and observational (prospective, retrospective, case control and cohort studies) studies were included. Animal studies, editorials, letters, case reports, reviews, case series, eminence-based opinions and conference abstracts were excluded. Systematic reviews of interventions were excluded but included studies from relevant systematic reviews were assessed for inclusion.

We included studies of adults (age 18 or older) patients with any forms of nonvalvular AF (paroxysmal, persistent or permanent) with history of falls or that are at risk of falls comparing NOACs to VKAs. Patients were defined at risk of falls if they had one of these criteria based on a revised list from Steffel *et al.* [25]: prior history of falls; lower extremity weakness; poor balance; cognitive impairment; vision and/or hearing impairment; orthostatic hypotension; use of psychotropic or antihistaminic, or anticholinergic, or antihypertensive drugs; severe arthritis; dizziness; frailty; polypharmacy defined as a minimum of six pharmaceutical treatments and multimorbidity defined as a minimum of four comorbidities.

Studies including patients receiving ablation, cardioversion, or left-atrial appendage closure were excluded.

The primary efficacy outcome was the composite of ischemic stroke and/or systemic embolism (an acute vascular occlusion of an extremity or organ). The primary safety outcome was major bleeding (defined based on International Society on Thrombosis & Haemostasis for major bleeding in non-surgical patients) [26]. Secondary outcomes included: intracranial hemorrhage (Including all intracerebral, subdural, epidural, subarachnoid hemorrhage and hemorrhagic stroke); gastrointestinal bleeding; clinically relevant non-major bleeding (defined based on International Society on Thrombosis & Haemostasis for major bleeding in non-surgical patients) [27]; myocardial infarction; ischemic stroke; systemic embolism; hemorrhagic stroke; cardiovascular mortality and all-cause mortality.

2.2. Search methods for identification of studies

The following bibliographic databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, Embase (via OVID); MEDLINE (via OVID), Scopus and Web of Science. We also searched the following trials register: the US National Institutes of Health Register (www.clinicaltrials.gov). Finally, we double-checked the reference lists of all the relevant studies and reviewed the articles to identify additional relevant studies. English-language articles published from

inception to March 2022 were identified. Regular alerts were also established to identify subsequent publications.

The search strategy for bibliographic databases was developed from the research question and implemented by a health sciences librarian with expertise in searches for systematic reviews. A combination of terms of medical subject headings (MeSH) and keywords was used in the search strategy for MEDLINE (ESM Table S2). For Embase, similar terms and search limits were used. MeSH terms were replaced with Emtree indexing terms and/or keywords, as appropriate. The search strategies for MEDLINE and Embase was adapted for use in Scopus, Web of Science and the other bibliographic databases. The search results were entered into the EndNote X8 reference management software for screening, once duplicate records were removed using EndNote X8.

2.3. Data collection and analysis

2.3.1 Selection of studies

Two independent reviewers (TG and GC) performed study selection. During stage 1, titles and abstracts were screened to identify potentially relevant studies applying the inclusion and exclusion criteria. At stage 2, full-text review established the final set of included studies, with discrepancies resolved by a third reviewer (GL). The reason for exclusion were noted for all articles rejected at stage 2. Study authors were contacted in cases further information was needed to make a screening decision. A PRISMA flow diagram was developed to record the study selection process [24].

Data was extracted from each eligible study using a custom data extraction template by one reviewer (TG) and cross-checked with the source article by a second reviewer (GC). Discrepancies and differences in interpretation were resolved through discussion, and if necessary, by consultation with a third reviewer (PL or GL). Where insufficient data were presented, we requested additional information from the study authors. The following were collected from each study: study characteristics (publication year, authors, title, study objectives and study outcomes), study population (such as age, gender, and diagnostic criteria), study design, intervention and control

details, and outcomes (hazard ratios, standard error or 95% confidence intervals). For observational studies, adjusted results were preferred over non adjusted, when available.

2.3.2 Assessment of risk of bias in included studies

In this systematic review, risk of bias in observational studies was appraised with the Risk Of Bias In Non-randomized Studies - of Interventions I tool (ROBINS-I tool) [28]. Using this tool, studies are scored as low, moderate, serious or critical risk of bias. Confounding domains included demographics, comorbidities, bleeding risk, stroke risk and concomitant treatments. Co-interventions included anti-platelet agents. The effect of interest was the effect of assignment. Risk of bias was independently evaluated by two reviewers (TG and GC) and we resolved any disagreements with a third reviewer (GL).

2.4. Statistical Analysis

Data synthesis was conducted based on the sufficient clinical homogeneity regarding participant characteristics, types of intervention and outcomes, and comparability between methods and ability to aggregate data. Statistical heterogeneity as consequence of clinical and/or methodological diversity was evaluated both by visual inspection of the forest plots and a formal statistical test, using Cochran Q test and I^2 statistic [29]. If heterogeneity was low or minor, a fixed effect model was used to pool the data; if heterogeneity was moderate-to-substantial a random-effects model was used instead.[29] For the fixed effect model, the generic inverse variance method was used. For the random-effects model, data was pooled across studies using the DerSimonian and Laird model [30].

For outcomes that included studies with multiple effect sizes (e.g., when a study provided separate effect sizes for different NOACs, or different subgroups of patients being at risk of falls) a multilevel random effects meta-analysis was conducted which takes into account the hierarchical structure of the dataset [31,32]. We assumed that effect sizes within studies were correlated with a correlation coefficient $\rho=0.5$ to calculate the variance-covariance matrix (sensitivity analyses were conducted using $\rho=0.3$ and $\rho=0.7$) [32,33]. The restricted maximum likelihood method was used to estimate

model overall effect. Confidence intervals of the model coefficients were calculated with robust variance estimation [34].

Results of meta-analysis were presented as pooled HRs with 95% CIs. We assessed the publication bias using Funnel plot and Egger's regression test for outcomes reported in at least 5 studies. A modified version of the Egger's regression test was used with robust variance estimation for handling dependency for outcomes that included studies with multiple effect sizes [35]. Statistical analyses were performed in R using RStudio version 4.0.0 (meta and metafor packages) [36].

2.5. Quality of evidence

Two reviewers (TG and GC) assessed the quality of evidence with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system which considers study design, risk of bias, inconsistency of results, indirectness, imprecision and other factors [37]. GRADE Guidelines 18 was followed as we assessed non-randomized studies with the ROBINS-I tool [38]. Disagreements were resolved by a third review author (PL or GL). Assessment results were described in summary of findings (SoF) tables; GRADEpro GDT was used to create SoF tables [39].

3. Results

3.1. Study selection and characteristics

During the search process, 919 abstracts were identified. Following the removal of duplicates, 693 abstracts were excluded at stage 1, 155 full-text articles were assessed further for eligibility, and 10 met eligibility criteria for inclusion in this review [25,40–48]. Reasons for exclusion included study design (22 articles), comparator (15 articles), outcome (six articles), population (80 articles), and research question (22 articles). The PRISMA flow diagram is presented in Fig. 1. All studies were non-randomized. Five articles were retrospective cohorts [41,44,46–48], and the others were subgroup analyses of randomized clinical trials (one pre-specified subgroup analysis of ENGAGE-AF-TIMI trial [25,49], three post-hoc analyses of the ARISTOTLE trial [40,42,43,50] and one post-hoc analysis of the ROCKET AF trial [45,51]). Lip *et al.* 2020 [46], Hohmann *et al.* 2019 [48] and Martinez *et al.* 2018 [47] contributed three effect sizes each as they investigated either different NOACs compared to VKA, or

different subgroups of AF patients being at risk of falls. The subgroup analyses [40,42,43] of the ARISTOTLE trial also contributed three effect sizes as they analyzed distinctly different subgroups of AF patients being at risk of falls. Sample sizes ranged between 617 and 79,796 AF patients at moderate or high thromboembolic risk and with history of falls [40] or at risk of falls [25,41–48]. Most of the patients were elderly, mean age ranging from 71 to 83. The median follow-up period for studies ranged from 0.5 to 2.8 years. The main characteristics of the studies included are shown in Table 1.

3.2. Risk of bias of included articles

Based upon the ROBINS-I tool for non-randomized studies, the overall risk of bias ranged from moderate to serious according to the included articles (ESM Fig. S1). All studies conducted appropriate statistical methods to adjust for the confounders (domain 1), not always integrating all the confounding domains (3/10). They used either propensity score weighing (2/10) or matching (1/10) methods or multivariate Cox regression model (7/10) to reduce confounders and account for covariates that may impact the outcomes. Regarding selection bias and bias due to missing data (domains 2 and 5), the included studies were at low risk. In relation to bias in classification of the intervention (domain 3), bias due to deviation from the intended intervention (domain 4), bias in measurement of outcome and reporting bias (domains 6 and 7), included studies were at low or moderate risk of bias for these domains except Martinez *et al.* 2018 which was at serious risk of bias due to deviation from the intended intervention as they did not censor follow-up time for treatment switching [47].

3.3. Outcome assessment

In the prophylaxis of stroke or systemic embolism (15 effect sizes), NOACS were superior to VKAs (hazard ratio (HR) 0.82, 95% confidence interval (CI) [0.69–0.98]; $p<0.05$; $I^2=67.7\%$)), Fig. 2. Of the 10 articles included in the meta-analysis, seven evaluated the hazard for intracranial hemorrhage (15 effect sizes), which was lower with NOACs compared to VKA (HR 0.53, 95%CI [0.40–0.71]; $p<0,05$; $I^2=46\%$), Fig. 3. In reducing the risk of major bleeding (11 effect sizes), NOACs were not different from

VKAs (HR 0.88, 95%CI [0.74–1.04]; p=0.09) (ESM Fig. S2). There were no differences between NOACs and VKA regarding risks in ischemic stroke (HR 0.87, 95%CI [0.60-1.28], p=0.23; eight effect sizes), hemorrhagic stroke (HR 0.51, 95%CI [0.24–1.10]; p=0.10; nine effect sizes), gastro-intestinal bleeding (HR 1.04, 95%CI [0.89-1.23], p=0.44; 12 effect sizes), myocardial infarction (HR 0.76, 95%CI [0.47-1.24], p=0.27; fixed effect model, reported in two studies), cardiovascular mortality (HR 1.04, 95%CI [0.61–1.75]; p=0.89; random effect model, reported in two studies) and all-cause mortality (HR 1.23, 95%CI [0.35–4.29]; p=0.55; five effect sizes) (ESM Figures S3-S8). Sensitivity analyses results were aligned with the main results, regardless of the outcomes, for a correlation coefficient ρ=0.3 or ρ=0.7 (ESM Table S4).

3.4. Certainty of evidence

A detailed quality assessment of study outcomes for the comparisons of NOACs to VKAs, where two or more studies were available, is given in the summary of findings table (Table 2) and the GRADE evidence profile (ESM Table S3). In all comparisons the quality of the evidence was low or very low grade, according to Working Group GRADE of evidence. The quality of evidence was downgraded according to the different outcomes because of some concerns in regard to the risk of bias due to confounding and deviation from the intended intervention, inconsistency, imprecision and publication bias. There was evidence of publication bias for the intracranial hemorrhage outcome (Funnel plot asymmetry [ESM Fig. S9] and Egger's regression test, p<0.01), but not for ischemic stroke/systemic embolism (ESM Fig. S10 and Egger's regression test, p=0.06), major bleeding (ESM Fig. S11 and Egger's regression test, p=0.26) and gastro-intestinal bleeding (ESM Fig. S12 and Egger's regression test, p=0.68). Publication bias was not investigated for the other outcomes due the limited number of studies.

4. Discussion

This systematic review and meta-analysis of 10 studies is the first to compare NOACs to VKAs as anticoagulation strategies for patients with non-valvular atrial fibrillation and at risk of falls or with history of falls. The main findings from the pooled analyses were as follows: (1) there was a 18%

reduction in the risk of stroke or systemic embolism with NOACs compared to VKAs and a 47% reduction in the risk of intracranial hemorrhage. (2) The risk of major bleeding events is not different between groups, as were the risks for ischemic stroke, hemorrhagic stroke, gastro-intestinal bleeding, myocardial infarction, cardiovascular and all-cause mortality. While we found a 18% reduction in the risk of stroke or systemic embolism, there was no difference in ischemic stroke alone. However, the effect sizes were similar. This could be explained due to sample size as ischemic stroke rate alone is about 20-40% lower than ischemic stroke or systemic embolism rate.

Given the relatively modest improvement of NOACs in preventing thromboembolic events such as stroke or systemic embolism compared to VKA, the safety of each treatment is of paramount importance and must be rigorously considered to decide the most appropriate antithrombotic management. We found in our meta-analysis a 47% reduction in the risk of intracranial hemorrhage with NOACs as compared to VKAs. The shorter half-life of NOACs and the more targeted mechanism of anticoagulation (direct thrombin or factor Xa inhibition) have been implicated in the reduction of intracranial hemorrhage with these agents as compared to VKAs [49]. The 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation does not make specific recommendations for use of anticoagulation in AF patients at risk of falls or with history of falls [52] nor the 2019 update [53] with NOACs being preferred over VKAs overall. The 2020 European guidelines suggests that the increased risk of bleeding in patients at risk of falls does not outweigh the benefits of anticoagulants and suggests that NOACs have a better risk-benefit profile over VKAs based on evidence from studies on elderly AF patients [20]. The present meta-analysis adds to the limited body of evidence in AF patients at risk of falls or with history of falls suggesting that NOACs may be the optimal strategy for antithrombotic management, given the improved efficacy in preventing thromboembolic events and the improved safety profile as compared to VKAs. This study confirms that NOACs have a better risk-benefit profile than VKAs, as it was shown in the broader AF population or in elderly AF patients.

In the broader AF patients, large RCTs have shown that NOACs are at least as effective as VKAs for preventing stroke and systemic embolization and are also associated with significantly less intracranial hemorrhage and major bleeding events [49–51,54]. Meta-analyses of RCTs found NOACs to be superior to warfarin for the prevention of stroke and systemic embolism [55–58].

However, there is less evidence for the use of NOACs in AF patients at risk of falls or with history of falls. Related subgroup of AF patients made of older individuals, particularly those aged 75 years and over, have been studied substantially [59–62]. Meta-analyses including RCTs and observational studies showed that NOACs (i) were as effective as VKAs in reducing stroke and systemic embolism, (ii) were not significantly different for major bleeding and (iii) significantly reduced risk of intracranial hemorrhage [59–61]. A more recent meta-analysis in elderly AF patients which only included observational studies identified similar trends with the addition that NOACs increased the risk of gastro-intestinal bleeding [62]. There were no differences for this outcome in our meta-analysis, with a hazard ratio of 1.04 (95% CI: 0.89-1.23) associated with NOACs compared to VKAs.

The fear of bleeding complications and the risk of major bleeding in patients at risk of falls or with history of falls is still very low and similar for NOACs and VKAs and does not outweigh the benefits. Based on these elements and the reduced risk of intracranial hemorrhage, NOACs should also be considered as the first choice treatment in patients at risk of falls or with history of falls. Current strategies in the AF population at risk of falls require an individualized approach that should be discussed with the patients and that should consider comorbidities, costs, benefits, risks and lifestyle change before anticoagulation selection to best ensure safety and compliance. These results add to the existing evidence showing the improved safety and efficacy of NOACs compared to VKAs in the broader AF patients and would have implications for patients, physicians and healthcare providers.

Limitations and strengths

This study has limitations. In particular, the included studies were not randomized; five studies were retrospective, and the others were subgroup analyses of randomized clinical trials (one pre-specified

and four post-hoc). By design, included studies were at moderate to high risk of bias which may limit the applicability of the findings as illustrated in the GRADE assessment (Table 2). To investigate the effect of differential baseline prognosis between interventions, subgroup analyses were planned but could not be conducted due to the limited sample size. Similarly, we could not conduct a moderator analysis according to the different NOACs used but also due to the fact that some studies did not specify which NOAC was considered or did not stratify the results. All studies used statistical methods to adjust for differences in baseline characteristics to different extent according to the pre-specified confounding domains. Nonetheless, residual confounding could not be excluded. A potential limitation was confounding by indication related to previous use of VKAs. Studies considered previous VKA use in their design, either by incorporating it in statistical adjustment methods (i.e. multivariate cox regression, propensity score weighing) or by excluding previous VKA users. While the first approach does not eliminate the possibility of residual confounding since aspects such as duration of previous VKA use are not taken into account, the second may limit generalizability as many NOACs users are previous VKA users [63]. There was also some variation in the definition of risk of falls used by different studies. Although these definitions were similar according to our pre-specified protocol, we cannot exclude the possibility that standardized population definitions would have led to different results. Finally, due to the limited number of studies included, this systematic literature review and meta-analysis may still be underpowered to detect small but significant bleeding or thrombotic differences between VKAs and NOACs.

Our study has several strengths. It is the first to provide an up-to-date synthesis of the available literature in a dynamically evolving field and focusing on patients at risk of falls or with history of falls which have been underrepresented in the RCTs. Second, this study presents robust evidence on the comparative effectiveness and safety of NOACs compared to VKAs including the use of real world data which are more representative of patients being treated with anticoagulants in clinical practice. Third, it uses the latest development in meta-analysis methods in the presence of dependency, overcoming the limitations from the other methods suggested in Cochrane Handbook in the

presence of multi-arm studies [32]. These methods enable the use of all available effect sizes in the analyses, so all information can be preserved and maximum statistical power is achieved [33]. Finally, we used the ROBINS-I tool to evaluate the quality of the included studies, tools that enable a robust assessment of the risk of different biases such as confounding or selection bias. This multilevel meta-analysis highlighted the superiority of NOACs in terms of safety and efficacy compared to VKAs in AF patients at risk of falls or with history of falls. Further research should be conducted to evaluate which NOAC should be preferred in this patient population, using network meta-analysis methods.

5. Conclusions

Our systematic review and multilevel meta-analysis suggest that NOACs are reducing the risk of ischemic stroke or systemic embolism (-18%) and intracranial hemorrhage (-47%) compared to VKAs in patients with AF and at risk or with history of falls. There were no major differences in the risks of major bleeding, ischemic stroke, hemorrhagic stroke, gastro-intestinal bleeding, cardiovascular and all-cause mortality.

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7. Figures and tables

Fig. 1 PRISMA flow diagram of study screening and selection

Fig. 2 Forest plots representing meta-analysis results comparing NOACs versus VKAs for the risk of ischemic stroke and/or systemic embolism. HR: hazard ratio, CI: confidence interval, VKA: vitamin K antagonist, NOAC: non-vitamin K antagonist oral anticoagulant

Fig. 3 Forest plots representing meta-analysis results comparing NOACs versus VKAs for the risk of intracranial hemorrhage. HR: hazard ratio, CI: confidence interval, VKA: vitamin K antagonist, NOAC: non-vitamin K antagonist oral anticoagulant

570 Table 1 Study characteristics

Study	Design	Population	Size	Female (%)	Age (mean or median)	HAS-BLED (mean or median)	CHA_2DS_2-VASc (mean or median)	VKA naive (%)	PAF (%)	Follow-up (mean or median - years)	Treatment group	Size	Outcomes (event rate - %/year)								
													IS and/or SE	MB	ICH	GIB	MI	IS	HS	CVM	ACM
Steffel 2016 (ENGAGE-AF-TIMI 48) [25]	Pre-specified subgroup analysis of RCT	NVAF patients at risk of falls	617	49	77	2.9	5.1	32.2	30.1	2.8	Warfarin (VKA)	307	2.85	5.55	2.08	1.46	0.88	1.78	1.01	4.99	9.98
											Edoxaban (NOAC)	310	2.81	5.43	0.33	2.91	0.89	2.17	0.38	4.18	9.27
Miao 2019 [41]	Retrospective cohort	NVAF patients at risk of falls	25,144	NR	83	NR	4	100	NR	1.4	Warfarin (VKA)	12,117	1.51	NR	0.48	NR	NR	NR	NR	NR	NR
											Rivaroxaban or Apixaban (NOAC)	13,027	1.19	NR	0.28	NR	NR	NR	NR	NR	NR
Rao 2018 (ARISTOTLE) [40]	Post-hoc subgroup analysis of RCT	NVAF patients with history of falling within 1 year	753	47	75	2.4	4.2	42.9	20.3	1.8	Warfarin (VKA)	367	1.99	5.38	1.69	NR	NR	NR	0.45	2.4	6.74
											Apixaban (NOAC)	386	1.76	4.35	0.33	NR	NR	NR	0.14	3.42	6.41
Jaspers Focks 2016 (ARISTOTLE) [42]	Post-hoc subgroup analysis of RCT	NVAF patients at risk of falls with polypharmacy (9+)	4756	46.1	71	2.3	NR	36.9	NR	1.8	Warfarin (VKA)	2380	1.79	4.21	0.97	1.08	NR	NR	NR	NR	4.85
											Apixaban (NOAC)	2376	1.35	3.55	0.28	1.23	NR	NR	NR	NR	4.55
Alexander 2019 (ARISTOTLE) [43]	Post-hoc subgroup analysis of RCT	NVAF patients at risk of falls with high multimorbidity (6+)	2222	38	74	2.4	4.9	NR	NR	1.8	Warfarin (VKA)	NR	1.80	4.88	0.84	NR	1.60	NR	0.26	NR	7.89
											Apixaban (NOAC)	NR	1.67	3.99	0.23	NR	1.14	NR	0.21	NR	6.97
Fanning 2020 [44]	Retrospective cohort	NVAF patients at risk of falls with dementia	2399	54	82	NR	NR	NR	NR	NR	Warfarin (VKA)	1386	4.82	NR	0.76	1.28	NR	2.77	NR	NR	NR
											Rivaroxaban or Apixaban (NOAC)	1013	3.9	NR	0.35	3.32	NR	2.49	NR	NR	NR
Hohmann 2019 [48]	Retrospective cohort	NVAF patients at risk of falls with frailty	36,267	61	77	NR	4.5	NR	NR	2.3	Warfarin (VKA)	NR	1.8	NR	0.94	1.71	NR	NR	NR	NR	NR
											NOAC	NR	1.78	NR	0.58	1.88	NR	NR	NR	NR	NR
		NVAF patients at risk of falls with multimorbidity (4+)	26,410	45	77	NR	4.9	NR	NR	2.3	Warfarin (VKA)	NR	2.03	NR	1.05	2.13	NR	NR	NR	NR	NR
											NOAC	NR	2.22	NR	0.65	2.17	NR	NR	NR	NR	NR
		NVAF patients at risk of falls with polypharmacy (7+)	33,238	51	76	NR	4.5	NR	NR	2.3	Warfarin (VKA)	NR	1.74	NR	0.94	1.78	NR	NR	NR	NR	NR
											NOAC	NR	1.74	NR	0.60	1.90	NR	NR	NR	NR	NR
Piccini 2016 (ROCKET AF) [45]	Post-hoc subgroup analysis of RCT	NVAF patients at risk of falls with polypharmacy (10+)	1835	39	75	NR	NR	18	20	NR	Warfarin (VKA)	NR	NR	6.14	NR	NR	NR	NR	NR	NR	NR
											Rivaroxaban (NOAC)	NR	NR	6.54	NR	NR	NR	NR	NR	NR	NR
Lip 2021 [46]	Retrospective cohort	NVAF patients at risk of falls with frailty	NR	NR	NR	NR	NR	NR	NR	0.5-0.7	Warfarin (VKA)	34594	3.3	9.04	1.49	4.16	NR	2.35	0.80	NR	NR
											Apixaban (NOAC)	34594	2.18	6.05	0.83	2.87	NR	1.77	0.34	NR	NR
											Warfarin (VKA)	9263	3.06	8.89	1.42	4.29	NR	2.04	0.81	NR	NR
											Dagibatran (NOAC)	9263	2.6	7.07	0.65	3.99	NR	2.2	0.28	NR	NR
											Warfarin (VKA)	39898	3.13	8.88	1.45	4.22	NR	2.22	0.78	NR	NR
											Rivaroxaban (NOAC)	39898	2.5	10.24	1.03	5.63	NR	1.85	0.53	NR	NR
Martinez 2018 [47]	Retrospective cohort	NVAF patients at risk of falls with frailty	19077	NR	NR	NR	NR	NR	NR	0.9-1.8	Warfarin (VKA)	1392	2.15	4.41	0.37	3.09	NR	2.0	0.15	NR	NR
											Apixaban (NOAC)	1392	1.68	3.11	0.35	2.33	NR	1.4	0.28	NR	NR
											Warfarin (VKA)	1350	2.2	4.44	0.59	3.31	NR	1.93	0.32	NR	NR
											Dagibatran (NOAC)	1350	2.06	3.82	0.10	3.10	NR	1.73	0.10	NR	NR
											Warfarin (VKA)	2635	2.61	4.01	0.60	2.70	NR	2.18	0.36	NR	NR
											Rivaroxaban (NOAC)	2635	1.78	4.13	0.29	3.41	NR	1.51	0.26	NR	NR

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RCT: randomized clinical trial, NVAF: non-valvular atrial fibrillation, NR: not reported, VKA: vitamin K antagonist, NOAC: non-vitamin K antagonist oral anticoagulant, QD: once a day, BID: twice a day, PAF: paroxysmal atrial fibrillation, IS: ischemic stroke, SE: systemic embolism, MB; major bleeding, GIB: gastro-intestinal bleeding, ICH: intracranial hemorrhage, MI: myocardial infarction, HS: hemorrhagic stroke, CVM: cardiovascular mortality, ACM: all-cause mortality

575 Table 2 Summary of findings according to GRADE

NOACs compared to VKAs for the management of AF patient at risk (or with history) of falls

Patient or population: AF patient at risk (or with history) of falls

Comparison: VKAs

Intervention: NOACs

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with VKAs	Risk with NOACs			
Ischemic stroke and/or systemic embolism follow-up: range 0.5 years to 2.8 years	**Moderate** 24 per 1 000	**20 per 1000** (17 to 24)	**HR 0.82** (0.69 to 0.98)	Range from 617 to 79,796 (15 effect sizes, 7 non-randomized studies)	⊕◯◯◯ Very low[a,b]
Intracranial hemorrhage follow-up: range 0.5 years to 2.8 years	**Moderate** 10 per 1 000	**6 per 1000** (4 to 7)	**HR 0.53** (0.40 to 0.71)	Range from 617 to 79,796 (15 effect sizes, 7 non-randomized studies)	⊕◯◯◯ Very low[a,c]
Major bleeding follow-up: range 0.5 years to 2.8 years	**Moderate** 60 per 1 000	**53 per 1000** (45 to 62)	**HR 0.88** (0.74 to 1.04)	Range from 617 to 79,796 (11 effect sizes, 5 non-randomized studies)	⊕◯◯◯ Very low[a]
Ischemic stroke follow-up: range 0.5 years to 2.8 years	**Moderate** 22 per 1 000	**19 per 1000** (13 to 28)	**HR 0.87** (0.60 to 1.28)	Range from 617 to 79,796 (8 effect sizes, 4 non-randomized studies)	⊕◯◯◯ Very low[b,d,f]
Hemorrhagic stroke follow-up: range 0.5 years to 2.8 years	**Moderate** 6 per 1 000	**3 per 1000** (1 to 6)	**HR 0.51** (0.24 to 1.10)	Range from 617 to 79,796 (9 effect sizes, 4 non-randomized studies)	⊕◯◯◯ Very low[a,d]
Gastro-intestinal bleeding follow-up: range 0.5 years to 2.8 years	**Moderate** 26 per 1 000	**27 per 1000** (23 to 32)	**HR 1.04** (0.89 to 1.23)	Range from 617 to 79,796 (12 effect sizes, 6 non-randomized studies)	⊕◯◯◯ Very low[a,b,d]
Myocardial infarction follow-up: range 1.8 years to 2.8 years	**Moderate** 9 per 1 000	**7 per 1000** (4 to 11)	**HR 0.76** (0.47 to 1.24)	Range from 617 to 2222 (2 non-randomized studies)	⊕⊕◯◯ Low[d,e]
Cardiovascular mortality follow-up: range 0.5 years to 2.8 years	**Moderate** 37 per 1 000	**38 per 1000** (23 to 64)	**HR 1.04** (0.61 to 1.75)	1370 (2 non-randomized studies)	⊕⊕◯◯ Low[d,e]
All-cause mortality follow-up: range 1.4 years to 2.8 years	**Moderate** 74 per 1 000	**90 per 1000** (26 to 280)	**HR 1.23** (0.35 to 4.29)	Range from 617 to 4756 (5 effect sizes, 3 non-randomized studies)	⊕◯◯◯ Very low[b,d,e]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

576 [a]There was serious bias due to confounding and deviation from the intended intervention. [b]The
577 heterogeneity was substantial. [c]Asymmetrical Funnel plot and significant Egger's regression test.
578 [d]Boundaries of the CI cross the clinical decision threshold. [e]There was serious bias due to confounding.
579 [f]There was serious bias due to deviation from the intended intervention. HR: hazard ratio, CI: confidence
580 interval VKA: vitamin K antagonist, NOAC: non-vitamin K antagonist oral anticoagulant, AF: atrial
581 fibrillation