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Direct oral anticoagulants versus vitamin K antagonists in patients with atrial fibrillation and stage 5 chronic kidney disease under dialysis: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background In patients with atrial fibrillation (AF) and normal or slightly impaired renal function, the use of direct oral anticoagulants (DOACs) is preferable to vitamin K antagonists (VKAs). However, in patients undergoing hemodialysis, the efficacy, and safety of DOACs compared with VKAs are still unknown.

Purpose To review current evidence about the safety and efficacy of DOACs compared to VKAs, in patients with AF and chronic kidney disease under hemodialysis.

Methods We systematically searched PubMed, Scopus, and Cochrane databases for RCTs comparing DOACs with VKAs for anticoagulation in patients with AF on dialysis therapy. Outcomes of interest were: (1) stroke; (2) major bleeding; (3) cardiovascular mortality; and (4) all-cause mortality. Statistical analysis was performed using RevMan 5.1.7 and heterogeneity was assessed by I^2 statistics.

Results Three randomized controlled trials were included, comprising a total of 383 patients. Of these, 218 received DOACs (130 received apixaban; 88 received rivaroxaban), and 165 were treated with VKAs (116 received warfarin; 49 received phenprocoumon). The incidence of stroke was significantly lower in patients treated with DOACs (4.7%) compared with those using VKAs (9.5%) (RR 0.42; 95% CI 0.18–0.97; $p = 0.04$; $I^2 = 0\%$). However, the difference was not statistically significant in the case of ischemic stroke specifically (RR 0.42; 95% CI 0.17–1.04; $p = 0.06$; $I^2 = 0\%$). As for the major bleeding outcome, the DOAC group (11%) had fewer events than the VKA group (13.9%) but without statistical significance (RR 0.75; 95% CI 0.45–1.28; $p = 0.29$; $I^2 = 0\%$). There was no significant difference between groups regarding cardiovascular mortality (RR 1.23; 95% CI 0.66–2.29; $p = 0.52$; $I^2 = 13\%$) and all-cause mortality (RR 0.98; 95% CI 0.77–1.24; $p = 0.84$; $I^2 = 16\%$).

Conclusion This meta-analysis suggests that in patients with AF on dialysis, the use of DOACs was associated with a significant reduction in stroke, and a numerical trend of less incidence of major bleeding compared with VKAs, but in this case with no statistical significance. Results may be limited by a small sample size or insufficient statistical power.

Keywords Chronic kidney disease · Hemodialysis · Atrial fibrillation · Direct oral anticoagulants · Vitamin K antagonists

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Abbreviations

ACC/AHA	American College of Cardiology, American Heart Association
AF	Atrial Fibrillation
CKD	Chronic Kidney Disease
DOAC	Direct Oral Anticoagulant
HD	Hemodialysis
HF	Heart Failure
ISTH	International Society on Thrombosis and Hemostasis
OAC	Oral Anticoagulant
VKA	Vitamin K Antagonist

Introduction

Atrial fibrillation (AF) is the most frequent sustained arrhythmia, with its prevalence in the general population estimated between 0.5% and 1% [1, 2]. Chronic kidney disease (CKD) is one independent risk factor for presenting AF and for suffering a thromboembolic event. These risks are further amplified in individuals undergoing hemodialysis (HD), who also exhibit a high baseline bleeding risk [3]. However, there is no consensus regarding the appropriate use of anticoagulation in this specific population [4, 5].

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for management of AF in CKD cases suggest the use of direct oral anticoagulants (DOACs) can be useful in CKD stage 4 patients, despite the lack of data on their safety, effectiveness, and specific dosing recommendations [6]. Although vitamin K antagonists (VKAs) are the most widely used in patients with normal or slightly impaired renal function, their application for stroke prevention in patients with AF on dialysis remains controversial. Notably, most trials excluded patients on dialysis, further complicating the understanding of the applicability of DOACs in this specific population [7]. In addition, current data suggest that in patients with renal impairment, warfarin may not promote a thromboembolic risk reduction to the same extent as in patients without CKD [8]. Thus, the lack of high-quality evidence for both types of oral anticoagulants in the dialysis population has resulted in large practice variability and physician uncertainty.

Data from RCTs showed that DOACs were non-inferior to warfarin concerning the risk of thromboembolic events in patients without severe kidney disease [6, 9]. However, as DOACs have varying degrees of renal clearance (edoxaban at 50% of the absorbed dose, rivaroxaban at 35%, and apixaban at 27%), it is unclear whether their clinical benefits extend to the long-term dialysis population [6, 8, 10]. Currently, there are a few randomized controlled trials (RCTs) about the use of vitamin K antagonists (VKAs) or DOACs in HD patients [11–13]. The three, which integrated our analysis, compared rivaroxaban or apixaban with warfarin or phenprocoumon, showing non-inferiority from DOACs to VKAs.

A recent meta-analysis with data from observational and randomized studies demonstrated that in dialysis patients who need anticoagulation for AF, warfarin might be associated with a significant reduction in rates of minor bleeding, systemic embolization, and death compared with DOACs [14].

Considering this controversy and the lack of adequately powered RCTs in this population, we aimed to perform a meta-analysis including only randomized controlled trials that evaluate the efficacy and safety of DOAC compared with VKA treatment in patients with AF and CKD, specifically in the population on dialysis therapy.

Methodology

Eligibility criteria

Inclusion in this meta-analysis was restricted to studies that met the following eligibility criteria: (1) randomized controlled trials; (2) comparing DOAC with VKA; and (3) enrolling patients with chronic kidney disease on dialysis therapy. Furthermore, studies were only included if they reported any clinical outcomes of interest. We excluded studies with (1) no control group; (2) VKA or DOAC treatment in both groups; (3) enrolling patients with chronic kidney disease without dialysis treatment; or (4) overlapping patient populations, that is, studies that reported results referring to the same sample group already reported in the present review.

Search strategy and data extraction

We systematically searched PubMed, Scopus, and Cochrane Central Register of Controlled Trials from inception to March 2023 with the following search terms: “atrial fibrillation”, “direct oral anticoagulation”, “novel oral anticoagulation”, “DOAC”, “NOAC”, “factor Xa inhibitors”, “dabigatran”, “rivaroxaban”, “apixaban”, “edoxaban”, “betrixaban”, “hemodialysis”, “end-stage kidney disease”, “chronic kidney disease”, and “renal replacement therapy”. The references from all included studies, previous systematic reviews, and meta-analyses were also searched manually for any additional studies. Two authors (L.L. and C.S.) independently extracted the data following predefined search criteria and quality assessment. The prospective meta-analysis protocol was registered on PROSPERO on April 03, 2023, under protocol CRD42023410113.

Endpoints and subanalyses

Outcomes included all-cause mortality, cardiovascular (CV) death, stroke, and ischemic stroke. The safety outcome of interest was major bleeding. Major bleeding was defined according to the International Society on Thrombosis and Hemostasis (ISTH) criteria in Pokorney and Reinecke's studies [12, 13]. In De Vriese's, the authors divided the major bleeding ISTH definition into "Life-threatening bleeding" and "major bleeding" (Online Resource 1) [11].

One study also randomized a group of patients to analyze rivaroxaban 10 mg daily with a vitamin K supplement [11]. Due to this, we performed a subgroup analysis comparing VKA therapy with DOACs only (without the arm using vitamin K2).

Quality assessment

We evaluated the risk of bias using version 2 of the Cochrane Risk of Bias assessment tool (RoB-2) [15]. Two independent authors completed the risk of bias assessment (L.L. and M.F.). The authors resolved disagreements through consensus after discussing reasons for discrepancy.

Statistical analysis

This systematic review and meta-analysis were performed and reported following the Cochrane Collaboration Handbook for Systematic Review of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement guidelines [16, 17]. Relative risk (RR) with 95% confidence intervals were used to compare treatment effects for categorical endpoints. Continuous outcomes were compared with standardized mean differences. We assessed heterogeneity with I^2 statistics and the Cochran Q test; p-values < 0.1 and $I^2 > 25\%$ were considered significant for heterogeneity. We used a fixed-effect model for outcomes with low heterogeneity ($I^2 < 25\%$). Otherwise, a DerSimonian and Laird random-effects model was used. Review Manager 5.4.1 (Cochrane Center, The Cochrane Collaboration, Denmark) was used for statistical analysis.

Results

Study selection and baseline characteristics

The initial search yielded 5936 results. After removing duplicate records and ineligible studies, we reviewed the title and abstract of 4063 studies, 20 remained and were fully reviewed based on inclusion criteria (Fig. 1). Of those, 3 RCTs were included, comprising a total of 383 patients. DOACs were used in 218 patients (130 received apixaban; 88 received rivaroxaban, of which 42 also used vitamin K2), and 165 were treated with VKAs (116 received warfarin; 49 received phenprocoumon). Baseline characteristics were comparable between groups. The target international normalized ratio (INR) in the VKA group was set at a range of 2.0–3.0 across all included studies. The follow-up period ranged from 330 days to 660 days. Studies characteristics are reported in Table 1.

In De Vriese et al., 10 mg of rivaroxaban was administered daily. In Pokorney et al., the usual apixaban dosage was 5 mg twice a day, however, patients who were 80 years of age or older, or who weighed 60 kg or less, received 2.5 mg twice a day. In Reinecke et al., 2.5 mg of apixaban was administered twice a day. Reinecke et al. claims that this dosage regimen was developed using data from an unpublished pharmacokinetic research that estimated the lower dose of apixaban in that particular population and revealed plasma levels that were comparable to those advised for individuals without renal impairment [11–13].

Pooled analyses of all studies

In those receiving DOAC, the incidence of stroke was significantly lower (4.7%) when compared to the VKA group (9.5%) (RR 0.42; 95% CI 0.18–0.97; $p = 0.04$; $I^2 = 0\%$) (Fig. 2a). In the case of ischemic stroke, there was no statistically significant difference between the groups (RR 0.42; 95% CI 0.17–1.04; $p = 0.06$; $I^2 = 0\%$) (Fig. 2b).

The reported major bleeding events had a similar incidence between DOACs (11%) and VKA (13.9%) groups (RR 0.75; 95% CI 0.45–1.28; $p = 0.29$; $I^2 = 0\%$) (Fig. 3a). There was also no statistically significant difference between the therapies in terms of cardiovascular mortality (RR 1.23; 95% CI 0.66–2.29; $p = 0.52$; $I^2 = 13\%$) (Fig. 3b) and all-cause mortality (RR 0.98; 95% CI 0.77–1.24; $p = 0.84$; $I^2 = 16\%$) (Fig. 3c).

Subgroup analyses

As shown in Supplemental Figs. 1 and 2 (Online Resources 2 and 3), when comparing VKA therapy with DOACs only (without the arm using vitamin K2), there was no significant difference in terms of stroke (RR 0.51; 95% CI 0.20–1.31; $p = 0.16$; $I^2 = 0\%$) (Supplemental Fig. 1a), ischemic stroke (RR 0.50; 95% CI 0.18–1.33; $p = 0.17$; $I^2 = 0\%$) (Supplemental Fig. 1b), major bleeding (RR 0.82; 95% CI 0.47–1.43; $p = 0.48$; $I^2 = 0\%$) (Supplemental Fig. 2a), and mortality outcomes (Supplemental Fig. 2b and c).

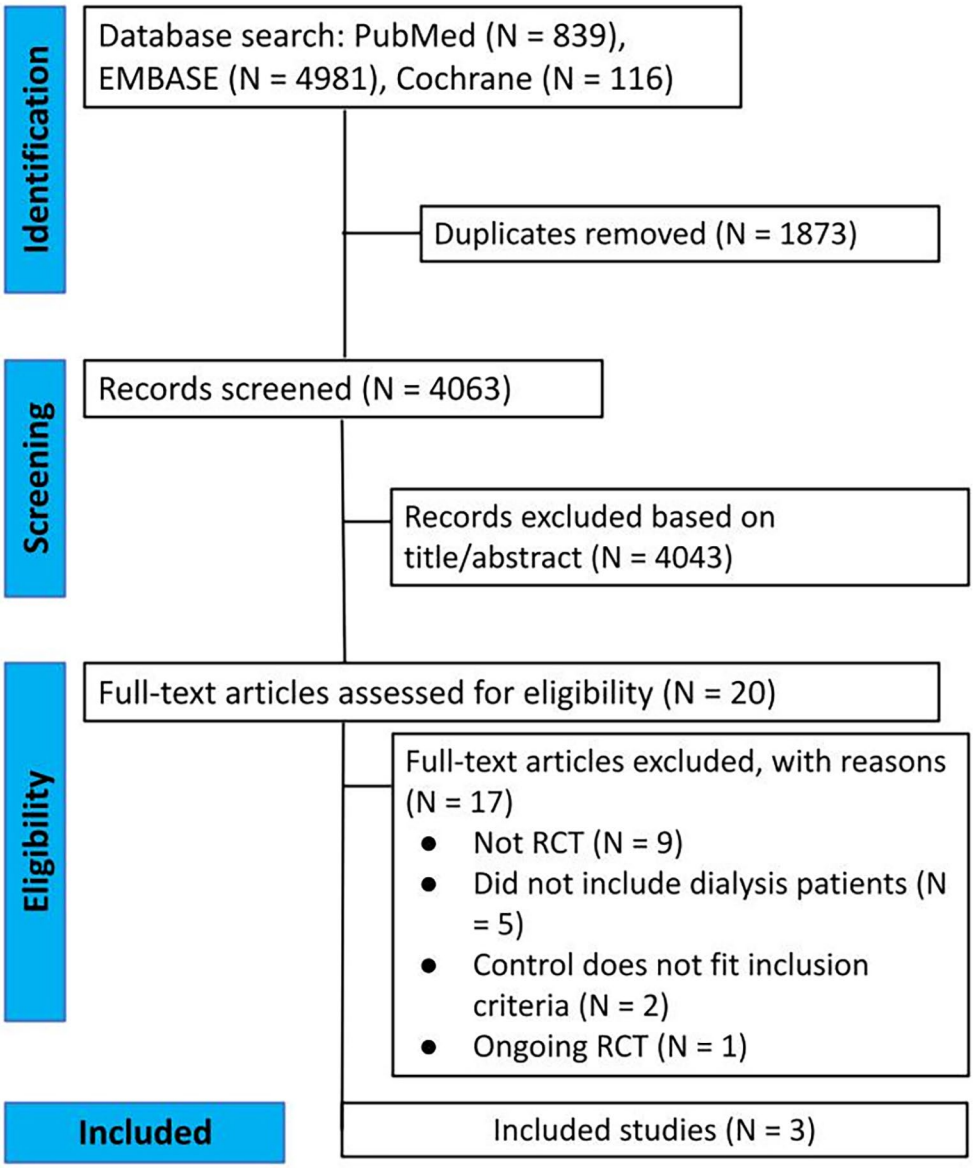


Fig. 1 PRISMA flow diagram of study screening and selection

Quality assessment

The Cochrane RoB-2 tool was used to assess both RCTs and indicated a low risk of bias for the trials [15]. The appraisal of RCTs is reported in Supplemental Table 2 (Online Resource 4). Patients and investigators were unblinded in all RCTs. The studies of Pokorney et al. and Reinecke et al. used the prospective, randomized, open-label, blinded-outcome evaluation (PROBE) [12, 13].

Discussion

To the best of our knowledge, this is the most recent meta-analysis of RCTs evaluating the efficacy and safety profiles of DOACs vs. VKAs as anticoagulation strategies for patients with AF undergoing hemodialysis. In this systematic review and meta-analysis, we included 3 RCTs, totalizing 383 patients enrolled. The result showed that: (1) stroke incidence was reduced in DOACs group when compared with VKAs; (2) DOACs were as effective as VKAs in the prevention of (3) ischemic stroke and (4) major bleeding; and (5) there was no difference between both therapy strategies in terms of cardiovascular death or all-cause mortality.

In the most extensive study included, the RENAL-AF trial, with 154 patients, Pokorney et al. found no significant

Table 1 Design and baseline characteristics of the included studies

First author, study date	Study design	NOAC group (n) VKA group (n)	Age (years), mean (SD)	Sex (%male)	CHA_2DS_2-VASc score, mean (SD)	HAS-BLED risk score, mean (SD)	Time since the first dialysis, mean years (SD)	Prior stroke and/or SE (n,%)	Previous MI (n, %)	DM (n, %)	Heart Failure (n, %)	Aspirin (n, %)	Time of Follow up, mean (SD)/ median [IQR] days or months
De Vriese, 2021 [11]	RCT	Rivaroxaban (46) Rivaroxaban + VK2 (42) Warfarin (44)	79.4 (7.3) 78.6 (7.6) 78.6 (9.8)	35 (76.1) 28 (66.7) 25 (56.8)	4.7 (1.4) 4.5 (1.4) 4.8 (1.5)	4.6 (0.8) 4.7 (0.9) 4.7 (0.9)	3.2 (3.8) 2.8 (3.5) 2.6 (3.9)	15 (32.6) 9 (21.4) 16 (36.4)	21 (45.7) 19 (45.2) 21 (47.7)	20 (43.5) 22 (52.4) 20 (45.5)	17 (37.0) 15 (35.7) 9 (20.5)	15 (32.6) 17 (40.5) 14 (31.8)	18 months 18 months 18 months
Pokorney, 2022 [12]	RCT	Apixaban (82) Warfarin (72)	68.6 (11.3) 66.9 (9.0)	48 (58.5) 50 (69.4)	4.0 (1.5) 4.0 (1.5)	NI NI	3.4 (3.1) 3.5 (3.9)	17 (20.7) 12 (16.7)	16 (19.5) 22 (30.5)	42 (51.2) 47 (65.3)	43 (52.4) 41 (56.9)	29 (36.7) 32 (45.7)	330 [NI] days* 340 [NI] days*
Reinecke, 2023 [13]	RCT	Apixaban (48) Phenprocoumon (49)	74.7 (8.1) 74.8 (7.9)	31 (64.8%) 37 (75.5%)	4.5 (1.6) 4.5 (1.5)	4.2 (1.0) 4.1 (1.0)	4.3 (3.6) 4.9 (7.3)	8 (16.7) 8 (16,3)	9 (18.8) 12 (24.5)	NI NI	NI NI	16 (33.3) 17 (34.7)	429 [174–702] days 506 [289–702] days

DM = Diabetes Mellitus; IQR = Interquartile Range; MI = Myocardial Infarction; NI = Not informed; NOAC = Novel Oral Anticoagulant; RCT = Randomized Controlled Trial; SE = Systemic Embolism; VKA = Vitamin K Antagonist; VK2 = Vitamin K2

* IQR not informed in the study

difference between both groups: apixaban 5 mg vs. warfarin (2,4% vs. 2,8% in the occurrence of stroke). Mortality occurred in 1 out of 5 patients, and bleeding was greater than ischemic events in the group using DOACs, drawing attention to the risk-benefit of anticoagulation in this pool of patients. However, half of the bleeding events was related to local complications at the venous access site to HD [12]. The AXADIA-AFNET 8 study, from Reinecke and collaborators, similarly to RENAL-AF, showed no significant difference in mortality, ischemic, or bleeding events using apixaban 2.5 mg BID compared with phenprocoumon. Almost 23% of all patients enrolled died, 11% had major bleeding, and there was only one stroke [13]. De Vriese et al. demonstrated in the Valkyrie study that rivaroxaban 10 mg reduced the fatal and non-fatal cardiovascular events - mainly at the expense of lower limb ischemia - as well as reduced major and life-threatening bleeding when compared with warfarin [11].

This meta-analysis clarifies some of the results from the studies. The incidence of ischemic stroke in DOACs group (3.2%) was numerically lower compared with the group taking warfarin (6.1%), but showed no significant statistical difference. Although, it is possible that the fewer number of events reported in the sample size analyzed might have reduced statistical power in these results. In terms of major bleeding events, the incidence was also not significantly different between groups. It is important to note that the number of bleeding events in both groups was substantially relevant, compared to the number of ischemic events (61 and 20, respectively), reinforcing the need for more data about this outcome in this context of patients. Cardiovascular death and all-cause mortality in previous studies such as ARISTOTLE, ENGAGE AF-TIMI 48, and RE-LY, was similar between DOAC and warfarin treatments, which is in accordance to our study results that showed no significant difference between the two groups regarding those outcomes [18–21].

Similar findings to ours were recently reported in a meta-analysis by Faisaluddin et al. [22]. However, their analysis lacked a subgroup assessment for ischemic stroke and cardiovascular mortality outcomes. Furthermore, they chose not to analyze the full population of De Vriese's study. While Faisaluddin et al. did analyze minor bleeding and gastrointestinal bleeding outcomes, which we did not assess, their results did not demonstrate statistical significance.

In order to assess the consistency of the results, a subgroup analysis was performed excluding the patients taking vitamin K supplementation in the Valkyrie study. The same trend as the previous results were observed, with no significant difference in all outcomes analyzed. However, the lower number of events brings the possibility of not having achieved sufficient statistical power in those results. It

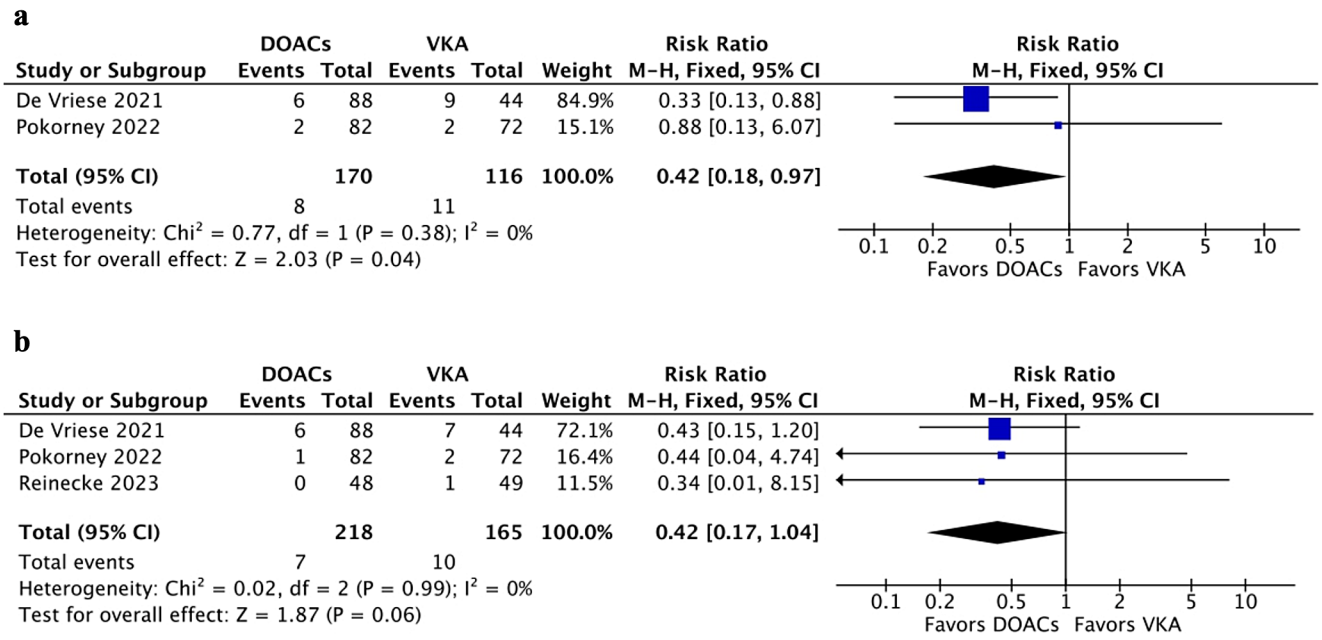


Fig. 2 **a**: Stroke was significantly lower in patients treated with DOACs ($P=0.04$). **b**: The incidence of ischemic stroke was not significantly different between groups ($P=0.06$). CI = confidence interval; M-H = Mantel-Haenszel method; DOAC = direct oral anticoagulant; VKA = vitamin K antagonist

is essential to mention that even though some patients had the supplementation, De Vriese et al. found no difference between the groups regarding vascular calcification [11].

The FDA and ACC/AHA recent guidelines state that using apixaban may be reasonable in dialysis-dependent patients with AF. In this case, the recommended dose is apixaban 2.5 mg twice daily since the dose of 5 mg twice a day, permitted by the FDA, has been associated with supratherapeutic levels [6, 23, 24]. Furthermore, pharmacokinetic studies showed that a dose of rivaroxaban 10 mg daily in HD patients is appropriate, while the FDA also allows rivaroxaban 15 mg QD in this population [25, 26]. However, there are not robust data on those aspects of treatment for this specific population.

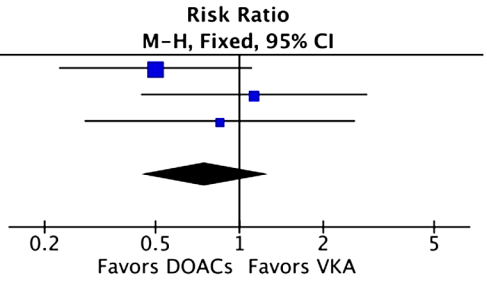
Previously, two large retrospective cohorts evaluated comparative results between apixaban and warfarin in dialysis patients with non-valvular atrial fibrillation, based on the United States Renal Data System [24, 27]. The most extensive observational studies included more than 25,000 patients who started treatment with oral anticoagulation between 2010 and 2015, with 91% using warfarin and 9% using apixaban (approximately, almost equally divided between a dose of 5 mg twice a day and a dose of 2.5 mg twice a day). Each patient using apixaban was matched with three patients using warfarin: for risk of stroke or systemic embolism, although a slightly higher event rate was found in the DOAC group (compared to the lower dose, the higher was associated with reductions in thromboembolic risk and mortality), there was no difference between groups; similarly, for major bleeding events, the risk was significantly lower with apixaban (no difference between the two doses), with a 28% reduction, similar to the ARISTOTLE study findings [19], except for intracranial hemorrhage, with no difference in the cohort; regarding mortality, the rate of events was higher with warfarin, but without statistical significance.

A previous meta-analysis of observational studies comparing oral anticoagulants (OAC) with no anticoagulation in HD patients showed that OACs were not associated with a reduced risk of thromboembolism, while VKAs and rivaroxaban were associated with significantly higher bleeding risk compared with apixaban and no anticoagulant [28]. Also, a meta-analysis published in 2022 by Elfar et al. brought data from 5 studies, among them 3 observational studies and 2 RCTs, showing that warfarin may be associated with reduced rates of minor bleeding, systemic embolism, and death in HD patients with HF when compared with DOACs [14]. Both studies investigated larger populations than ours, which might have impacted the contrasting findings compared to our analysis. Nonetheless, in both studies, the majority of analyzed outcomes displayed significant variability, without any observed statistical significance. Additionally, observational studies are susceptible to confounding bias and can establish associations but not causality. Patients with AF and end-stage/dialysis CKD were excluded from reference trials concerning stroke prevention with DOAC in patients with AF.

a

Study or Subgroup	DOACs Events	DOACs Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
De Vriese 2021	10	88	10	44	49.9%	0.50 [0.23, 1.11]
Pokorney 2022	9	82	7	72	27.9%	1.13 [0.44, 2.88]
Reinecke 2023	5	48	6	49	22.2%	0.85 [0.28, 2.60]
Total (95% CI)		**218**		**165**	**100.0%**	**0.75 [0.45, 1.28]**
Total events	24		23			

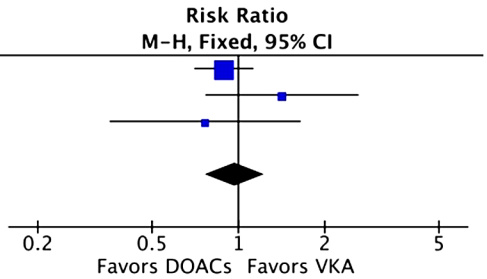
Heterogeneity: $Chi^2 = 1.78$, df = 2 (P = 0.41); $I^2 = 0\%$
Test for overall effect: Z = 1.05 (P = 0.29)



b

Study or Subgroup	DOACs Events	DOACs Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
De Vriese 2021	57	88	32	44	62.4%	0.89 [0.70, 1.13]
Pokorney 2022	21	82	13	72	20.2%	1.42 [0.77, 2.62]
Reinecke 2023	9	48	12	49	17.4%	0.77 [0.36, 1.65]
Total (95% CI)		**218**		**165**	**100.0%**	**0.98 [0.77, 1.24]**
Total events	87		57			

Heterogeneity: $Chi^2 = 2.37$, df = 2 (P = 0.31); $I^2 = 16\%$
Test for overall effect: Z = 0.20 (P = 0.84)



c

Study or Subgroup	DOACs Events	DOACs Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
De Vriese 2021	6	88	5	44	42.0%	0.60 [0.19, 1.86]
Pokorney 2022	9	82	4	72	26.8%	1.98 [0.64, 6.14]
Reinecke 2023	7	48	5	49	31.2%	1.43 [0.49, 4.19]
Total (95% CI)		**218**		**165**	**100.0%**	**1.23 [0.66, 2.29]**
Total events	22		14			

Heterogeneity: $Chi^2 = 2.29$, df = 2 (P = 0.32); $I^2 = 13\%$
Test for overall effect: Z = 0.64 (P = 0.52)

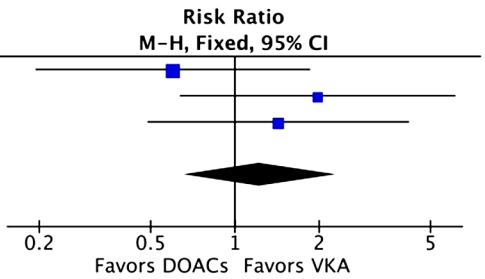


Fig. 3 **a**: The incidence of major bleeding was similar between the groups ($P = 0.29$). **b**: There was no difference in all-cause mortality between the OACs therapies ($P = 0.84$). c: DOAC and VKA groups show no significant differences related to CV death ($P = 0.52$). CI = confidence interval; M-H = Mantel-Haenszel method; OAC = oral anticoagulant; DOAC = direct oral anticoagulant; VKA = vitamin K antagonist

Some aspects of the trials included in this analysis should be highlighted. In the RENAL-AF trial, the study was terminated early and presented a slow recruitment and limited resources, which resulted in a short time with the INR in the therapeutic range (TTR) using warfarin (44.3%) [12]. In the case of the AXADIA-AFNET 8 Study, the TTR was 50.7% and the adherence in the apixaban group was greater than 80%, similar to that found in other 2 studies [13]. While in De Vriese et al. the TTR was 48%, with a longer subtherapeutic INR time [11]. Regarding this assessment of the quality of anticoagulation monitoring, a TTR value of at least 60% is recommended for adequate control of the use of warfarin [29]. However, in the case of hemodialysis patients using warfarin, the limited evidence available shows that their TTR tends to be lower compared to the general population, with only two retrospective studies and one prospective study available, which reported TTRs of 49.2%, 45.1% and 54%, respectively [30–32]. Likewise, in all studies analyzed, especially in RENAL-AF, the TTR was below the recommended value, denoting a greater probability of hemorrhagic or thrombotic adverse events and the apparent difficulty in delivering an anticoagulation therapy using VKA in patients on hemodialysis, as also observed in the 2 other randomized trials. Consequently, the potential benefits of warfarin might not be evident among hemodialysis patients, partly due to their suboptimal TTRs.

It is relevant to mention that in patients using VKA, 31.8% discontinued anticoagulation, rising to 42.9% if only treatment-naïve individuals are considered, which may reflect the difficulty in terms of dosage and pharmacokinetic stability when compared to DOACs [11]. Another important limitation of the studies is the absence of a group without the use of oral anticoagulants, thereby hindering a more comprehensive evaluation

of the risk-benefit of the proposed treatment concerning the lack of anticoagulation in the dialysis scenario.

This study has limitations. There was some variation in the definition of major bleeding used by De Vriese compared to the other two studies. De Vriese et al. divided the ISTH definition of major bleeding into two categories: life-threatening and major bleeding [11]. Although the junction of these definitions was comparable with the major bleeding definition used in the other two studies (ISTH descriptions), we cannot exclude the possibility that standardized outcome definitions would have led to different results. Additionally, different DOAC drugs with different doses were used: De Vriese used Rivaroxaban 10 mg daily; whereas Pokorney and Reinecke used Apixaban 5 mg bid and 2.5 mg bid, respectively). Furthermore, some studies did not clearly define the stroke subtypes and systemic embolism nor clarify the etiology of bleeding endpoints (e.g., cerebral hemorrhage). Moreover, the population in this study may still be underpowered to detect significant differences in bleeding and thrombotic outcomes between VKAs and DOACs, as also limited the number of events in other possible outcomes of interest to include in the analysis, such as: minor, gastrointestinal and catheter site bleeding, and systemic thromboembolism.

Conclusion

This meta-analysis of randomized controlled trials including 383 patients highlights the efficacy and safety of DOACs for anticoagulation in patients with AF under hemodialysis. The incidence of stroke was significantly reduced in the DOAC group, but the ischemic stroke rate was not significantly different from rates in VKAs group. Moreover, major bleeding, CV death, and all-cause mortality were not significantly reduced with DOACs. It is important to note that the results may be limited by small population size or lack of power. Furthermore, the trials used different dosing strategies, some differing from the FDA recommendations, therefore, this work cannot be used to suggest a specific dosing strategy for patients receiving dialysis.

Even though our findings support the use of DOACs in patients with AF on dialysis, as the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommended, these conclusions need to be validated by further extensive randomized studies to address the best strategy to deal with the increased risk of thrombotic events and bleeding inherent in these patients, preferably with an additional control group without the use of anticoagulation and another with antiplatelet therapy.

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Declarations

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