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ORIGINAL ARTICLE

Safety and efficacy of direct oral anticoagulants in chronic kidney disease: a meta-analysis

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Abstract

Background: Direct oral anticoagulants (DOACs) have emerged as the first-line therapy for venous thromboembolism and stroke prophylaxis in atrial fibrillation. As DOACs are partially excreted renally, their safety in patients with chronic kidney disease (CKD) is unclear.

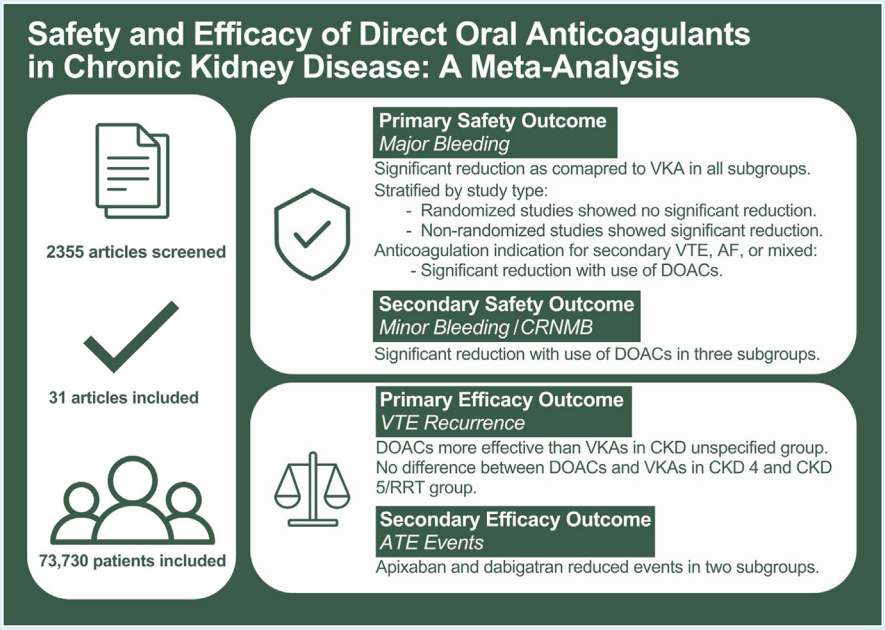
Objectives: To synthesize primary evidence on the safety profile of DOACs in patients with CKD.

Methods: We searched MEDLINE and Embase from inception to June 2023 for randomized and nonrandomized cohort studies comparing DOACs with vitamin K antagonists (VKAs) in CKD patients. Screening and data collection were conducted in duplicate. The primary safety outcome was major bleeding, defined by International Society on Thrombosis and Haemostasis criteria, stratified by CKD severity. Meta-analysis was done using the Mantel–Haenszel random-effects model, presented as odds ratios (ORs) with corresponding 95% CIs.

Results: Of the 2355 articles captured in the literature search, 25 nonrandomized studies (n = 6832) and 6 randomized studies (n = 66,898) were included. DOACs reduced major bleeding compared with VKAs in all subgroups (stage 4: OR, 0.73; 95% CI, 0.58, 0.93; stage 5/renal replacement therapy: OR, 0.70; 95% CI, 0.50, 0.98; stage unspecified: OR, 0.72; 95% CI, 0.63, 0.83). Apixaban and rivaroxaban both reduced major bleeding in stage 5/renal replacement therapy patients (apixaban: OR, 0.66; 95% CI, 0.52, 0.85; rivaroxaban: OR, 0.58; 95% CI, 0.35, 0.94).

Conclusion: In this meta-analysis, DOACs reduced major bleeding compared with VKAs in stage 4, stage 5/renal replacement therapy, and CKD stage unspecified patients. Future analysis should evaluate the impact of specific DOACs and dosage on safety and efficacy in this population.

Daniel Tham and Lucy Zhao contributed equally to this study.



KEYWORDS
chronic, factor Xa inhibitors, hemorrhage, renal insufficiency, venous thromboembolism, warfarin

Essentials

- The safety of direct oral anticoagulants (DOACs) is unclear in chronic kidney disease.
- A meta-analysis was conducted comparing major bleeding in DOACs and vitamin K antagonists (VKAs).
- DOACs reduced major bleeding compared with VKAs in severe stages of chronic kidney disease.
- DOACs appear to be a safe and efficacious alternative to VKAs in advanced chronic kidney disease.

1 | INTRODUCTION

Patients with chronic kidney disease (CKD) face an increased risk of bleeding and thrombosis, with the highest risk for fatal bleeding and thromboembolism in patients with advanced CKD (estimated glomerular filtration rate [eGFR] < 30 mL/min) [1]. Direct oral anticoagulants (DOACs) are the current standard of care for primary and secondary prevention of venous thromboembolism (VTE) and primary prevention of stroke in most patients with atrial fibrillation (AF) [2,3]. Compared with vitamin K antagonists (VKAs), DOACs have several advantages, including fewer monitoring requirements, more immediate drug onset, and fewer drug and food interactions [4]. Unlike VKAs, primarily metabolized in the liver, the metabolism of DOACs involves renal and hepatic pathways [5–7]. Renal clearance profiles for DOACs range from 27% (apixaban) to more than 80% (dabigatran) [5–7]. In patients with CKD, alterations in transmembrane receptor activity, such as the P-glycoprotein, which are crucial to the elimination of many drugs, including DOACs, increase drug bioavailability and decrease clearance [8–12]. The decision to use DOACs in CKD patients is complicated, given the risks of drug accumulation [8–12].

Data describing DOAC use in patients with impaired renal function is limited. Landmark randomized controlled trials (RCTs) evaluating DOACs have historically excluded patients on dialysis or creatinine clearances < 25 to 30 mL/min [13–17]. Although some larger trials included patients with CKD stage 4 (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [ROCKET-AF], Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation [ARISTOTLE]), there is little data on DOACs in patients with advanced CKD stages or on hemodialysis [14,15]. The lack of evidence and concerns surrounding the impact of renal impairment on drug clearance has led to uncertainty in the safety profile of DOACs in patients with severe CKD. As a measure of caution, VKAs have been historically recommended over DOACs for anticoagulation in patients with CKD.

Recent evidence suggests DOACs have a similar bleeding risk compared with warfarin and low-molecular-weight heparins (LMWHs) in patients with normal to mild renal impairment (eGFR > 60 mL/min) [18–20]. Major clinical guidelines (American Heart Association, Canadian Cardiovascular Society, American College of Chest Physicians, European Heart Rhythm Association, European Society of Cardiology, Kidney Disease: Improving Global Outcomes, and Thrombosis Canada) endorse DOAC usage for patients with CKD up to stage 3 [2,21–30]. However, recommendations are variable surrounding DOAC use in patients with CKD stage 4, stage 5, and end-stage renal disease [2,31]. Emerging evidence suggests that DOACs may be safe in patients with severe CKD beyond stage 3, but conclusive safety profiles in this population are unclear [2,4,23]. Clinical uncertainty in this population makes the decision to prescribe DOACs over VKAs and LMWHs highly individualized [4].

Given the importance of balancing the benefits and risks of anticoagulation in patients with severe CKD, there is a need to synthesize currently available data on this subject. This review aimed to assess the efficacy and safety of DOACs compared with VKAs for the management of bleeding and thromboembolic events for CKD stages 4 to 5 and patients on renal replacement therapy (RRT).

2 | METHODS

This systematic review and meta-analysis is reported according to the 2020 Preferred Reporting Instructions for Systematic Reviews and Meta-analysis guidelines [32] (Supplementary Table S1).

2.1 | Search strategy

MEDLINE and Embase were searched from inception to June 2023. The search strategy consisted of keywords pertaining to CKD (chronic kidney disease, renal insufficiency, dialysis, renal replacement therapy, end-stage renal disease, and kidney failure) and oral anticoagulants (direct oral anticoagulants, oral anticoagulants, apixaban, rivaroxaban, edoxaban, and dabigatran). The references of relevant articles from the initial search were also manually reviewed for articles not captured in the search. All citations identified in the initial and manual searches were uploaded to the Covidence software (Veritas Health Innovation).

Title, abstract, and full-text screening of articles was done independently and in duplicate. Discrepancies were resolved by consensus or input from additional authors (A.L., P.L., and A.E.).

2.2 | Inclusion and exclusion criteria

Articles were included if they met the following criteria: 1) cohort studies (prospective or retrospective) or RCTs, 2) contained patients with chronic renal impairment/CKD, 3) compared a DOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) with VKAs, LMWHs, or no anticoagulation and, 4) reported data for 1 of the 4 study outcomes of interest (International Society on Thrombosis and Haemostasis [ISTH] major bleeding, ISTH minor bleeding, VTE recurrence, or arterial thromboembolic [ATE] events—summarized in Table 1) [33–35].

TABLE 1 Definition of study outcomes.

Study outcome	Definition
ISTH major bleeding [33]	Fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin levels of 1.24 mmol/L (20 g/L or greater) or more or leading to a transfusion of 2 U or more of whole blood or red cells.
CRNMB/minor bleeding [34]	All reported bleeding events not classified as ISTH major bleeding events.
VTE recurrence [35]	Objectively confirmed, fatal, or nonfatal DVT (of the leg or pelvis) or PE, or a death to which PE contributed or could not be ruled out (in patients being treated with secondary prophylaxis for VTE).
ATE events	Stroke, MI, and cardioembolic events, ie, acute limb ischemia.

ATE, arterial thromboembolism; CRNMB, clinically relevant nonmajor bleeding; DVT, deep vein thrombosis; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; PE, pulmonary embolism; VTE, venous thromboembolism.

Articles were excluded if they contained any of the following: 1) cross-sectional, case-control, and/or case series studies, or any study that was neither a cohort nor RCT, 2) studies with nonhuman or pediatric populations, 3) studies containing patients with acute kidney injuries, 4) studies without clinical outcomes, 5) studies without a full-text article, 6) studies without English translation, or 7) studies in which data specific to CKD patients could not be ascertained.

2.3 | Data extraction

Data were extracted using predesigned data collection templates on Microsoft Excel (Microsoft Corporation). Data collection was done independently and in duplicate, and discrepancies were resolved through consensus or consultation with additional authors of this paper (A.L., P.L., or A.E.). Data extracted included general characteristics, baseline patient data, anticoagulation regimen, details pertaining to CKD, including stage or use of dialysis at the time of anticoagulation, and information related to predefined study outcomes.

2.4 | Study endpoints

The primary safety outcome of this study was major bleeding as defined by ISTH criteria [33]. In studies where ISTH criteria were not

explicitly stated, ISTH criteria were applied if sufficient data were reported. The primary efficacy outcomes of this study were treatment failure depending on the study context, ie, recurrence of VTE and ATE (stroke, myocardial infarction, and cardioembolic events). The secondary outcome was a composite outcome of minor bleeding and clinically relevant nonmajor bleeding (CRNMB) as defined by ISTH criteria. Data were stratified into 3 groups based on CKD stage as defined by Kidney Disease: Improving Global Outcomes guidelines described in Table 2 [36]: A) CKD 4 (eGFR 15-29 mL/min), B) CKD 5 (eGFR < 15 mL/min) and/or RRT, and C) CKD unspecified (patients with creatinine clearance or eGFR range < 44 mL/min but organized patients into categories that did not fit into CKD 3, 4, or 5) [36]. For the primary safety outcome of major bleeding, further stratification based on the trial type was performed within each of the 3 CKD subgroups, which pooled data into groups containing exclusively A) randomized trials or B) nonrandomized trials. For both safety outcomes (major bleeding and the composite outcome of CRNMB and minor bleeding), additional stratification according to indication for anticoagulation therapy was also performed, with the outcomes in each study CKD subgroup being split into indications for VTE secondary prophylaxis/treatment, AF, or mixed indication (study reported patients receiving anticoagulation therapy for both VTE treatment and AF without reporting outcomes within each indication class).

2.5 | Outcome definitions

Outcome definitions are detailed in Table 1. ISTH major bleeding was defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ and/or bleeding causing a fall in hemoglobin level of 20 g/L or requiring a transfusion requiring 2 or more units of whole blood/red cells [33]. VTE recurrence was defined as objectively confirmed fatal or nonfatal deep vein thrombosis (of the leg or pelvis) or pulmonary embolism or death to which pulmonary embolism contributed or could not be ruled out [35]. ATE events included the events of stroke, myocardial infarction, or cardioembolic events, ie, acute limb ischemia. Minor bleeding and CRNMB were defined according to ISTH criteria [34]. Any bleeding event not classified as a major bleeding event was included in the composite outcome of minor bleeding and CRNMB [34].

TABLE 2 Classification of study patient subgroups.

CKD severity	Definition [36]
Stage 4	eGFR = 15-29 mL/min
Stage 5	eGFR < 15 mL/min
RRT	Patients identified as receiving dialysis (hemodialysis or peritoneal) for CKD

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy.

2.6 | Synthesis of evidence

Baseline descriptive characteristics were reported as means with associated SDs or medians with associated IQRs. Data were meta-analyzed using the Mantel–Haenszel random-effects model and presented as odds ratios (ORs) with corresponding 95% CIs [37]. Heterogeneity between studies was assessed using the I^2 statistic. Meta-analysis was done using the Review Manager version 5.4 software (The Cochrane Collaboration).

2.7 | Quality assessment

The quality and risk of bias (ROB) of nonrandomized studies were evaluated using the Risk of Bias In Nonrandomized Studies or Interventions tool [38]. Randomized studies were evaluated using the Cochrane Risk of Bias tool [39]. Quality assessment was completed independently and in duplicate. The certainty of evidence was determined using the Grading of Recommendations, Assessment, Development, and Evaluations tool [40].

3 | RESULTS

3.1 | Study selection

The literature search captured a total of 2355 articles, of which 6 were randomized (n = 6832) and 25 were nonrandomized (n = 66,898; Figure).

The baseline patient characteristics from the included studies are summarized in Table 3 [10,17,41–69] and Supplementary Table S2. All included studies directly compared DOACs with VKAs [10,17,41–69]. Of the 25 nonrandomized studies, 23 were retrospective, with patient data spanning from 2001 to 2020. The 6 randomized studies contained patient data spanning from 2005 to 2022.

Three studies provided data for DOACs in patients with CKD 4, 10 studies provided data for patients with CKD 5/RRT, and 18 studies provided data for patients in multiple CKD stages. Patients in 13 studies were anticoagulated for longer than 3 months but less than 1 year, and 15 studies used anticoagulation regimens longer than 1 year. In studies utilizing a single DOAC, apixaban was most commonly used (n = 13), followed by rivaroxaban (n = 4), dabigatran (n = 2), and edoxaban (n = 1). In 11 studies, the DOAC comparator group included multiple DOACs in which the patient population was prescribed apixaban, rivaroxaban, dabigatran, or edoxaban. The most common DOACs used in the multiple DOAC group were rivaroxaban (11/11), followed by apixaban (10/11), dabigatran (8/11), and edoxaban (5/11). The most common indication for anticoagulation was AF (n = 19), followed by secondary prophylaxis for VTE (n = 5). Seven studies enrolled patients with multiple indications, including AF or VTE prophylaxis.

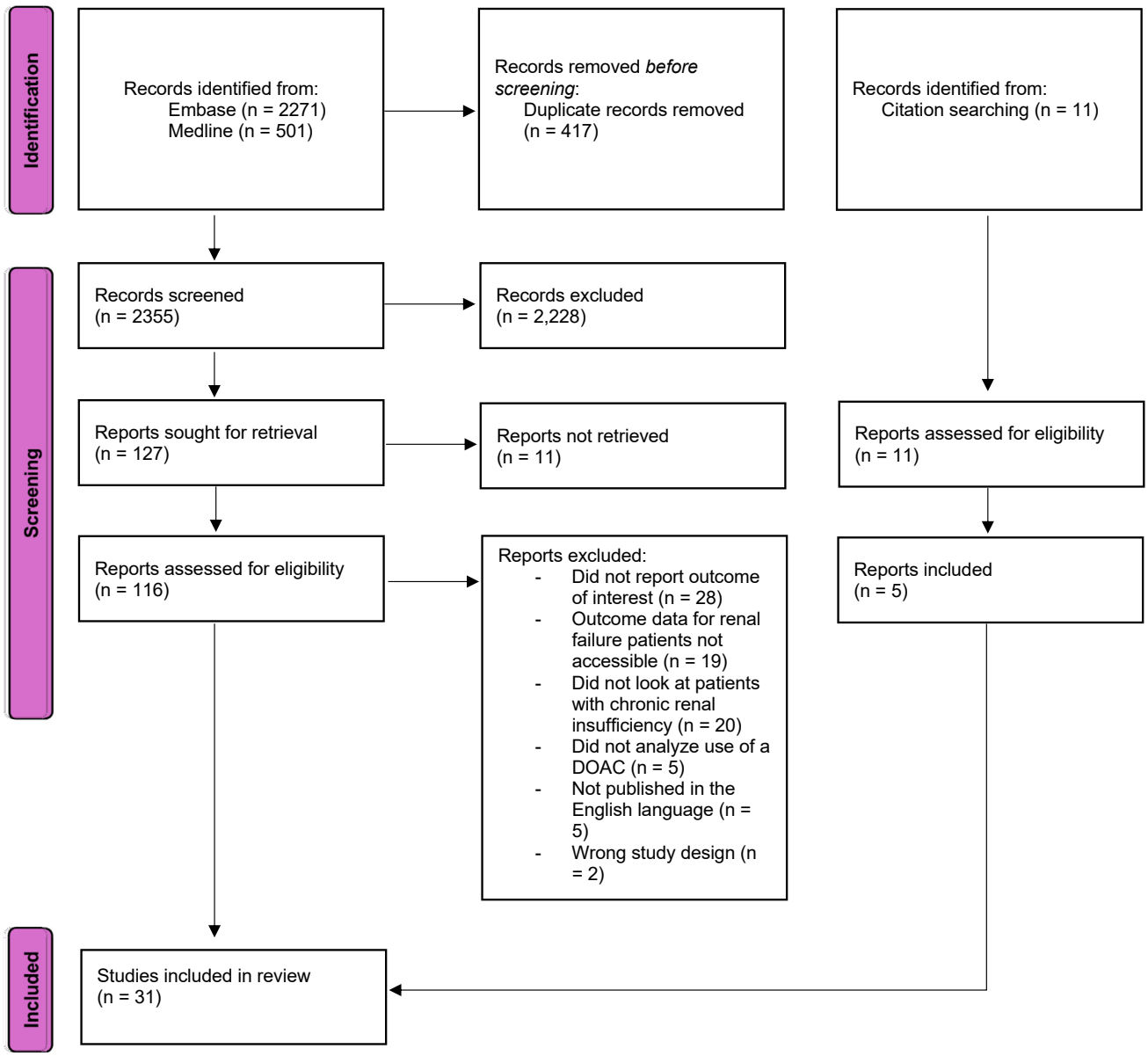


FIGURE Preferred Reporting Instructions for Systematic Reviews and Meta-analysis flowchart. DOAC, direct oral anticoagulant.

3.2 | Primary and secondary outcomes

Table 4 summarizes the effect estimates for each study outcome. For the primary safety outcome of major bleeding, DOACs significantly reduced major bleeding compared with VKAs in patients in all CKD subgroups (CKD 4: OR, 0.73; 95% CI, 0.58, 0.93; I^2 = 0 %; *n* = 6482; 6 studies; CKD 5/RRT: OR, 0.70; 95% CI, 0.50, 0.98; I^2 = 86%; *n* = 45,453; 13 studies; CKD unspecified: OR, 0.72; 95% CI, 0.63, 0.83; I^2 = 45%; *n* = 51,786; 16 studies). Apixaban and rivaroxaban both reduced major bleeding in CKD 5/RRT patients (apixaban: OR, 0.66; 95% CI, 0.52, 0.85; I^2 = 57%; *n* = 25,138; 8 studies; rivaroxaban: OR, 0.58; 95% CI, 0.35, 0.94; I^2 = 45%; *n* = 11,671; 3 studies). In CKD 5/RRT patients, dabigatran was associated with an increase in major bleeding compared with VKAs (OR, 2.02; 95% CI, 1.58, 2.59; I^2 = NA; *n* = 8345; 1 study). Apixaban showed a reduction in major bleeding compared with VKAs in the CKD unspecified group (OR, 0.68; 95% CI, 0.61, 0.75; I^2 = 0%; *n* = 38,360; 6 studies).

For the outcome of major bleeding stratified by study type (randomized or nonrandomized), significant reductions in major bleeding with the use of any type of DOAC were observed in the CKD 4 subgroup based on evidence from 1 randomized trial and 8 nonrandomized trials, and the CKD unspecified subgroup based on evidence from 3 randomized trials and 13 nonrandomized trials. In the CKD 5/RRT subgroup, a significant reduction in major bleeding was no longer observed among exclusive RCTs (OR, 0.66; 95% CI, 0.30, 1.43; I^2 = 35%; *n* = 34; 3 studies). However, the reduction in major bleeding within the analysis only containing nonrandomized studies remained significant (OR, 0.70; 95% CI, 0.48, 1.02; I^2 = 89%; *n* = 45,112; 10 studies).

For the outcome of major bleeding stratified by the anticoagulation indication of VTE secondary prophylaxis/treatment,

TABLE 3 Baseline characteristics for studies included in the final analysis.

Author-year	Total sample size	% Female	% Female (DOAC)	% Female (control)	Sample size (DOAC)	Sample size (control)	CKD stage (4, 5, or multiple)	DOAC used	DOAC indication	Country	Study design
Chan et al. 2015 [41]	8589	40	59.8	38.8	525	8064	CKD5/RRT	Multiple DOACs	AF	USA	RC
Sarratt et al. 2017 [42]	180	51	50	51.7	40	140	CKD5/RRT	Apixaban	Multiple indications	USA	RC
Stanifer et al. 2020 [43]	267	61	61.8	59.4	135	132	CKD4	Apixaban	AF	Multiple	RCT
Reed et al. 2018 [44]	124	44	48.6	38	74	50	CKD5/RRT	Apixaban	Multiple indications	USA	RC
Siontis et al. 2018 [45]	9404	46	45.6	45.7	2351	7053	CKD5/RRT	Apixaban	AF	USA	RC
Chang et al. 2019 [46]	800	56	56.1	55.4	280	520	Multiple CKD stages	Multiple DOACs	AF	Taiwan	RC
Heleniak et al. 2020 [47]	182	35	34.4	35.9	90	92	CKD4	Multiple DOACs	AF	Poland	RC
Herndon et al. 2020 [48]	111	0	0	0	54	57	Multiple CKD stages	Apixaban	Multiple indications	USA	RC
Yao et al. 2020 [49]	917	43	43.2	43.1	588	329	CKD4	Multiple DOACs	AF	NR	RC
De Vriese et al. 2021 [50]	90	33	23.9	43.2	46	44	CKD5/RRT	Rivaroxaban	AF	Belgium	RCT
Lin et al. 2021 [51]	3273	51	57	51	88	3185	CKD5/RRT	Rivaroxaban	AF	Taiwan	RC
Cohen et al. 2022 [52]	7376	56	56.1	56.1	2640	4736	Multiple CKD stages	Apixaban	VTE – secondary prophylaxis	USA	RC
Cline et al. 2023 [53]	1697	70	72.4	68.9	626	1071	CKD5/RRT	Multiple DOACs	Multiple indications	USA	RC
Ellenbogen et al. 2022 [54]	11,565	54	54.3	54.3	2302	9263	CKD5/RRT	Apixaban	VTE – secondary prophylaxis	USA	RC
Pokorney et al. 2022 [55]	154	36	41.5	30.6	82	72	CKD5/RRT	Apixaban	AF	USA	RCT
Reinecke et al. 2023 [56]	97	30	35.4	24.5	48	49	CKD5/RRT	Apixaban	AF	Germany	RCT
Hijazi et al. 2014 [57]	3484	30	29.5	36.7	2358	1126	Multiple CKD stages	Dabigatran	AF	Multiple	RCT

(Continues)

TABLE 3 (Continued)

Author-year	Total sample size	% Female	% Female (DOAC)	% Female (control)	Sample size (DOAC)	Sample size (control)	CKD stage (4, 5, or multiple)	DOAC used	DOAC indication	Country	Study design
(unspecified)											
Lee et al. 2010 [10] (unspecified)	233	63	65.9	62.3	59	174	Multiple CKD stages	Multiple DOACs	AF	South Korea	RC
Bohula et al. 2016 [17] (unspecified)	2740	54	NR	NR	1379	1361	Multiple CKD stages	Edoxaban	AF	Multiple	RCT
Stanton et al. 2017 [58] (unspecified)	146	60	60.3	58.9	73	73	Multiple CKD stages	Apixaban	Multiple indications	USA	RC
Goldhaber et al. 2017 [59] (unspecified)	220	40	40.4	40.5	106	114	Multiple CKD stages	Dabigatran	VTE – secondary prophylaxis	Multiple	RCT – pooled
Schafer et al. 2018 [60] (unspecified)	604	50	54	46	302	302	Multiple CKD stages	Apixaban	Multiple indications	USA	RC
Shin et al. 2018 [61] (unspecified)	2244	47	47	46	1122	1122	Multiple CKD stages	Multiple DOACs	AF	USA	RC
Yanagisawa et al. 2018 [62] (unspecified)	231	47	NR	NR	93	138	Multiple CKD stages	Multiple DOACs	AF	Japan	RC
Weir et al. 2020 [63] (unspecified)	2317	60	61.6	59.3	781	1536	Multiple CKD stages	Rivaroxaban	AF	USA	RC
Hanni et al. 2020 [64] (unspecified)	861	53	57.8	52.4	128	733	Multiple CKD stages	Apixaban	Multiple indications	USA	RC
Makani et al. 2020 [65] (unspecified)	10,653	50	50.7	49.3	4748	5905	Multiple CKD stages	Multiple DOACs	AF	USA	RC
Fu et al. 2021 [66] (unspecified)	3250	43	43.02	42.28	1625	1625	Multiple CKD stages	Apixaban	AF	Taiwan	RC
Di Lullo et al. 2021 [67]	347	43	42	45.7	247	100	Multiple CKD stages	Rivaroxaban	AF	Italy	PC

(Continues)

TABLE 3 (Continued)

Author-year	Total sample size	% Female	% Female (DOAC)	% Female (control)	Sample size (DOAC)	Sample size (control)	CKD stage (4, 5, or multiple)	DOAC used	DOAC indication	Country	Study design
(unspecified)											
Ahuja et al. 2021 [68] (unspecified)	56	57	54	59	17	39	Multiple CKD stages	Multiple DOACs	VTE – secondary prophylaxis	USA	RC
Haas et al. 2012 [69] (unspecified)	1518	49	48.7	48.4	843	675	Multiple CKD stages	Multiple DOACs	VTE – secondary prophylaxis	Multiple	PC

AF, atrial fibrillation; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; NR, not reported; PC, prospective cohort; RC, retrospective cohort; RCT, randomized controlled trial; RRT, renal replacement therapy; USA, United States of America; VTE, venous thromboembolism.

statistically significant reductions in major bleeding were observed with the use of any type of DOAC within the CKD 5/RRT and CKD unspecified subgroups (CKD 5/RRT: OR, 0.75; 95% CI, 0.65, 0.85; I^2 = 0%; *n* = 15,133; 2 studies; CKD unspecified: OR, 0.72; 95% CI, 0.59, 0.87; I^2 = 0%; *n* = 16,506; 4 studies). For the outcome of major bleeding stratified by the indication of AF for anticoagulation, significant reductions with the use of DOACs were observed in the CKD 4 and CKD unspecified subgroups (CKD 4: OR, 0.62; 95% CI, 0.38, 0.99; I^2 = 32%; *n* = 1767; 4 studies; CKD unspecified: OR, 0.70; 95% CI, 0.53, 0.92; I^2 = 66%; *n* = 12,967; 8 studies). For studies with mixed indications for anticoagulation, a significant reduction in major bleeding was associated with the prescription of DOACs in the CKD 5/RRT and CKD unspecified subgroups (CKD 5/RRT: OR, 0.64; 95% CI, 0.49, 0.84; I^2 = 26%; *n* = 20,398; 4 studies; CKD unspecified: OR, 0.52; 95% CI, 0.35, 0.77; I^2 = 0%; *n* = 2599; 3 studies). For the secondary safety outcome of CRNMB/minor bleeding, a significant reduction associated with DOACs was observed in the CKD 4, CKD 5/RRT, and CKD unspecified subgroups when the indication for anticoagulation therapy was VTE secondary prophylaxis/treatment (CKD 4: OR, 0.67; 95% CI, 0.54, 0.84; I^2 = NA; *n* = 3808; 1 study; CKD 5/RRT: OR, 0.74; 95% CI, 0.59, 0.93; I^2 = 71%; *n* = 15,133; 2 studies; CKD unspecified: OR, 0.67; 95% CI, 0.58, 0.78; I^2 = 0%; *n* = 19,637; 3 studies).

For the primary efficacy outcome of VTE recurrence in studies where patients were anticoagulated for VTE secondary prophylaxis, DOACs overall were more effective than VKAs in the CKD unspecified group (OR, 0.73; 95% CI, 0.55, 0.96; I^2 = 14%; *n* = 20,058; 7 studies). In the CKD 4 and CKD 5/RRT groups, there were no significant differences between DOACs overall and VKAs in VTE recurrence (CKD 4: OR, 0.67; 95% CI, 0.42, 1.07; I^2 = NA; *n* = 3808; 1 study; CKD 5/RRT: OR, 0.66; 95% CI, 0.38, 1.16; I^2 = 70%; *n* = 15,582; 4 studies).

For the secondary outcomes, rivaroxaban produced a statistically significant increase in minor bleeding/CRNMB within the CKD 4 group (OR, 4.58; 95% CI, 1.14, 18.40; I^2 = NA; *n* = 121; 1 study). In the CKD 5/RRT group, dabigatran reduced minor bleeding/CRNMB compared with VKAs (OR, 0.63; 95% CI, 0.50, 0.81; I^2 = NA; *n* = 8345 patients; 1 study) and apixaban reduced ATE events compared with VKAs (OR, 0.63; 95% CI, 0.50, 0.81; I^2 = 0%; *n* = 9655; 3 studies). In the CKD unspecified group, rivaroxaban reduced minor bleeding/CRNMB compared with VKAs (OR, 0.20; 95% CI, 0.07, 0.56; I^2 = NA; *n* = 347; 1 study). Apixaban and dabigatran both reduced ATE events compared with VKAs (apixaban: OR, 0.75; 95% CI, 0.63, 0.89; I^2 = 16%; *n* = 22,887; 4 studies, dabigatran: OR, 0.71; 95% CI, 0.50, 0.99; I^2 = NA; *n* = 3554; 1 study).

3.3 | Quality of studies and certainty in evidence

Of the included nonrandomized studies, 1 had a low ROB, 16 had a moderate ROB, and 8 had a serious ROB. Of the 8 studies with a serious ROB, 6 failed to control for baseline confounding, and 2 failed to control for time-varying confounding in their statistical analysis.

TABLE 4 Summary of findings for chronic kidney disease stage 4, chronic kidney disease stage 5/renal replacement therapy, and chronic kidney disease unspecified subgroups.

Endpoint	DOAC agent	OR (95% CI)	*P* value	I^2, %	No. studies (no. patients)	Certainty of evidence (GRADE)	Justification for GRADE recommendation
CKD 4							
Major bleeding	Apixaban	0.69 (0.46, 1.05)	.09	31	5 (4992)	Low	1. High sample size (*n* = 4992) 2. Moderate trial diversity (5 trials) 3. Low heterogeneity (I^2 = 31%; chi-square = 5.78; *P* = .22) 4. Low indirectness 5. Narrow 95% CI 6. Moderate risk of bias 7. Nonsignificant (*P* = .09)
	Dabigatran	0.41 (0.09, 1.79)	.24	NA	1 (399)	Low	1. Low sample size (*n* = 399) 2. Low trial diversity (1 trial) 3. Heterogeneity not applicable 4. Low indirectness 5. Narrow 95% CI (imprecision) 6. Moderate risk of bias 7. Nonsignificant (*P* = .24)
	Rivaroxaban	0.64 (0.31, 1.32)	.22	0	2 (660)	NA	NA
	Multiple DOACs	0.65 (0.31, 1,32)	.21	NA	1 (501)	Low	1. Low sample size (*n* = 660) 2. Low trial diversity (2 trials) 3. Moderate heterogeneity (I^2 = 0%; chi-square = 0.51; *P* = .51) 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Serious risk of bias 7. Nonsignificant (*P* = .22)
	Overall	0.73 (0.58, 0.93)	.01	0	6 (6482)	Low	1. Low sample size (*n* = 501) 2. Low trial diversity (1 trial) 3. Heterogeneity not applicable 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Moderate risk of bias 7. Nonsignificant (*P* = .21)
CRNMB & minor bleeding	Apixaban	0.73 (0.41, 1.31)	.3	31	3 (4228)	Moderate	1. High sample size (*n* = 6482) 2. Moderate trial diversity (6 trials) 3. Low heterogeneity (I^2 = 0%; chi-square = 7.25; *P* = .51) 4. Low indirectness 5. Narrow 95% CI 6. Moderate risk of bias 7. Significant (*P* = .01)
	Rivaroxaban	4.58 (1.14, 18.40)	.03	NA	1 (121)	Low	1. High sample size (*n* = 4228) 2. Low trial diversity (3 trials) 3. Moderate heterogeneity (I^2 = 31%; chi-square = 2.90; *P* = .23) 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Moderate risk of bias 7. Nonsignificant (*P* = .30)
	Overall	1.13 (0.44, 2.87)	.8	70	3 (4349)	NA	NA

(Continues)

TABLE 4 (Continued)

Endpoint	DOAC agent	OR (95% CI)	*P* value	I^2, %	No. studies (no. patients)	Certainty of evidence (GRADE)	Justification for GRADE recommendation
VTE secondary prophylaxis	Apixaban	0.67 (0.42, 1.07)	.09	NA	1 (3808)	NA	NA
	Overall	0.67 (0.42, 1.07)	.09	NA	1 (3808)	Low	1. Low sample size (*n* = 4992) 2. Low trial diversity (1 trial) 3. Heterogeneity not applicable 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Serious risk of bias 7. Nonsignificant (*P* = .03)
ATE primary prophylaxis	Apixaban	1.01 (0.56, 1.81)	.98	0	3 (1059)	NA	NA
	Dabigatran	0.35 (0.02, 6.34)	.48	NA	1 (399)	Low	1. High sample size (*n* = 4349) 2. Low trial diversity (3 trials) 3. High heterogeneity (I^2 = 70%; chi-square = 9.94; *P* = .02) 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Moderate risk of bias 7. Nonsignificant (*P* = .80)
	Rivaroxaban	0.72 (0.04, 0.52)	.7	43	2 (660)	Low	1. High sample size (*n* = 3808) 2. Low trial diversity (1 trial) 3. Heterogeneity not applicable 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Moderate risk of bias 7. Nonsignificant (*P* = .09)
	Multiple DOACs	0.15 (0.04, 0.52)	.002	NA	1 (501)	NA	NA
	Overall	0.66 (0.32, 1.34)	.25	48	4 (2599)	NA	NA
CKD 5/RRT							
Major bleeding	Apixaban	0.66 (0.52, 0.85)	.001	57	8 (25,138)	NA	NA
	Dabigatran	2.02 (1.58, 2.59)	<.00001	NA	1 (8345)	Low	1. High sample size (*n* = 3808) 2. Low trial diversity (1 trial) 3. Heterogeneity not applicable 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Moderate risk of bias 7. Nonsignificant (*P* = .09)
	Rivaroxaban	0.58 (0.35, 0.94)	.03	45	3 (11,671)	Low	1. Moderate sample size (*n* = 1059) 2. Low trial diversity (3 trials) 3. Low heterogeneity (I^2 = 0%; chi-square = 1.75; *P* = .42) 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Moderate risk of bias 7. Nonsignificant (*P* = .98)
	Multiple DOACs	0.46 (0.16, 1.35)	.16	NA	1 (299)	Low	1. Low sample size (*n* = 399) 2. Low trial diversity (1 trial) 3. Heterogeneity not applicable 4. Low indirectness 5. Wide 95% CI (imprecision)

(Continues)

TABLE 4 (Continued)

Endpoint	DOAC agent	OR (95% CI)	*P* value	I^2, %	No. studies (no. patients)	Certainty of evidence (GRADE)	Justification for GRADE recommendation
							6. Moderate risk of bias 7. Nonsignificant (*P* = .48)
	Overall	0.70 (0.50, 0.98)	.04	86	13 (45,453)	NA	NA
CRNMB & minor bleeding	Apixaban	0.81 (0.64, 1.03)	.08	47	6 (15,688)	Low	1. Low sample size (*n* = 660) 2. Low trial diversity (2 trials) 3. Moderate heterogeneity (I^2 = 43%; chi-square = 1.76; *P* = .18) 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Moderate risk of bias 7. Nonsignificant (*P* = .70)
	Dabigatran	0.63 (0.50, 0.81)	.0002	NA	1 (8345)	Low	1. Low sample size (*n* = 501) 2. Low trial diversity (1 trial) 3. Heterogeneity not applicable 4. Low indirectness 5. Moderate 95% CI 6. Moderate risk of bias 7. Significant (*P* = .002)
	Rivaroxaban	0.65 (0.40, 1.07)	.09	69%	3 (11,671)	Low	1. Moderate sample size (*n* = 2599) 2. Low trial diversity (4 trials) 3. Moderate heterogeneity (I^2 = 48%; chi-square = 11.61; *P* = .07) 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Moderate risk of bias 7. Nonsignificant (*P* = .25)
	Overall	0.72 (0.59, 0.89)	.002	66	10 (35,704)		
VTE secondary prophylaxis	Apixaban	0.71 (0.39, 1.29)	.26	77	3 (15,257)	Moderate	1. High sample size (*n* = 25,138) 2. Moderate trial diversity (8 trials) 3. Moderate heterogeneity (I^2 = 57%; chi-square = 16.14; *P* = .02) 4. Low indirectness 5. Narrow 95% CI 6. Moderate risk of bias 7. Significant (*P* = .001)
	Multiple DOACs	0.37 (0.08, 1.72)	.21	NA	1 (325)	Low	1. High sample size (*n* = 8345) 2. Low trial diversity (1 trial) 3. Heterogeneity not applicable 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Low risk of bias 7. Significant ($P \leq .00001$)
	Overall	0.66 (0.38, 1.16)	.15	70	4 (15,582)	NA	NA
ATE primary prophylaxis	Apixaban	0.63 (0.50, 0.81)	.0002	0	3 (9655)	Low	1. High sample size (*n* = 11,671) 2. Low trial diversity (3 trials) 3. Moderate heterogeneity (I^2 = 45%; chi-square = 3.65; *P* = .16) 4. Low indirectness 5. Moderate 95% CI

(Continues)

TABLE 4 (Continued)

Endpoint	DOAC agent	OR (95% CI)	*P* value	I^2, %	No. studies (no. patients)	Certainty of evidence (GRADE)	Justification for GRADE recommendation
							6. Moderate risk of bias 7. Significant (*P* = .03)
	Dabigatran	1.55 (0.88, 2.75)	.13	NA	1 (8345)	Low	1. Low sample size (*n* = 299) 2. Low trial diversity (1 trial) 3. Heterogeneity not applicable 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Moderate risk of bias 7. Nonsignificant (*P* = .16)
	Rivaroxaban	0.48 (0.18, 1.24)	.13	0	3 (11,671)	High	1. High sample size (*n* = 45,453) 2. High trial diversity (13 trials) 3. High heterogeneity (I^2 = 86%; chi-square = 88.52; *P* ≤ .00001) 4. Low indirectness 5. Narrow 95% CI 6. Moderate risk of bias 7. Significant (*P* = .04)
	Multiple DOACs	0.23 (0.04, 1.24)	.09	0	2 (624)	Moderate	1. High sample size (*n* = 15,688) 2. Moderate trial diversity (6 trials) 3. Moderate heterogeneity (I2 = 47%; chi-square = 9.40; *P* = .09) 4. Low indirectness 5. Narrow 95% CI 6. Moderate risk of bias 7. Nonsignificant (*P* = .08)
	Overall	0.61 (0.38, 1.00)	.05	57	9 (30,295)	Low	1. High sample size (*n* = 8345) 2. Low trial diversity (1 trial) 3. Heterogeneity not applicable 4. Low indirectness 5. Narrow 95% CI 6. Low risk of bias 7. Significant (*P* = .0002)
CKD unspecified (CrCl ranges that do not perfectly fit into CKD 4 or CKD 5)							
Major bleeding	Apixaban	0.68 (0.61, 0.75)	<.00001	0	6 (38,360)	Low	1. High sample size (*n* = 11,671) 2. Low trial diversity (3 trials) 3. Moderate heterogeneity (I^2 = 69%; chi-square = 6.55; *P* = .04) 4. Low indirectness 5. Moderate 95% CI 6. Moderate risk of bias 7. Nonsignificant (*P* = .09)
	Dabigatran	1.01 (0.81, 1.27)	.91	0	2 (3774)	NA	NA
	Edoxaban	0.73 (0.56, 0.96)	.02	NA	1 (2728)	High	1. High sample size (*n* = 35,704) 2. High trial diversity (10 trials) 3. Moderate heterogeneity (I^2 = 66%; chi-square = 26.46; *P* = .002) 4. Low indirectness 5. Narrow 95% CI 6. Moderate risk of bias 7. Significant (*P* = .002)

(Continues)

TABLE 4 (Continued)

Endpoint	DOAC agent	OR (95% CI)	*P* value	I^2, %	No. studies (no. patients)	Certainty of evidence (GRADE)	Justification for GRADE recommendation
	Rivaroxaban	0.34 (0.04, 3.20)	.34	88	2 (2664)	Low	1. High sample size (*n* = 15,354) 2. Low trial diversity (4 trials) 3. High heterogeneity (I^2 = 77%; chi-square = 8.71; *P* = .01) 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Moderate risk of bias 7. Nonsignificant (*P* = .26)
	Multiple DOACs	0.68 (0.49, 0.95)	.02	0	5 (4260)	NA	NA
	Overall	0.72 (0.63, 0.83)	<.0001	45	16 (51,786)	NA	NA
CRNMB & minor bleeding	Apixaban	0.77 (0.58, 1.01)	.06	75	6 (35,221)	NA	NA
	Dabigatran	0.62 (0.30, 1.25)	.18	NA	1 (220)	Low	1. Low sample size (*n* = 325) 2. Low trial diversity (1 trial) 3. Heterogeneity not applicable 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Moderate risk of bias 7. Nonsignificant (*P* = .21)
	Rivaroxaban	0.20 (0.07, 0.56)	.002	NA	1 (347)	Low	1. High sample size (*n* = 15,679) 2. Moderate trial diversity (5 trials) 3. High heterogeneity (I^2 = 70%; chi-square = 10.13; *P* = .02) 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Moderate risk of bias 7. Nonsignificant (*P* = .15)
	Multiple DOACs	0.93 (0.41, 2.13)	.87	69	4 (2742)	Low	1. High sample size (*n* = 9655) 2. Low trial diversity (3 trials) 3. Low heterogeneity (I^2 = 0%; chi-square = 0.25; *P* = .88) 4. Low indirectness 5. Narrow 95% CI 6. Moderate risk of bias 7. Significant (*P* = .0002)
	Overall	0.78 (0.59, 1.03)	.07	81	12 (38,530)	Low	1. High sample size (*n* = 8345) 2. Low trial diversity (1 trial) 3. Heterogeneity not applicable 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Low risk of bias 7. Nonsignificant (*P* = .13)
VTE secondary prophylaxis	Apixaban	0.83 (0.66, 1.05)	.12	0	3 (16,550)	NA	NA
	Dabigatran	0.09 (0.01, 1.72)	.11	NA	1 (237)	Low	1. High sample size (*n* = 11,671) 2. Low trial diversity (3 trials) 3. High heterogeneity (I^2 = 72%; chi-square = 7.20; *P* = .03) 4. Low indirectness 5. Wide 95% CI (imprecision)

(Continues)

TABLE 4 (Continued)

Endpoint	DOAC agent	OR (95% CI)	*P* value	I^2, %	No. studies (no. patients)	Certainty of evidence (GRADE)	Justification for GRADE recommendation
							6. Moderate risk of bias 7. Nonsignificant (*P* = .13)
	Multiple DOACs	0.62 (0.40, 0.96)	.03	4	3 (3271)	Low	1. Low sample size (*n* = 624) 2. Low trial diversity (3 trials) 3. Low heterogeneity (I^2 = 0%; chi-square = 0.48; *P* = .49) 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Moderate risk of bias 7. Nonsignificant (*P* = .09)
	Overall	0.73 (0.55, 0.96)	.03	14	7 (20,058)	Moderate	1. High sample size (*n* = 30,295) 2. Moderate trial diversity (9 trials) 3. Moderate heterogeneity (I^2 = 57%; chi-square = 18.78; *P* = .02) 4. Low indirectness 5. Moderate 95% CI 6. Moderate risk of bias 7. Significant (*P* = .05)
ATE primary prophylaxis	Apixaban	0.75 (0.63, 0.89)	.001	16	4 (22,887)		
	Dabigatran	0.71 (0.50, 0.99)	.04	NA	1 (3554)	Moderate	1. High sample size (*n* = 38,360) 2. Moderate trial diversity (6 trials) 3. Low heterogeneity (I^2 = 0%; chi-square = 4.36; *P* = .50) 4. Low indirectness 5. Narrow 95% CI 6. Moderate risk of bias 7. Significant ($P \leq .00001$)
	Edoxaban	0.88 (0.65, 1.20)	.43	NA	1 (2740)	Low	1. Moderate sample size (*n* = 3774) 2. Low trial diversity (2 trials) 3. Low heterogeneity (I^2 = 0%; chi-square = 0.18; *P* = .68) 4. Low indirectness 5. Narrow 95% CI 6. Moderate risk of bias 7. Nonsignificant (*P* = .91)
	Rivaroxaban	0.07 (0.00, 54.74)	.44	95	2 (2664)	Low	1. Moderate sample size (*n* = 2728) 2. Low trial diversity (1 trial) 3. Heterogeneity not applicable 4. Low indirectness 5. Narrow 95% CI 6. Moderate risk of bias 7. Significant (*P* = .02)
	Multiple DOACs	0.65 (0.47, 0.89)	.007	40	7 (16,600)	Low	1. Moderate sample size (*n* = 2664) 2. Low trial diversity (2 trials) 3. High heterogeneity (I^2 = 88%; chi-square = 8.01; *P* = .005) 4. Low indirectness 5. Wide 95% CI (imprecision) 6. Serious risk of bias 7. Nonsignificant (*P* = .34)

(Continues)

TABLE 4 (Continued)

Endpoint	DOAC agent	OR (95% CI)	*P* value	I^2, %	No. studies (no. patients)	Certainty of evidence (GRADE)	Justification for GRADE recommendation
	Overall	0.72 (0.59, 0.87)	.0005	59	15 (48,445)	Moderate	1. Moderate sample size (n = 4260) 2. Moderate trial diversity (5 trials) 3. Low heterogeneity (I^2 = 0%; chi-square = 3.33; P = .50) 4. Low indirectness 5. Narrow 95% CI 6. Moderate risk of bias 7. Significant (P = .02)

ATE, arterial thromboembolism; CKD, chronic kidney disease; CrCl, creatinine clearance; CRNMB, clinically relevant nonmajor bleeding; DOAC, direct oral anticoagulant; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; NA, not applicable; OR, odds ratio; RRT, renal replacement therapy; VTE, venous thromboembolism.

One study with a serious ROB introduced a 24-month minimum follow-up period as part of their inclusion criteria, which introduced critical bias in patient selection. The 16 studies with a moderate ROB and 1 study with a low ROB utilized appropriate analysis methods to account for baseline and time-varying confounding, such as multivariate regression, propensity score matching, or inverse probability weighting.

All included randomized studies were found to be at a moderate ROB. Five studies had a moderate ROB due to missing outcome data, with 3 failing to report information on missing data and 2 containing concerning amounts of data left out of the final analysis. One study did not report its statistical plan or how deviations from study protocol would be addressed but properly addressed missing data in its methodology. ROB evaluations can be found in the online Supplementary material.

4 | DISCUSSION

This systematic review and meta-analysis assessed the safety and efficacy of DOACs in patients with CKD. DOACs were associated with a decrease in ISTH major bleeding compared with VKAs in patients with stage 4 and stage 5/RRT CKD alongside patients' populations with unspecified CKD severity. Nine studies in the CKD 5/RRT subgroup and 6 studies in the CKD unspecified subgroup collectively reported that apixaban was safer than VKAs for major bleeding. Within the CKD 5/RRT subgroup, 3 studies demonstrated that rivaroxaban was safer than VKAs, while 1 study demonstrated a greater risk of major bleeding with dabigatran compared with VKAs. When evaluating the impact of DOACs on safety outcomes stratified by indication for anticoagulation, DOACs were associated with reductions in major bleeding within the CKD 5/RRT and CKD unspecified patient subgroups when indicated for VTE secondary prophylaxis. Patients anticoagulated for VTE secondary prophylaxis also showed a reduction in CRNMB/minor bleeding in the CKD 4, CKD 5/RRT, and CKD unspecified subgroups. In patients with AF, DOACs were associated with reductions in major bleeding in the CKD 4 and CKD unspecified subgroups.

Current guidelines list apixaban and rivaroxaban as safe in patients with CKD stage 4 [2,23–25,27,30,36]. The results of this study support the use of DOACs (with the exception of dabigatran) overall in patients with CKD stage 4. Although still contraindicated in patients receiving dialysis under European and Canadian guidelines (European Heart Rhythm Association, European Society of Cardiology, Canadian Cardiovascular Society, and Thrombosis Canada), apixaban can be considered in patients with severe renal disease or on dialysis based on the US Food and Drug Administration approved package insert, and American Heart Association and American College of Chest Physicians guidelines [2,4,23,25]. The latter recommendations are supported by our study, given the reduced risk of bleeding associated with apixaban in patients with stage 5 CKD or RRT. Current US Food and Drug Administration package inserts approve rivaroxaban for eGFR < 15 mL/min despite other guidelines recommending against rivaroxaban in this population [41,70]. This meta-analysis found that rivaroxaban was comparable with VKAs for safety and efficacy for patients with CKD 5/RRT [41,50,51]. The findings of this meta-analysis are plausible given that the safety of apixaban and rivaroxaban would theoretically be least impacted by impaired renal function and have the lowest potential for inappropriate retention based on DOAC pharmacological profiles.

Within the CKD stage 5/RRT subgroup, evidence from 10 nonrandomized studies showed a significant reduction in major bleeding with DOACs overall compared with VKAs. Evidence from 3 randomized studies in the same population did not show this association. This finding was presented in the context of 2 randomized studies demonstrating reductions in major bleeding, like nonrandomized evidence, and 1 study demonstrating harm in CKD stage 5/RRT patients using DOACs [55]. The study demonstrating harm had significant limitations in methodological design, with the authors noting premature trial termination due to enrollment challenges and that, as a result, definitive conclusions could not be drawn due to an underpowered sample [55]. It is possible that with adequate enrollment, the

impact of DOACs on major bleeding may have more closely reflected findings from the other randomized and nonrandomized trials in this population. Assessing the current body of evidence comparing DOACs with VKAs in severe CKD patients, there is a clear need for more randomized data. Emerging trials in this area include the recently completed "Strategies for the Management of Atrial Fibrillation in patients Receiving Dialysis (SAFE-D)" trial (NCT03987711) and the ongoing "Stroke Prophylaxis with Apixaban in Chronic Kidney Disease Stage 5 Patients With Atrial Fibrillation (SACK)" trial (NCT05679024) with a target enrollment of 1400 patients and estimated completion in December 2028 [71,72]. As more data become available, the optimal anticoagulation regimen for patients with advanced CKD patients will become clearer.

The results of this study should be interpreted considering its limitations. First, many of the primary studies in this review did not provide specific data regarding the dosing of DOACs, which inherently introduces heterogeneity in the meta-analysis while also impacting bleeding risks. Second, only 1 observational study in this analysis was deemed as having a low risk of overall bias, and all studies had at least a moderate risk of confounding bias present in patient cohorts. While this analysis appears to support currently available literature and guidelines, these findings should be interpreted as accounting for the high degree of confounding and heterogeneity inherent to nonrandomized data. The potential for discrepancies between randomized and observational data is also highlighted by differences in effect sizes observed when separating randomized and nonrandomized data for the safety outcome of major bleeding. Finally, this analysis is limited by the differing durations of anticoagulation found among the included studies. All studies included in this analysis followed patients for a minimum of 3 months, and most studies reported average periods of follow-up ranging from 3 months to 1 year. However, a small number of studies reported average follow-up durations of longer than 1 year, introducing a minor source of heterogeneity in the meta-analysis. Overall, the strength of conclusions from this meta-analysis is limited by the quality of currently available data and the small number of randomized studies directly comparing DOACs with VKAs in this patient population.

Despite these limitations, this study has several strengths. To our knowledge, this analysis, which includes more than 70,000 patients, is the largest systematic review in this patient population and is the first systematic review to stratify safety and efficacy outcomes by specific DOAC agents in patients with CKD. When interpreted in the context of its limitations, the large volume of patient data and findings pertaining to specific DOAC agents in this analysis provides a much-needed update to inform or provide guidance on safety and efficacy outcomes related to DOACs in patients with severe CKD.

5 | CONCLUSION

DOACs appear to be a safe and efficacious alternative to VKAs in patients with advanced CKD. Of the DOACs, apixaban may be preferable in patients with severe renal impairment, but more randomized data evaluating the safety of DOACs in this population are needed. Future research should aim to expand on the results of this meta-analysis through the inclusion of ongoing trials and confounder adjustment stratifying by specific DOAC agent, dosage, and CKD stage.

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AUTHOR CONTRIBUTIONS

D.T. and L.Z. are equal contributors and co-first authors of this manuscript. D.T. and L.Z. performed title, abstract, and full-text screening, data extraction, and bias assessment, as well as drafted and edited the manuscript. W.Y. and J.K. performed title, abstract, and full-text screening, data extraction, and bias assessment. R.K. performed the bias assessment and manuscript editing. P.Y.L., A.L., A.E., and M.A.C. conceptualized the project and coordinated the manuscript draft editing and review. A.L., A.E., and P.Y.L. conducted the search strategy and developed the methodology. P.Y.L. performed the data analysis. M.A.C. undertook a supervision role for oversight and leadership responsibilities of the research team and provided the required support for the project.

RELATIONSHIP DISCLOSURE

A.L. and A.E. are recipients of the American Society for Hematology HONORS award. In the last 36 months, M.A.C. has received personal funding, including but not limited to the preparation of educational material, participation in Advisory Boards, or providing expert testimony for Bayer, AstraZeneca, Pfizer, Hemostasis Reference Laboratories, Syneos Health, and Eversana. He has participated in various medicolegal activities relating to thrombosis, anticoagulant drugs, or other aspects of internal medicine and hematological practice. He has also worked with multiple for-profit and not-for-profit entities, such as UpToDate and medical communication companies. He holds the Leo Pharma Chair in Thromboembolism, endowed at McMaster University. All other authors have no conflicts of interest to declare.

DATA AVAILABILITY

All contributory authors agree that data from the entirety of this manuscript is made publicly available on online medical databases and published articles. For questions on data or Supplementary material, contact the corresponding author.

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SUPPLEMENTARY MATERIAL

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