

ORIGINAL RESEARCH

Anticoagulation for Patients With Concomitant Atrial Fibrillation and End-Stage Renal Disease: A Systematic Review and Network Meta-Analysis

Ting-Wei Kao , MD; Zheng-Wei Chen , MD; Yen-Hung Lin , MD, PhD

BACKGROUND: Concomitant atrial fibrillation and end-stage renal disease is common and associated with an unfavorable prognosis. Although oral anticoagulants have been well established to prevent thromboembolism, the applicability in patients under long-term dialysis remains debatable. The study aimed to determine the efficacy and safety of anticoagulation in the dialysis-dependent population.

METHODS AND RESULTS: An updated network meta-analysis based on MEDLINE, EMBASE, and the Cochrane Library was performed. Studies published up to December 2022 were included. Direct oral anticoagulants (DOACs, dabigatran, rivaroxaban, apixaban 2.5/5 mg twice daily), vitamin K antagonists (VKAs), and no anticoagulation were compared on safety and efficacy outcomes. The outcomes of interest were major bleeding, thromboembolism, and all-cause death. A total of 42 studies, including 3 randomized controlled trials, with 185 864 subjects were pooled. VKAs were associated with a significantly higher risk of major bleeding than either no anticoagulation (hazard ratio [HR], 1.47; 95% CI, 1.34–1.61) or DOACs (DOACs versus VKAs; HR, 0.74 [95% CI, 0.64–0.84]). For the prevention of thromboembolism, the efficacies of VKAs, DOACs, and no anticoagulation were equivalent. Nevertheless, dabigatran and rivaroxaban were associated with fewer embolic events. There were no differences in all-cause death with the administration of VKAs, DOACs, or no anticoagulation.

CONCLUSIONS: For dialysis-dependent populations, dabigatran and rivaroxaban were associated with better efficacy, while dabigatran and apixaban demonstrated better safety. No anticoagulation was a noninferior alternative, and VKAs were associated with the worst outcomes.

Key Words: anticoagulation ■ atrial fibrillation ■ chronic kidney disease ■ dialysis ■ meta-analysis

Atrial fibrillation (AF) is a common comorbidity in patients with end-stage renal disease, with a reported prevalence of around 10%.¹ Shared risk factors for AF and chronic kidney disease (CKD) constitute a vicious cycle, and both can lead to a prothrombotic state.² Nevertheless, patients with coexisting AF and end-stage renal disease are associated with a remarkably elevated risk of major bleeding. Although

anticoagulation has been well established to improve the prognosis of individuals with AF, randomized controlled trials have predominantly excluded those under maintenance dialysis. Observational studies have also reported contradictory results regarding the administration of vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs), and no anticoagulation. Current evidence is thus inadequate to solidly endorse any

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CLINICAL PERSPECTIVE

What Is New?

- Dabigatran and rivaroxaban exhibited superior efficacy in preventing thromboembolism, while dabigatran and apixaban were associated with lower risk of bleeding.
- Opting for no anticoagulation also emerged as a valid noninferior choice.
- The use of vitamin K antagonists was consistently linked to the most unfavorable outcomes.

What Are the Clinical Implications?

- The strategy of anticoagulation should be individualized for patients undergoing dialysis.
- Future randomized trials are warranted to investigate the efficacy and safety of anticoagulation in the setting of advanced renal insufficiency.

Nonstandard Abbreviations and Acronyms

ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
AXADIA-AFNET 8	Compare Apixaban and Vitamin K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease
DOAC	direct oral anticoagulant
RENAL-AF	Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation
VKA	vitamin K antagonist

anticoagulants or whether to administer anticoagulants in this population.

VKAs have traditionally been used to prevent systemic embolism in patients with AF, but few studies have focused on patients undergoing dialysis. Such patients have an elevated risk of thromboembolism; however, a meta-analysis found that VKAs were associated with an insignificant protective effect on embolism, potentially due to limited longevity in patients with AF and CKD.³ In addition, VKAs also contribute to an increased risk of bleeding. Unstable renal function, drug–drug interactions, and dietary factors all affect the prothrombin time when patients are undergoing dialysis. Evidence supporting DOACs in patients on renal replacement therapy is also scarce. Only apixaban has

been approved for such patients in limited regions on the basis of a small-sized pharmacokinetic study involving 8 patients.⁴ Furthermore, it is challenging to estimate the bleeding risk in patients undergoing dialysis. An observational study suggested that the HAS-BLED score was useful only to predict bleeding rate at the catheter puncture site, and clinical parameters of the score, except for renal function impairment, failed to stratify the risk of systemic embolism.⁵

The aim of this network meta-analysis was therefore to elucidate the safety and efficacy of anticoagulants in patients with AF and end-stage renal disease undergoing dialysis. Different types of DOACs and 2 dosages of apixaban were compared with VKAs as well as no anticoagulation.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The protocol of this study has been registered in the International Prospective Register of Systematic Reviews (No. CRD42022380239). The analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses guidelines. Requirements for institutional review board approval were waived because the data set used in the present study had been previously published.

Data Sources, Search Strategies, and Outcomes

The network meta-analysis was based on the following inclusion criteria: (1) study group including individuals with both AF and end-stage renal disease undergoing dialysis; and (2) reported data of all-cause death or thromboembolism or major bleeding. Ischemic and hemorrhagic stroke were applied as thromboembolic and major bleeding events, respectively, if the information was otherwise unavailable in the study. MEDLINE, EMBASE, and the Cochrane Library were searched from inceptions to December 2022. The search keywords were “oral anticoagulant”, “warfarin”, “vitamin K antagonist”, “factor Xa inhibitor”, “rivaroxaban”, “edoxaban”, “apixaban”, “dabigatran”, “dialysis”, and “atrial fibrillation” as well as related keywords (Table S1). Outcomes of interest in the study were set as all-cause death, thromboembolism, and major bleeding events. No language restriction was imposed. The target population was set as adult only. Only published manuscripts were considered, whereas gray literature such as conference abstracts were not included. Two investigators (T.W.K. and

Z.W.C.) independently reviewed the titles and abstracts to determine eligibility of the manuscripts for inclusion. Confidence in Network Meta-Analysis was used to assess the quality of the included studies. Disputes on the selected studies at any stage were resolved by consensus from the author panel.

Data Extraction

Demographic and clinical parameters of the included studies were summarized (if available), including age, sex, CHA₂DS₂-VASc score, HAS-BLED score, prior stroke, prior bleeding, study type (ie, cohort and randomized trial), dialysis modality, DOAC type and dosing, concurrent use of antiplatelets, follow-up duration, and study period. In terms of effect sizes, adjusted risk estimates in conjunction with the corresponding 95% CI were extracted, including hazard ratio (HR), subdistribution HR, odds ratio, and the like. When several models with different numbers of covariate adjustments were performed, the most adjusted risk estimates in the multivariable model (eg, logistic regression Fine and Gray model, and Cox proportional hazard model) were chosen. The numbers of patients and outcomes were extracted when the risk estimates were not available in the study. The relative risk was calculated on the basis of data from the tables in the studies with unavailable adjusted risk estimates.

Categorization of Anticoagulants

First, the efficacy and safety of DOACs, VKAs, and no anticoagulation were compared. Second, DOACs were subgrouped into rivaroxaban, dabigatran, and apixaban to investigate their respective effect. Third, apixaban was stratified on the basis of 2 different dosages (2.5 and 5 mg twice daily).

Statistical Analysis

This frequentist-approach network meta-analysis was performed with R version 4.3.0 (R Project for Statistical Computing, Vienna, Austria) and the package “net-meta” version 2.8-2. In studies featuring multiarm groups (ie, 3 groups), each contributed 3 pairwise comparisons. However, only 2 of these pairwise comparisons (eg, rivaroxaban versus VKA and apixaban versus VKA) were presented, leaving the estimate of the third pairwise comparison (eg, rivaroxaban versus apixaban) dependent on the other 2. To address this, and appropriately adjust for correlations in risk estimates arising from studies with multiple arms, the correct standard errors were approximated by assuming they were proportional to the reciprocal of the square root of the patient number ($1/\sqrt{n}$).⁶ Network plots were generated to depict network geometry, and the width of connecting bars indicated the abundance of studies compared. Concerning the potential substantial heterogeneity among the included studies, a

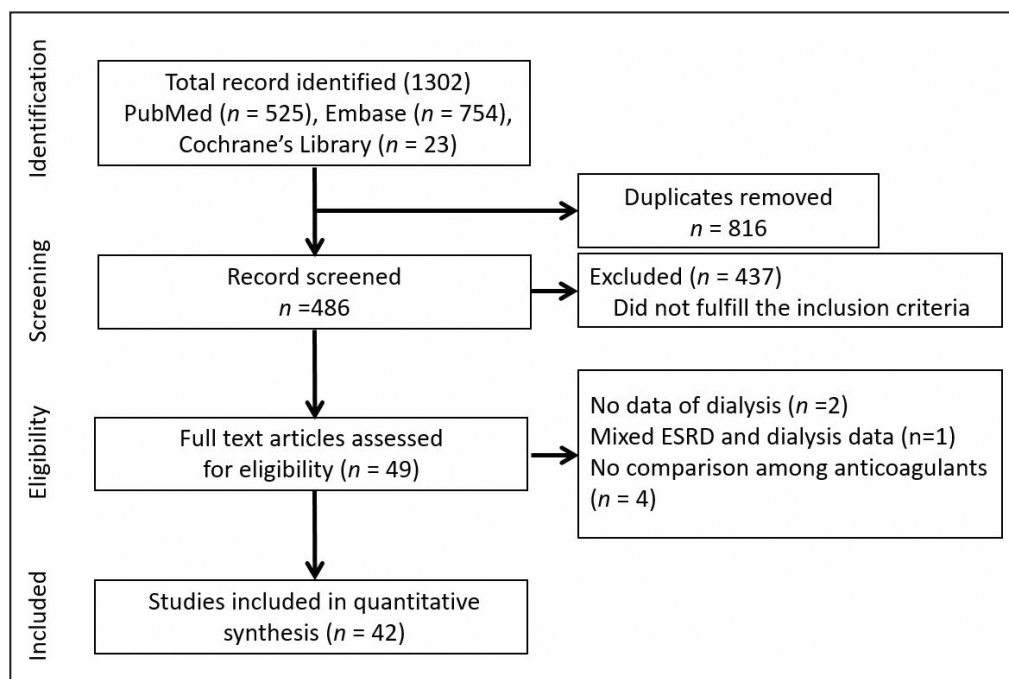


Figure 1. Literature search.

Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram illustrates the process for study inclusion. ESRD indicates end-stage renal disease.

Table 1. Demographic and Clinical Characteristics of Included Studies (Original Data Before Matching)

	Comparators	Patient number			Age		Male, %			Dialysis modality (%)
		VKA	DOAC	None	VKA	None	DOAC	VKA	None	
Chan, 2009 ⁸	VKA/none	508		480	72.6±0.4			58	54	HD
Lai, 2009 ⁹	VKA/none	51		42						HD
Winkelmayr, 2011 ¹⁰	VKA/none	249		2064	68.6±12.1			42.60%	42.50%	HD
Olesen, 2012 ¹¹	VKA/none	223		678						HD (77.9), PD (15.4)
Sood, 2013 ¹²	VKA/none	2513		23 177	65.3±13.9			55	57	HD
Bonde, 2014 ¹³	VKA/none									HD (72), PD (25.1)
Chen, 2014 ¹⁴	VKA/none	294		2983						
Shah, 2014 ¹⁵	VKA/none	756		870	75.3±8.1			61	61	HD + PD
Wakasugi, 2014 ¹⁶	VKA/none	28		32	67.8±9.4			57	72	HD
Chan, 2015 ¹⁷	VKA/D VKA/R	8064	281 244		70.6±11	68.4±12/66.9±12		61.20	59.2/60.5	HD
Genovesi, 2015 ¹⁸	VKA/none	1838		10 446	x	x		64.20	56.40	HD
Shen, 2015 ¹⁹	VKA/none	661		2438	61.2±12.4			49.70	48.70	HD
Brancaccio, 2016 ²⁰	VKA/none	119		183	71.42±9.67			60	57	HD
Garg, 2016 ²¹	VKA/none	365		692	75±7			55.40	51.30	HD
Hayashi, 2016 ²²	VKA/none	27		55	68.8±10.6			69.90	62.90	HD
Mitsuma, 2016 ²³	VKA/none				69.4±8.3			74	71	HD
Toida, 2016 ²⁴	VKA/none	59		82						HD
Wang, 2016 ²⁵	VKA/none	30		54	59.8±10.5			77	69	HD (68.8), PD (31.2)
Yodogawa, 2016 ²⁵	VKA/none	134		156	69.5±10.7			80	65	HD
Genovesi, 2017 ²⁶	VKA/none	989		3297	76			64.20	56.40	HD
Kai, 2017 ²⁷	VKA/none	590		5150	69.2±11.2			63.20		HD
Lee, 2017 ²⁸	VKA/none	27		94	68.8±10.6			42.20	45.30	HD
Lin, 2017 ²⁹	VKA/none	1838		10 446						NA
Sarratt, 2017 ³⁰	A 2.5/VKA A 5/VKA	120	40		66.5	70.9		48.30	50	HD
Yoon, 2017 ³¹	VKA/none	2921		7053	67.8±11			59.90	57.50	HD
Reed, 2018 ³²	A 2.5/VKA A 5/VKA	50	74		62±14.4	59.5±14.7		62	51.40	HD (99.2), PD (0.8)
Siontis, 2018 ³³	A 2.5/VKA A 5/VKA	23 172	2351		68.9±11.5	68.2±11.9		54.30	54.40	HD (94.6), PD (5.4)
Voskamp, 2018 ³⁴	VKA/none	244		1474	67.6			59.80	61.60	HD (64.4), PD (35.6)
Phan, 2019 ³⁵	VKA/none	115		361	67.3±10.8			58.30	57.60	PD
Tan, 2019 ³⁶	VKA/none	1651		4114	73.9			43.60	43	HD (96.7), PD (3.3)

(Continued)

Table 1. Continued

	Comparators	Patient number			Age			Male, %			Dialysis modality (%)		
		VKA	DOAC	None	VKA	DOAC	None	VKA	DOAC	None			
Agarwal, 2020 ³⁷	VKA/none	6682		16089	71.4±8.7		74.3±8.7	96.10		95.20	NA		
Mavrakanas, 2020 ³⁸	A 5/none A 2.5/none		521	10976		68±11	67±13		54	54	HD (89.4), PD (10.6)		
De Vriese, 2021 ³⁹	R/VKA	44	46		80.3	79.9		56.80	76.10		HD		
Ionescu, 2021 ⁴⁰	A 2.5/VKA A 5/VKA	563	144		67.2±13.5	68.8±16		59.10	56.30		HD		
See, 2021 ⁴¹	DOACs/VKA	448	448		75.2±10.9	74.3±10.9		47.50%	49.60				
Kang, 2021 ⁴²	VKA/none	177		547									
Kim, 2021 ⁴³	VKA/none A 2.5/none	27		62									
Pokorney, 2022 ⁴⁴	A/VKA	72	82		68	69		69.40	58.50		HD		
Reinecke, 2022 ⁴⁵	A 2.5/VKA	48	49		74.8±7.9	74.7±8.1		75.50	64.60		HD		
Sy, 2022 ⁴⁶	VKA/none	3458		20670	75±9		78±9	96		95	HD		
Weitmore, 2022 ⁴⁷	A 2.5/VKA A 5/VKA	12 517	4639		NA			62.5	61.40		HD		
Akbar, 2023 ⁴⁸	VKA/none	44		44	51.2±14.08		53.2±11.83	25	11.83	27.27	HD (92.3), PD (7.7)		
		Prior bleeding, %			Prior stroke, %			CHA ₂ DS ₂ -VASc, %			Concomitant antiplatelet therapy, %		
		VKA	DOAC	None	VKA	DOAC	None	VKA	DOAC	None	VKA	DOAC	None
Chan, 2009 ⁸							1						
Lai, 2009 ⁹													
Winkelmayer, 2011 ¹⁰	6.8			16.9			23.6						
Olesen, 2012 ¹¹													
Sood, 2013 ¹²	6.7			6.5			11.8				23		0
Bonde, 2014 ¹³													
Chen, 2014 ¹⁴													
Shah, 2014 ¹⁵	9			16			5				26		35
Wakasugi, 2014 ¹⁶							26				61		47
Chan, 2015 ¹⁷	5.3	6.9 8.5				11.2 14.6					5.6 3.4		3.1
Genovesi, 2015 ¹⁸	11.9			26.3			14.1				20.2		71.8
Shen, 2015 ¹⁹	2.2			6			26.8				21.5		23
Brancaccio, 2016 ²⁰							16				27		32
Garg, 2016 ²¹							23				91.5		86.4

(Continued)

Table 1. Continued

	Prior bleeding, %			Prior stroke, %			CHA ₂ DS ₂ -VASc, %			Concomitant antiplatelet therapy, %		
	VKA	DOAC	None	VKA	DOAC	None	VKA	DOAC	None	VKA	DOAC	None
Hayashi, 2016 ²²										49		41.3
Mitsuma, 2016 ²³	33		29			22				48		31
Toida, 2016 ²⁴												
Wang, 2016 ⁵	10		17			15.9	3.9±1.7		3.7±1.6	3.40		2.4
Yodogawa, 2016 ²⁵	3		7			2				40		54
Genovesi, 2017 ²⁶	11.9		26.3			14.1				23.90		68.6
Kai, 2017 ²⁷	30.1		32.8			25.2	5.2±1.7		5±1.8	39.60		45.2
Lee, 2017 ²⁸	5.4		7.6			5.8				89.70		78
Lin, 2017 ²⁹												
Sarratt, 2017 ³⁰	13.3	15			15		5	5		44.20	37.5	
Yoon, 2017 ³¹										70.20		86.6
Reed, 2018 ³²					5.40		4±1.4	4.1±1.2		36	28.4	
Slonitis, 2018 ³³	9.2	9.9			33.20		5.27±1.77	5.24±1.79		6.60	7.3	
Voskamp, 2018 ³⁴										9.80		25.7
Phan, 2019 ³⁵	23.50		24.4			21.1	4.6±1.6		4.2±1.8	40		50.7
Tan, 2019 ³⁶	22.5		32.5			22.6				25.90		25.1
Agarwal, 2020 ³⁷	23.9		38.4			43.7	5.1±2.1		6±2	11.40		5.6
Mavrakanas, 2020 ³⁸		49	58		34	4					23	25
De Vriese, 2021 ³⁹	27.3	19.6			32.60		4.8±1.5	4.7±1.4		31.8	32.6	
Ionescu, 2021 ⁴⁰	23.8	20.8			27.10					50.8	5	
See, 2021 ⁴¹	3.4	3.6			19.60		4.7±1.9	4.5±1.9				
Kang, 2021 ⁴²												
Kim, 2021 ⁴³												
Pokorney, 2022 ⁴⁴	2.8	9.8			20.70		4	4	NA	47.1	39.3	
Reinecke, 2022 ⁴⁵							4.54±1.49	4.5±1.62		34.7	33.3	
Sy, 2022 ⁴⁶	37		38			66	6		7			
Wetmore, 2022 ⁴⁷					19.40		4.5±1.7	4.3±1.7		16.8	17.1	
Akbar, 2023 ⁴⁸						1.14				23.86		6.81

A indicates apixaban; D, dabigatran; DOAC, direct oral anticoagulant; HD, hemodialysis; NA, not applicable; PD, peritoneal dialysis; R, rivaroxaban; and VKA, vitamin K antagonist.

Table 2. Outcomes of the Included Studies

	Comparators	Major bleeding				Thromboembolism				All-cause death			
		VKA	DOAC	None	RR (95% CI)	VKA	DOAC	None	RR (95% CI)	VKA	DOAC	None	RR (95% CI)
Chan, 2009 ⁸	VKA/none	NA							1.74 (1.11–2.72)	333		425	1.1 (0.93–1.30)
Lai, 2009 ⁹	VKA/none	NA				5		16		NA			
Winkelmayr, 2011 ¹⁰	VKA/none	11		21	2.38 (1.15–4.96)	135		29	0.92 (0.61–1.37)	181		750	1.06 (0.90–1.24)
Olesen, 2012 ¹¹	VKA/none				1.27 (0.91–1.77)				0.44 (0.26–0.74)	NA			
Sood, 2013 ¹²	VKA/none				1.30 (1.11–1.52)				1.1 (0.9–1.4)				1.16 (1.07–1.26)
Bonde, 2014 ¹³	VKA/none	NA							2.01 (1.74–2.33)				0.85 (0.72–0.99)
Chen, 2014 ¹⁴	VKA/none	NA							1.017 (0.673–1.537)	NA			
Shah, 2014 ¹⁵	VKA/none	149		126	1.41 (1.09–1.81)	52		55	1.17 (0.79–1.75)	NA			
Wakasugi, 2014 ¹⁶	VKA/none	3		4	0.85 (0.19–3.64)	8		5	1.94 (0.63–5.93)	9		9	1.00 (0.40–2.52)
Chan, 2015 ¹⁷	VKA/D VKA/R				1.48 (1.21–1.81) 1.38 (1.03–1.83)				1.71 (0.97–2.99) 1.80 (0.89–3.64)	NA NA			
Genovesi, 2015 ¹⁸	VKA/none				3.96 (1.15–13.68)				0.12 (0.00–3.59)	NA			
Shen, 2015 ¹⁹	VKA/none	29		192	0.82 (0.37–1.81)	63		503	0.68 (0.47–0.99)	832		4595	1.01 (0.92–1.11)
Branaccio, 2016 ²⁰	VKA/none	NA				NA				661		2438	0.76
Garg, 2016 ²¹	VKA/none	26		26	1.53 (0.94–2.51)	13		21	0.93 (0.48–1.82)	97		145	1.03 (0.91–1.15)
Hayashi, 2016 ²²	VKA/none	60		54	2.53 (0.66–3.90)	23		43	0.64 (0.32–1.28)	86		120	1.08 (0.75–1.57)
Mitsuma, 2016 ²³	VKA/none	7		9		3		5		8		27	
Toida, 2016 ²⁴	VKA/none	3		6		5		13		NA			
Wang, 2016 ²⁵	VKA/none	22		24		8		11		44		64	
Yodogawa, 2016 ²⁵	VKA/none	3		1		2		5	1.07 (0.20–5.74)	6		15	
Genovesi, 2017 ²⁶	VKA/none				1.16 (0.48–2.82)				0.44 (0.16–1.20)				0.91 (0.56–1.48)
Kai, 2017 ²⁷	VKA/none	20		12	0.8 (0.2–2.9)	58		88	0.67 (0.45–0.99)	433		496	0.78 (0.67–0.89)
Lee, 2017 ²⁸	VKA/none	8		37	0.84 (0.32–2.19)	48		151	0.92 (0.57–1.48)	350		1051	1.04 (0.88–1.23)
Lin, 2017 ²⁹	VKA/none				3.69 (0.93–14.67)	NA							6.62 (2.56–17.16)
Sarratt, 2017 ³⁰	A 2.5/VKA A 5/VKA	7 7	0 0			NA NA				NA NA			
Yoon, 2017 ³¹	VKA/none	84		50	1.56 (1.10–2.22)	204		201	0.95 (0.78–1.15)	NA			
Reed, 2018 ³²	A 2.5/VKA A 5/VKA	11 11	0 4		0.15 (0.05–0.46)	NA NA				NA NA			
Siontis, 2018 ³³	A 2.5/VKA A 5/VKA	1034 1317	54 75		0.71 (0.53–0.95) 0.71 (0.56–0.91)	160 213	26 55		0.64 (0.42–0.97) 1.11 (0.82–1.50)	310 421	48 111		0.63 (0.46–0.85) 1.07 (0.87–1.33)
Voskamp, 2018 ³⁴	VKA/none	NA				NA				141		540	1.2 (1.0–1.5)
Phan, 2019 ³⁵	VKA/none	2		3	2.00 (0.32–12.8)	10		11	2.3 (0.9–5.4)	32		98	0.80 (0.53–1.20)
Tan, 2019 ³⁶	VKA/none	407		1559	1.63 (1.45–1.83)	93		644	0.93 (0.74–1.16)	476		3349	0.72 (0.65–0.80)

(Continued)

Table 2. Continued

	Comparators	Major bleeding			Thromboembolism			All-cause death					
		VKA	DOAC	None	RR (95% CI)	VKA	DOAC	None	RR (95% CI)	VKA	DOAC	None	RR (95% CI)
Agarwal, 2020 ³⁷	VKA/none				1.34 (1.25–1.43)				1.23 (1.15–1.32)				0.93 (0.89–0.98)
Mavranakas, 2020 ³⁸	A 5/none				4.61 (1.91–11.15)				2.24 (1.03–4.86)	NA			
	A 2.5/none				2.02 (0.58–7.04)				1.11 (0.43–2.85)	NA			
De Vriese, 2021 ³⁹	R/VKA	24	43			0	0			32	57		
Ionescu, 2021 ⁴⁰	A 2.5/VKA	9	0			37	7			NA			
	A 5/VKA	9	0			37	0			NA			
See, 2021 ⁴¹	DOACs/VKA				0.98 (0.64–1.51)				1.21 (0.76–1.92)	NA			
Kang, 2021 ⁴²	VKA/none				1.59 (1.08–2.36)				0.986 (0.716–1.356)				1.151 (0.908–1.459)
Kim, 2021 ⁴³	VKA/none				4.85 (1.12–21.1)				NA				0.26 (0.09–0.81)
	A 2.5/none				5.35 (0.73–39.35)				1.76 (0.17–18.03)				0.71 (0.20–2.57)
Pokorney, 2022 ⁴⁴	A/VKA	7	9			2	1			13	21		
Reinecke, 2022 ⁴⁵	A 2.5/VKA	6	5			1	0			12	9		
Sy, 2022 ⁴⁶	VKA/none				1.38 (1.25–1.52)				1.44 (1.23–1.69)	NA			
Weitmore, 2022 ⁴⁷	A 2.5/VKA	1226	117		0.68 (0.55–0.84)	421	54		0.85 (0.62–1.17)		741	6096	0.97 (0.98–1.05)
	A 5/VKA	1226	127		0.67 (0.55–0.81)	421	52		0.89 (0.65–1.21)		716	6096	0.85 (0.78–0.92)
Akbar, 2023 ⁴⁸	VKA/none	3		3	0.564 (0.034–9.386)	30		16	0.435 (0.103–1.846)	36		40	0.782 (0.494–1.237)

A indicates apixaban; D, dabigatran; DOAC, direct oral anticoagulant; NA, not applicable; R, rivaroxaban; RR, relative risk; and VKA, vitamin K antagonist.

random-effects model was applied. The variance of the combined effect sizes was characterized using the τ statistic, which signifies the SD of the true effect sizes. A 2-sided P value <0.05 was considered to be statistically significant.

Quality of Evidence and Risk of Bias

Confidence in Network Meta-Analysis was used to assess the quality of evidence for outcomes including the following 6 domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence.⁷ Revised Cochrane Risk of Bias tool and Risk of Bias in Nonrandomized Studies of Interventions were used to evaluate the risk of bias for randomized controlled trials and cohort studies, respectively. Full-text screening for eligibility assessment and the risk-of-bias assessment were conducted independently.

RESULTS

Search Results

The initial search identified a total of 1302 studies, of which 816 were removed due to duplication. Among the preliminarily screened articles, 437 were excluded due to irrelevant titles or abstracts. Full texts of the remaining manuscripts were reviewed, and 7 articles were removed due to contradicting inclusion criteria. Eventually, 42 articles were selected for network

meta-analysis (Figure 1).^{5,8-48} Of them, 8 studies consisted of 3 treatment groups.^{17,30,32,33,38,40,43,47} Risk of bias was evaluated (Table S2).

Study and Cohort Characteristics

A total of 185 864 subjects were analyzed from the 42 included studies. After excluding 1728 participants from 1 study reported with ratio only, 184 136 individuals from 41 studies were specified with coagulation strategies. Among these patients, 8861 (4.81%) patients received DOACs, 70047 (38.04%) patients received VKAs, and 105228 (57.15%) patients were not anticoagulated. Apixaban, rivaroxaban, and dabigatran were used as the DOACs in 8, 2, and 1 study, respectively, whereas 1 study did not specify the type of DOAC. Three studies were randomized controlled trials,^{39,44,45} and the others were observational studies. The modality of renal replacement therapy was predominantly hemodialysis. Concomitant antiplatelet therapy was common. Detailed demographic and clinical parameters are summarized in Table 1.

VKAs, DOACs, and No Anticoagulation

The outcomes were assessed among patients who received VKAs, DOACs, or no anticoagulation (Table 2; Figure 2). Compared with no anticoagulation, the use of VKAs (pooled relative risk, 1.47 [95% CI, 1.34–1.61]) but not DOACs (HR, 1.08 [95% CI, 0.92–1.27]) was

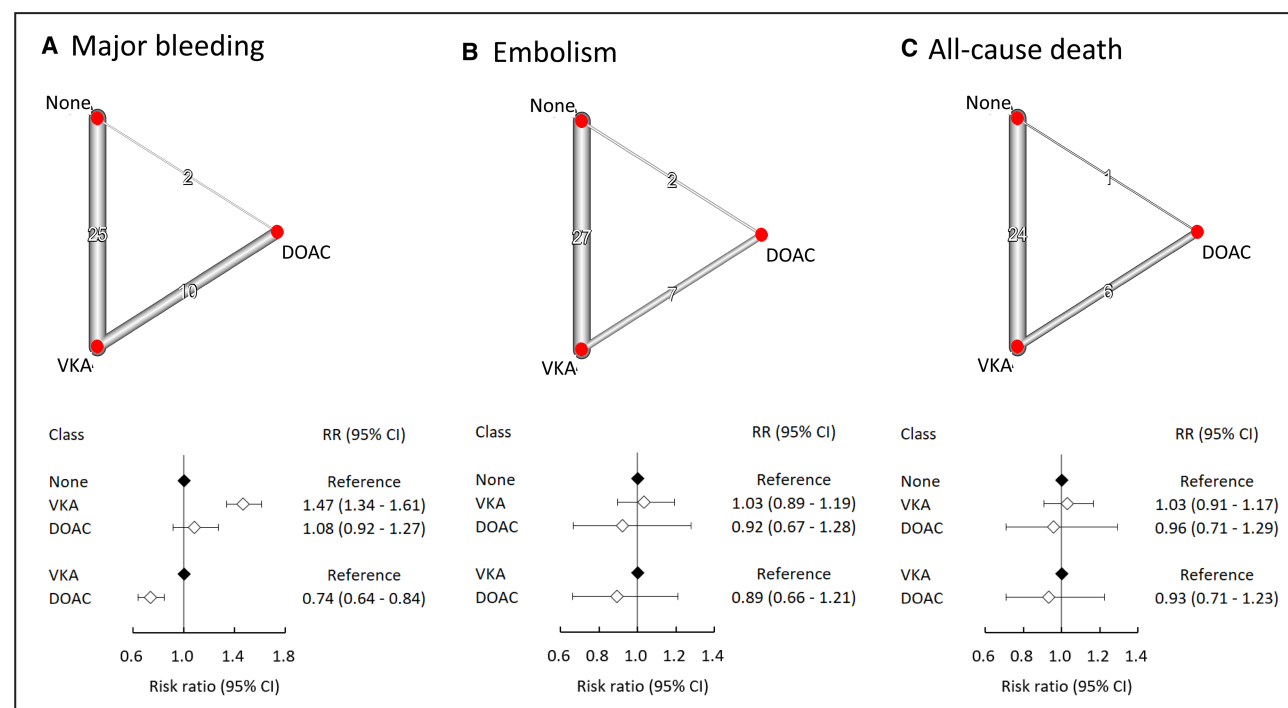


Figure 2. Summaries of the network meta-analysis for the efficacy and safety assessment among patients receiving no anticoagulants, VKAs, and DOACs on the risk of (A) major bleeding, (B) thromboembolism, and (C) all-cause death.

Left: network diagram; middle: forest plot. DOAC indicates direct oral anticoagulant; RR, relative risk; and VKA, vitamin K antagonist.

associated with a remarkably elevated rate of major bleeding. In addition, the use of DOACs was associated with a significantly lower risk of bleeding compared with VKAs (HR, 0.74 [95% CI, 0.64–0.84]). There were no pronounced differences in embolism between VKAs (HR, 1.03 [95% CI, 0.89–1.19]) or DOACs (HR, 0.92 [95% CI, 0.67–1.28]) and no anticoagulation. VKAs (HR, 1.03 [95% CI, 0.91–1.17]), DOACs (HR, 0.96 [95% CI, 0.71–1.29]), and no anticoagulation demonstrated equivalent rates of all-cause death. The values of τ statistics were 0.112, 0.275, and 0.266 for bleeding, embolism, and all-cause death, respectively (data not shown in Figure 2).

Different DOACs

DOACs were stratified according to the different types for further comparisons (Figure 3). Compared with VKAs, the use of dabigatran (HR, 0.70 [95% CI, 0.53–0.93]), apixaban (HR, 0.72 [95% CI, 0.61–0.86]) and rivaroxaban (HR, 0.80 [95% CI, 0.61–1.04]) were associated with a lower risk of bleeding, though statistical significance was achieved only with the former 2. In addition, dabigatran and rivaroxaban were associated with a lower risk of embolism, albeit not statistically significant, compared with either no anticoagulation or VKAs. Nevertheless, the risk of all-cause death remained comparable between any 2 groups. The values of τ statistics were 0.109, 0.275,

and 0.270 for bleeding, embolism, and all-cause death, respectively (data not shown in Figure 3).

Different Dosages of Apixaban

Apixaban was further subgrouped into 2.5 and 5 mg twice daily according to respective study protocols (Figure 4). A minimal difference was found between either dosage of apixaban regarding bleeding rate. However, apixaban 5 mg twice daily was correlated with numerically better preventive effect against thromboembolism (HR, 0.87 [95% CI, 0.55–1.38]) and all-cause death (HR, 0.77 [95% CI, 0.51–1.15]) compared with apixaban 2.5 mg twice daily, although the difference was not statistically significant. The values of τ statistics were 0.099, 0.282, and 0.272 for bleeding, embolism, and all-cause death, respectively (data not shown in Figure 4).

Net Clinical Benefit

To further clarify the safety and efficacy profiles of different anticoagulants, all comparators were classified into quadrants to illustrate the risk estimates of bleeding and embolism (Figure 5). VKAs were associated with elevated rates of bleeding and embolism. Dabigatran and rivaroxaban were associated with more bleeding but fewer embolism events. Apixaban of either dosage was associated with suboptimal outcomes in bleeding

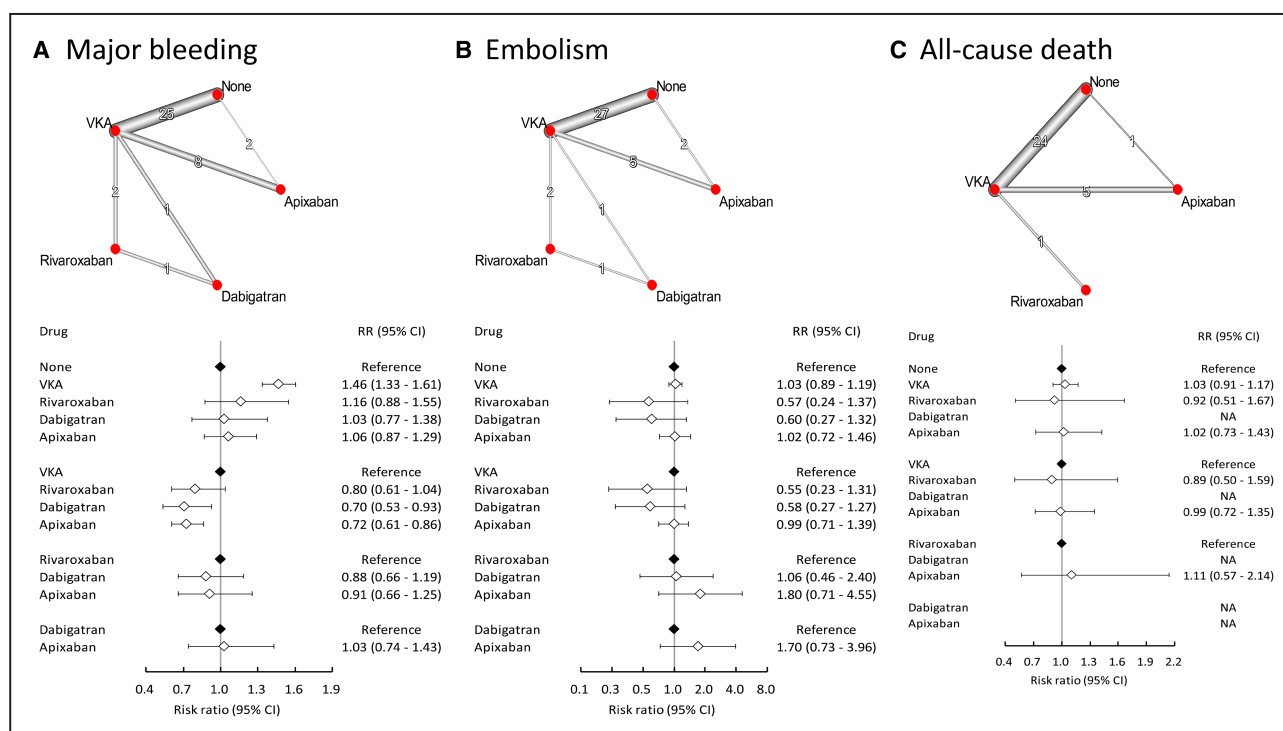


Figure 3. Summaries of the network meta-analysis for the efficacy and safety assessment among patients receiving different DOACs on the risk of (A) major bleeding, (B) thromboembolism, and (C) all-cause death.

Left: network diagram; middle: forest plot. CI indicates confidence interval; RR, relative risk; and VKA, vitamin K antagonist.

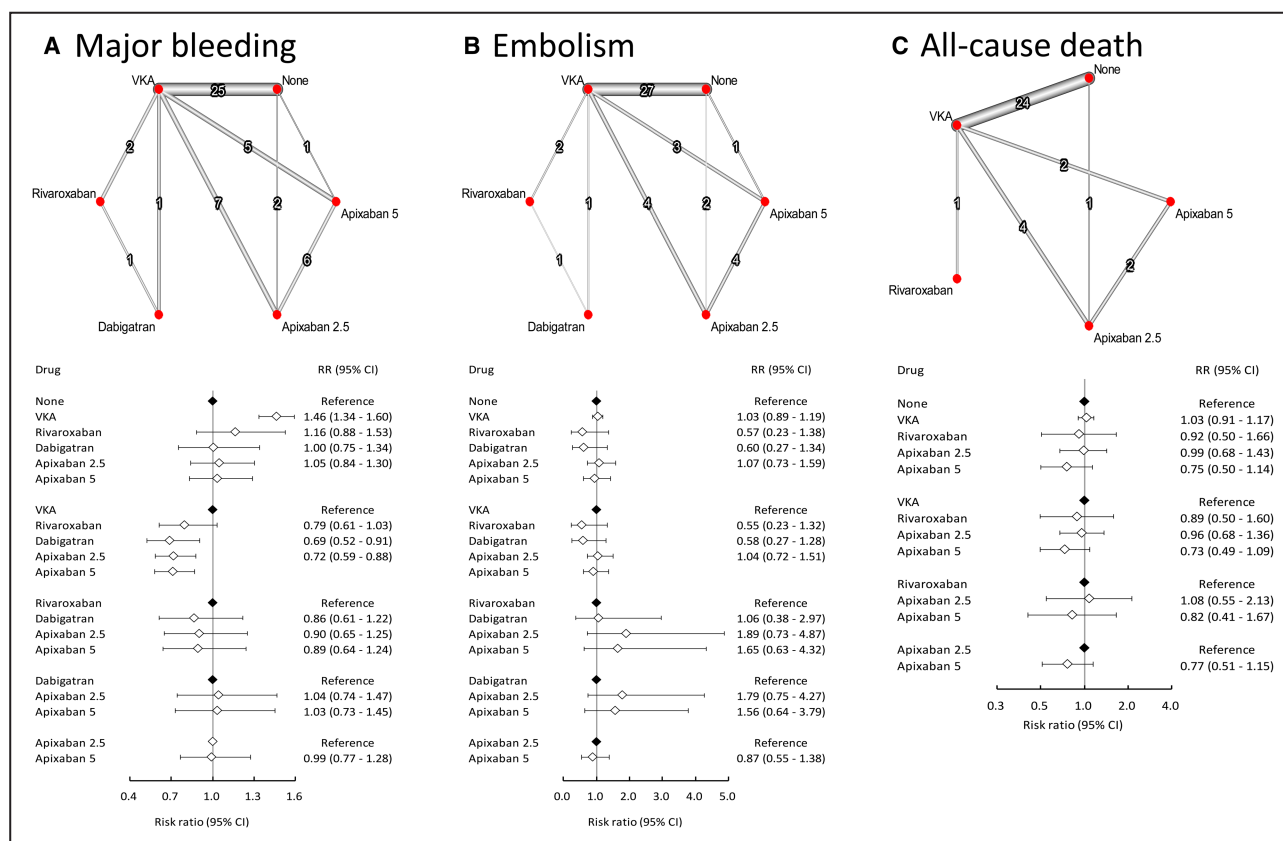


Figure 4. Summaries of the network meta-analysis for the efficacy and safety assessment among patients receiving a different dose of apixaban on the risk of (A) major bleeding, (B) thromboembolism, and (C) all-cause death.

Left: network diagram; middle: forest plot. RR indicates relative risk; and VKA, vitamin K antagonist.

and embolism, whereas apixaban 5 mg daily was associated with a better effect in preventing embolism. With only 1 study included concerning dabigatran,¹⁷ the efficacies and safety profiles were reevaluated following its exclusion. Despite this removal, comparable outcomes were maintained (Figures S1 through S3).

DISCUSSION

To our knowledge, this is the most updated network meta-analysis to evaluate the efficacy and safety of anticoagulation in patients with AF receiving renal replacement therapy. The major findings of this study are (1) VKA was associated with the least net clinical benefit compared with DOACs or no anticoagulation, (2) apixaban 5 mg twice daily was associated with the lowest risk of all-cause death, (3) dabigatran and rivaroxaban demonstrated the greatest efficacy in preventing thromboembolism, and (4) dabigatran and apixaban were associated with better safety.

Although CKD is associated with an elevated risk of thromboembolism,⁴⁹ the use of anticoagulation in individuals with AF and end-stage renal disease undergoing dialysis has long been under debate.

Studies comparing warfarin, DOACs, and no anticoagulation have reported discordant results in such patients. VKAs have been traditionally administered to individuals with long-term dialysis to prevent thromboembolism secondary to AF. A retrospective study suggested that VKAs could mitigate all-cause death and ischemic stroke²⁷; however, characterization of the potential confounding factors was not feasible due to the nonrandomized nature of the study. In addition, dose adjustment, albeit tailored by prothrombin time, remains clinically challenging due to the concomitant use of heparin during dialysis and altered metabolism caused by frequent uremia.⁵⁰ In a pooled analysis of 14 observational studies, VKAs were shown to be associated with an increased rate of bleeding and no significant improvement in the risk of thromboembolism in patients undergoing long-term dialysis.⁵¹ Suboptimal compliance with VKA therapy in such patients is another major concern.¹⁹ In the present study, we comprehensively included all studies comparing VKAs with either no anticoagulation or DOACs and confirmed a higher bleeding rate as well as no significant mitigation in thromboembolism with VKA therapy.

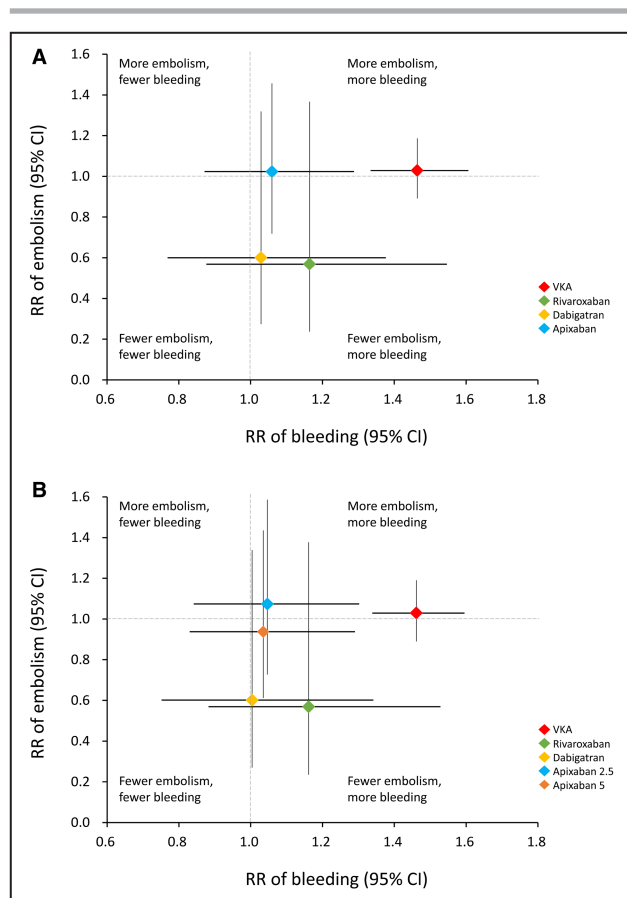


Figure 5. Net clinical benefit of different anticoagulants that combined (A) and separated (B) different doses of apixaban.

RR indicates relative risk; and VKA, vitamin K antagonist.

DOACs have emerged as an alternative in patients with CKD, but the extended application under renal replacement therapy remains questionable. To date, 3 randomized trials have assessed the use of VKAs and DOACs in subjects undergoing long-term dialysis. The RENAL-AF (Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation) study did not identify any superiority between apixaban and warfarin regarding bleeding events in patients undergoing dialysis.⁴⁴ However, the sample size in the study was relatively small. The AXADIA-AFNET 8 (Compare Apixaban and Vitamin K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease) study reported that the efficacy of DOACs was equivalent to that of warfarin, yet both groups presented with high cardiovascular risk.⁴⁵ The Valkyrie study demonstrated that VKAs were associated with higher risks of major bleeding and cardiovascular events compared with low-dose rivaroxaban.³⁸ However, the time in therapeutic range of the individuals was suboptimal in these studies and may have compromised interpretation of the results.

To date, only the cautious use of apixaban 5mg twice daily has been approved by the Food and

Drug Administration for patients undergoing dialysis. However, the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial and most cohort studies have excluded patients undergoing dialysis, and thus the evidence remains weak. In a previous meta-analysis by Kuno et al,⁵² apixaban 5mg twice daily was surprisingly shown to reduce death compared with warfarin or no anticoagulation. In addition, apixaban 2.5 or 5mg twice daily was further proposed to be associated with less bleeding but equivalent efficacy in preventing thromboembolism than warfarin. However, only 1 study on the use of apixaban was included in that study, whereas our study included 6 studies with apixaban. In our analysis, apixaban 5mg twice daily was associated with a more preferred net clinical benefit. We also studied the combined effect of apixaban with either a usual dose or a low dose. Consistent with the previous study, apixaban was demonstrated to be better than warfarin regarding safety among patients with advanced CKD.⁵³ We further found that apixaban was comparable with no anticoagulation regarding safety and efficacy. Our pooled analysis added a randomized controlled trial involving rivaroxaban and 7 studies with apixaban. However, the resultant major bleeding rate was greater only in the patients who received rivaroxaban, whereas the risk in the patients who received dabigatran was comparable to those who received apixaban of either dose.

We recognized a previous network meta-analysis, which preliminarily assessed the applicability of DOACs in patients undergoing dialysis.⁵² In that study, DOACs failed to demonstrate efficacy in preventing thromboembolism, while dabigatran and rivaroxaban, in conjunction with VKAs, potentiated the risk of bleeding. The AXADIA-AFNET 8 trial⁴⁵ and 9 other cohort studies were published subsequently and were incorporated into our study. Additionally, we included all literature reporting outcomes of anticoagulation in patients undergoing dialysis, including subgroup analyses, to enhance the statistical power. This updated meta-analysis offers valuable evidence to assist in selecting anticoagulants, particularly in the context of long-term dialysis.

In our analysis, we also classified the respective anticoagulants into quadrants to illustrate their net clinical benefits. Neither DOACs nor VKAs were associated with fewer bleeding or embolism events, and consequently the need to administer anticoagulants in patients undergoing long-term dialysis remains equivocal. Moreover, AF has not been well established as an independent risk factor for stroke in this population.⁵⁴ We thus propose that not using anticoagulants is also a reasonable strategy in patients with end-stage renal disease undergoing dialysis.

Future studies should aim to identify which clinical parameters can be used to tailor anticoagulant

use in such patients individually. Among the enrolled studies in our analysis, 5 applied the CHA₂DS₂-VASC score and 2 the HAS-BLED score to stratify the patients undergoing anticoagulant therapy. In the few studies evaluating warfarin use, prothrombin time was used to assess the safety and efficacy of VKAs. However, the other enrolled studies reported discordant characteristics to evaluate the risk of bleeding and thromboembolism. In addition, none of the included randomized trials further subgrouped patients with either parameter. Therefore, we could not identify clinical characteristics to guide anticoagulant use in such patients. Future prospective studies are warranted to determine the specific conditions for administering anticoagulants.

Our study has several limitations. First, anticoagulation in dialysis has been studied mostly in observational studies that retrospectively assessed different drugs without appropriate dose adjustment and using administrative codes or billing data, resulting in noise. The enrolled studies are hence predominantly observational in nature, which could potentially confound the interpretation of the associations. In addition, the sample size in each study was relatively small, which may have limited the significance of the effect of anticoagulation therapy. The findings were based on low-quality evidence. Second, studies regarding DOACs other than apixaban were very limited. No study specifically regarding edoxaban was included in the present network meta-analysis, and we therefore could not investigate its effect. The only study including dabigatran was administered using an ultra-low dose.¹⁷ Even though a pharmacodynamic study validated the bioavailability of DOACs under dialysis,⁵⁵ discrepancy in the protocol regarding dose adjustment for patients undergoing renal replacement therapy may have limited generalization of the results. Third, the patient-level data of each included study were unavailable. Analysis with prestratification according to different clinical parameters was therefore not possible. Fourth, concomitant antiplatelet therapy, as often required by the common presence of comorbidities in such patients, may have masked the effect of anticoagulants. Interpretation of the results should hence be prudent. Finally, our analysis yielded only 1 study that reported outcomes related to dabigatran, showing unexpectedly promising efficacy and safety despite its predominantly renal excretion. Given the significance of this finding, we opted to retain it. Moreover, similar pooled outcomes were observed even when the sole study on dabigatran was excluded. Further research is essential to validate the efficacy and optimal dosage of dabigatran in patients undergoing long-term dialysis.

In conclusion, the findings of this study updated the latest evidence for the use of anticoagulants in patients with end-stage renal disease undergoing dialysis.

Among DOACs, dabigatran and rivaroxaban were associated with a lower risk of thromboembolism, whereas fewer bleeding events were demonstrated in the patients receiving apixaban. VKAs were associated with worse safety and efficacy. There was no significant difference in the prognosis in the patients who did not receive anticoagulants compared with those who received either DOACs or VKAs. The anticoagulation strategy should therefore be tailored individually.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S2

Figures S1–S3

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