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ORIGINAL ARTICLE

Meta-analysis evaluating apixaban in patients with atrial fibrillation and end-stage renal disease requiring dialysis

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Abstract

Background: Warfarin is considered the primary oral anticoagulant for patients with atrial fibrillation and end-stage renal disease (ESRD) requiring dialysis. Although warfarin can offer significant stroke prevention in this population, the accompanying major bleeding risks make warfarin nearly prohibitive. Apixaban was shown to be superior to warfarin in preventing stroke or systemic embolism, with a lower risk of bleeding and mortality in a large, randomized trial of individuals with mostly normal renal function but none with ESRD.

Methods: We systematically reviewed evidence comparing apixaban versus warfarin for atrial fibrillation in this population, and evaluated outcomes of stroke or systemic embolism, and major bleeding using random-effects models. The main safety outcome was major bleeding, and the main effectiveness outcome was stroke or systemic embolism.

Results: We found five observational studies of 10036 patients (2638 receiving apixaban, and 7398 receiving warfarin) meeting inclusion criteria. Pooled analysis demonstrated a significant reduction in major bleeding with apixaban as compared to warfarin (odds ratio [OR] 0.51, 95% confidence interval [CI] 0.42–0.61; $p < .0001$). Apixaban was also associated with a reduction in intracranial bleeding (OR 0.58, 95% CI 0.37–0.92; $p = .02$) and in gastrointestinal bleeding (OR 0.61, 95% CI 0.51–0.73; $p < .0001$). Furthermore, apixaban was associated with a reduction in stroke/systemic embolism (OR 0.64, 95% CI 0.50–0.82; $p < .0001$).

Conclusion: Apixaban was associated with superior outcomes and reduced adverse events compared to warfarin in observational studies of patients with atrial fibrillation on dialysis. Randomized controlled studies are needed to confirm these findings.

KEYWORDS
anticoagulation, apixaban, atrial fibrillation, dialysis, warfarin

Vidal Essebag and Thao Huynh are co-senior authors.

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1 | INTRODUCTION

Patients with atrial fibrillation (AF) and end-stage renal disease (ESRD) requiring dialysis are at increased risk of systemic thromboembolism.[1] Paradoxically, they are also at risk of increased bleeding as a result of platelet and endothelial dysfunction because of uremia[2,3] and dietary deficiency of vitamin K.[4] Warfarin was associated with increased major bleeding in patients with ESRD.[2,3,5] However, data on stroke prevention in dialyzed patients are conflicting. Warfarin was associated with a stroke reduction in one observational study of AF patients with ESRD[1] while other investigators found no benefit or a paradoxical increase in stroke risk.[6,7] In a network meta-analysis of observational studies, Kuno et al. showed no benefit of warfarin in stroke prevention in these patients with a significantly higher risk of bleeding.[8]

Because of the contradictory results regarding the risks and benefits of oral anticoagulants (OAC) in ESRD patients, guidelines differ widely in their recommendations for these patients. Although the American Heart Association/American College of Cardiology guidelines[9] suggest anticoagulating these patients with warfarin, both the Kidney Disease: Improving Global Outcomes Controversies Conference[10] and the Canadian Cardiovascular Society guidelines[11] do not recommend routine OAC. Therefore, the optimal anticoagulation strategy in dialysis patients remains unclear. Of all the direct-acting oral anticoagulants, apixaban is least dependent on renal excretion and is approved to be used in dialysis patients by the Food and Drug Agency of the United States. However, this approval was based on only one pharmacokinetic study[12] and there remains limited data concerning the safety, efficacy, and effectiveness of apixaban in dialyzed patients with AF. We synthesized the published evidence to date comparing the safety, efficacy, and effectiveness of apixaban to warfarin in patients with atrial fibrillation and ESRD requiring dialysis.

2 | METHODS

This meta-analysis was performed in accordance with the standards set forth by the PRISMA statement. We searched Medline, Embase, BIOSIS, CINAHL, Web of Science, Scopus, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials from their dates of establishment until September 18, 2021. Our search strategy included terms for atrial fibrillation, anticoagulation, end-stage renal disease, and dialysis. No language restrictions were applied. We also hand searched references of retrieved publications, review articles, and guidelines to ensure that all relevant studies were included.

The first screening of titles and abstracts was performed independently by two authors (A.A.T. and A.D.) to identify potentially relevant articles. We excluded abstracts, review articles, case reports, and duplicates. Two authors (A.A.T. and A.D.) independently assessed the full text of selected articles to determine relevant articles for inclusion. Conflicts were resolved by consensus, and any discrepancy was resolved by discussion with a third author (M.M.).

We determined eligibility criteria for inclusion of studies a priori. We included randomized controlled trials (RCTs) and prospective or retrospective cohort studies that fulfilled the two following criteria: (1) Evaluated patients with ESRD who were receiving maintenance dialysis; dialysis could be either hemodialysis or peritoneal dialysis and (2) Reported at least one of the clinical outcomes listed below (major bleeding and/or stroke) for patients receiving apixaban and for patients receiving warfarin or no anticoagulation/placebo. Separate analyses were planned for apixaban versus warfarin and apixaban versus no anticoagulation/placebo.

Safety outcomes of interest were major bleeding, intracranial bleeding, and gastrointestinal bleeding. The main efficacy/effectiveness outcome was stroke or and systemic embolism. The definitions used by the included studies are summarized in Table 1. For studies that used two different doses of apixaban, we counted this as one single treatment arm of apixaban.

Two investigators (A.A.T and A.D.) independently extracted information on the study characteristics (author, study type, and publication year), duration of follow-up (mean, median, or maximum number of follow-up), sample size, and patient characteristics (gender, mean age, diabetes mellitus, hypertension, and coronary artery disease). We evaluated the quality of the observational studies by the Newcastle-Ottawa scale, on three specific aspects: the selection of the study groups, the comparability of the groups, and the ascertainment of exposure and outcome of interest.

We calculated odds ratios (OR) and 95% confidence intervals (CI) for each outcome for each study. We then pooled the odds ratios (OR) by a DerSimonian and Laird random-effects model. Meta-analyses were carried out using Comprehensive Meta-Analysis Software version 3.4 (Biostat, Inc). Publication bias was assessed visually using a funnel plot and quantified using Egger's test for small study effects. Heterogeneity among the studies was examined with the I^2 test.

3 | RESULTS

The initial search of databases yielded 896 results. Figure S1 shows the PRISMA flow chart of study selection. After title and abstract review, 28 full-text articles were retrieved for detailed review and retained six studies met inclusion criteria and were retained for data extraction; of these five were included in the apixaban versus warfarin analysis and one study compared apixaban to no anticoagulation.[7–10] The quality of included studies ranged from fair to good and is summarized in Table S1. There was little evidence of publication bias (Figure S2). However, Egger's test, funnel plots, and indeed testing for publication bias generally are unsuitable in the context of <10 studies included.

The five retained studies comparing apixaban to warfarin enrolled 10,036 patients with ESRD on dialysis. Apixaban was used in 2638 patients and warfarin was used in 7398 patients.[13–16] Of the five studies, four were retrospective observational studies[13–16] with one study matching patients in a 1:3 ratio to apixaban and

TABLE 1 Study characteristics.

Study (year)	Design	Enrollment period	Number of patients on apixaban (dose)	Number of patients in comparison group	Study population	Reported safety outcomes	Reported thromboembolic outcomes	Follow-up (months)
Mavrakanas (2020)	Matched Retrospective cohort study	2012–2015	521 (49% 2.5 mg)	1561[a]	ESRD on dialysis AF = 100%	Clinically important bleeding[b]	Stroke or systemic embolism	NA
Reed (2018)	Unmatched Retrospective cohort study	2014–2016	74 (20% 2.5 mg)	50	ESRD on dialysis AF = 49	Major (ISTH)	Ischemic stroke VTE	10
RENAL AF – (2019)	Randomized controlled trial	2016–2018	82 (29% 2.5 mg)	72	ESRD on dialysis AF = 100%	Major bleeding events[c]	Ischemic stroke	12
Sarrat (2017)	Unmatched Retrospective cohort study	2011–2015	40 (58% 2.5 mg)	120	ESRD on dialysis AF = 71%	Major bleeding events[c]	NR	NR
Schafer (2018)	Unmatched Retrospective cohort study	2013–2016	91 (57% 2.5 mg)	103	ESRD on dialysis AF = 81%	Major bleeding events[c]	Stroke or systemic embolism	12
Siontis (2018)	Matched Retrospective cohort study	2010–2015	2351 (56% 2.5 mg)	7053	ESRD on dialysis AF = 100%	Major bleeding events[c] GI bleeding Intracranial bleeding	Stroke or systemic embolism	

Abbreviations: AF, atrial fibrillation; ESRD, end-stage renal disease; GI, gastrointestinal; ISTH, International Society on Thrombosis and Hemostasis; NA, not applicable; NR, not reported; USA, United States of America; VTE, venous thromboembolism.

[a]Received no treatment with an oral anticoagulant (no warfarin).

[b]Defined as any bleeding resulting in death; any bleeding occurring at a critical site (intracranial, intraocular, retroperitoneal, intra-articular, pericardial, airway); or any gastrointestinal, urinary tract, or gynecologic bleeding requiring hospitalization.

[c]Defined as a composite of any acute, clinically overt bleeding plus at least one of the following: a decrease in hemoglobin of 2 g/dL or more, bleeding that required the transfusion of 2 units or more of blood products (packed red blood cells or fresh frozen plasma), bleeding in at least one critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding. All studies were from the USA.

warfarin respectively, based on a prognostic score.[16] There was one RCT (NCT02942407), which was terminated prematurely after randomization of 154 patients because of poor enrollment.[17] All studies were conducted in the United States of America. The mean follow-up ranged from 10 to 12 months. In the included studies, 20%–58% of patients were on the 2.5 mg apixaban dose; in the largest study by Siontis et al. 44% received the standard 5 mg dose and 56% received the lower 2.5 mg dose. We summarized the studies' characteristics in Table 1.

Generally, there were more females than males, and the mean age was higher in the apixaban group (Table 2). The mean age of patients ranged from 60 to 74 years in those receiving apixaban compared to 62 to 71 years in those receiving warfarin. The $CHADS_2$ score ranged from 2 to 5 in the apixaban group and from 3 to 5 in the warfarin group.

For safety outcomes, all studies reported major bleeding. Our pooled analysis showed that apixaban was associated with a reduced risk of major bleeding than with warfarin (odds ratio [OR] 0.51, 95% confidence interval [CI] 0.42–0.61; $p < .0001$; $I^2 = 0\%$) (Figure 1). Apixaban was also associated with a reduction in gastrointestinal bleeding (OR 0.61, 95% CI 0.51–0.73; $p < .0001$; $I^2 = 0\%$) (Figure 2). Furthermore, apixaban was associated with a reduction in intracranial hemorrhage (OR 0.58, 95% CI 0.37–0.92; $p = .02$; $I^2 = 0\%$) (Figure 3). For efficacy outcomes, apixaban was associated with a reduction in stroke (OR 0.64, 95% CI 0.50–0.82; $p < .0001$; $I^2 = 0\%$) (Figure 4). Finally, there was no difference in all-cause mortality between the two treatment arms (OR 1.02, 95% CI 0.59–1.76; $p = .95$; $I^2 = 80\%$) (Figure 5). Heterogeneity was also assessed using tau, tau^2, and Q-value with similar results.

Only one study compared apixaban to no treatment. In the observational study by Mavrakanas and colleagues, 2082 dialyzed patients with nonvalvular atrial fibrillation receiving apixaban (521 patients) were propensity score matched for relevant baseline characteristics with patients not treated with any anticoagulant (1561 patients). There was no benefit of apixaban in reduction of a composite of stroke, transient ischemic attack, or systemic embolism compared to no anticoagulation (hazard ratio 1.24, 95% CI 0.69 to 2.23; $p = .47$). However, a higher incidence of fatal or intracranial

TABLE 2 Patient characteristics.

	Apixaban							Warfarin or no anticoagulation						
Study first author (year)	Age	Male	HTN	DM	Prior stroke	CAD	$CHADS_2$	Age	Male	HTN	DM	Prior stroke	CAD	$CHADS_2$
Mavrakanas (2020)[a]	68	54	100	80	34	74	NR	68	53	100	80	36	74	NR
Reed (2018)	59.5	51.4	NR	NR	5.4	NR	NR	62.0	62.0	NR	NR	6.0	NR	NR
RENAL AF	69	35	NR	NR	17	NR	4[b]	68	53	NR	NR	12	NR	4[b]
Sarrat (2017)	70.9	20	33	22	6	20	2	66.5	58	97	59	29	56	3
Schafer (2018)[c]	73.5	46	82	47	19		4.8[b]	70.6	54	78	46	20	NR	4.8[b]
Siontis (2018)	68.9	54	100	75	33	27	5.27[b]	68.1	54	100	75	34	27	5.27[b]

[a]Compared apixaban to no anticoagulation while the remaining studies compared apixaban to warfarin.

[b]CHADS2VASC score.

[c]These numbers are for all patients included in the study, not only the dialysis patients (91 + 103 = 194).

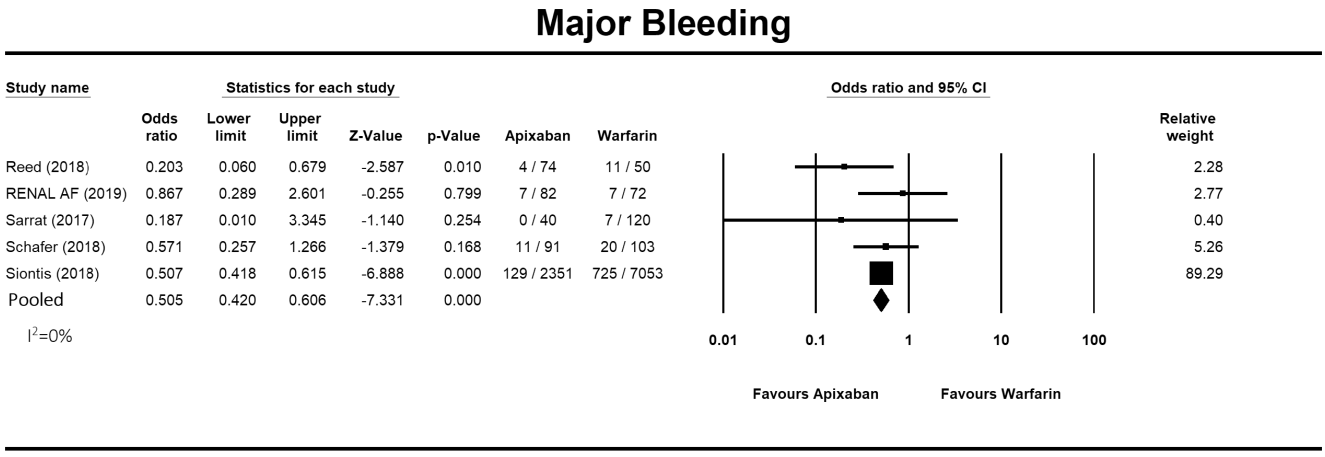


FIGURE 1 Risk of major bleeding in dialyzed patients with atrial fibrillation with apixaban versus warfarin.

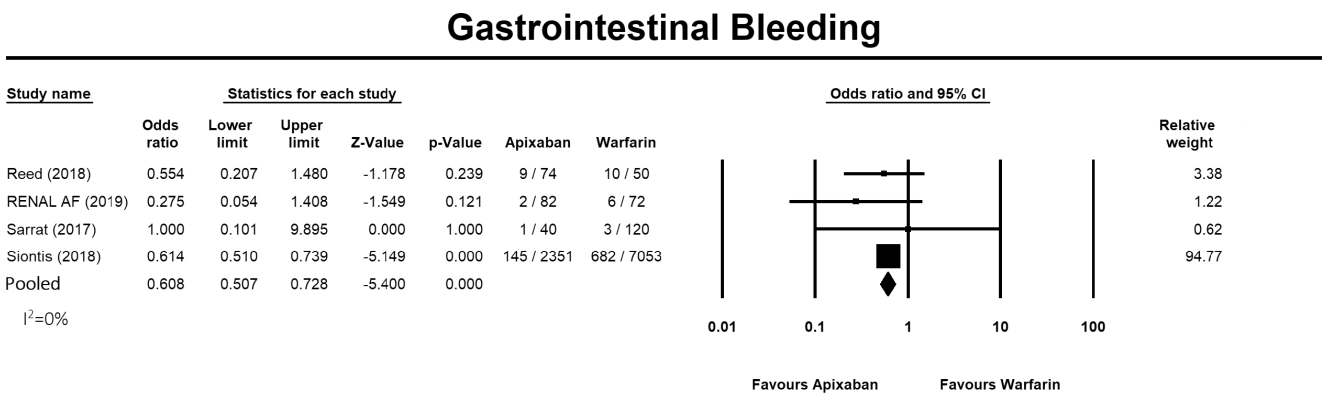


FIGURE 2 Risk of gastrointestinal bleeding in dialyzed patients with atrial fibrillation with apixaban versus warfarin.

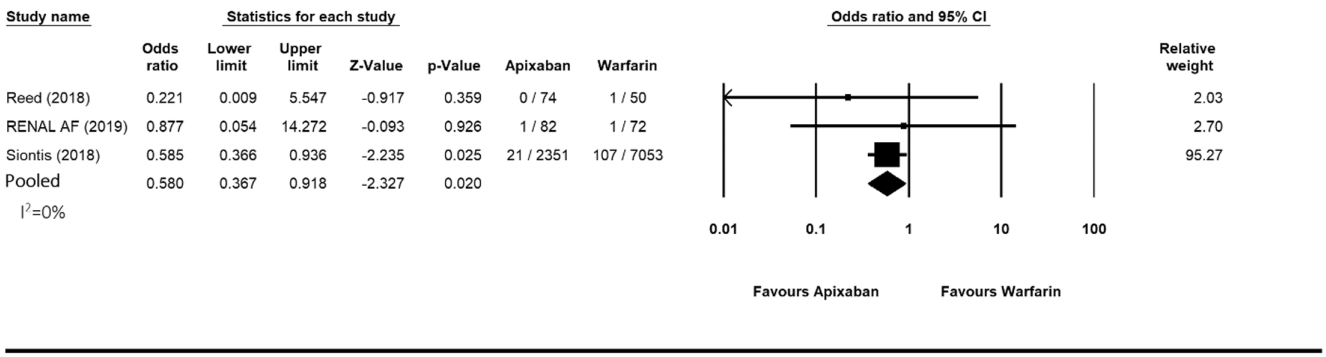


FIGURE 3 Risk of intracranial bleeding in dialyzed patients with atrial fibrillation with apixaban versus warfarin.

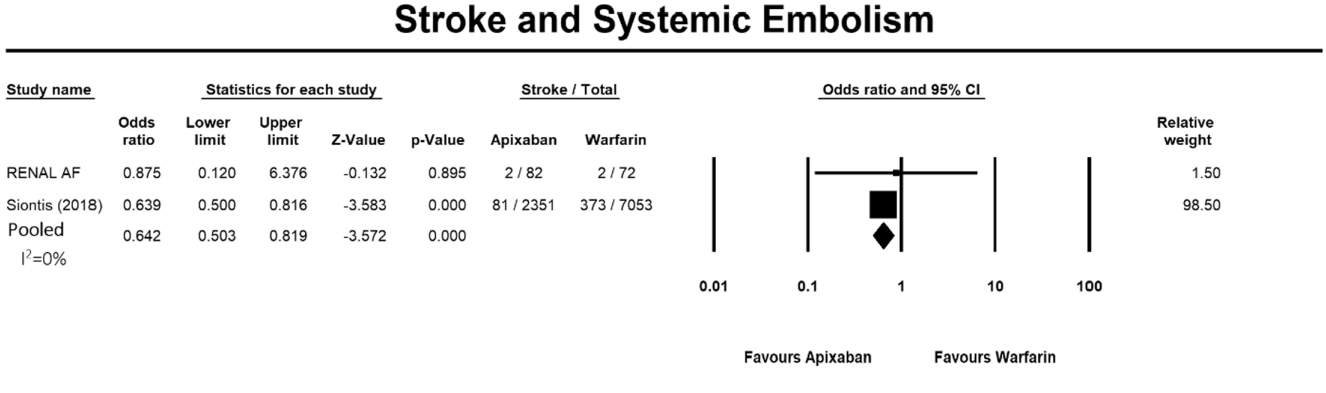
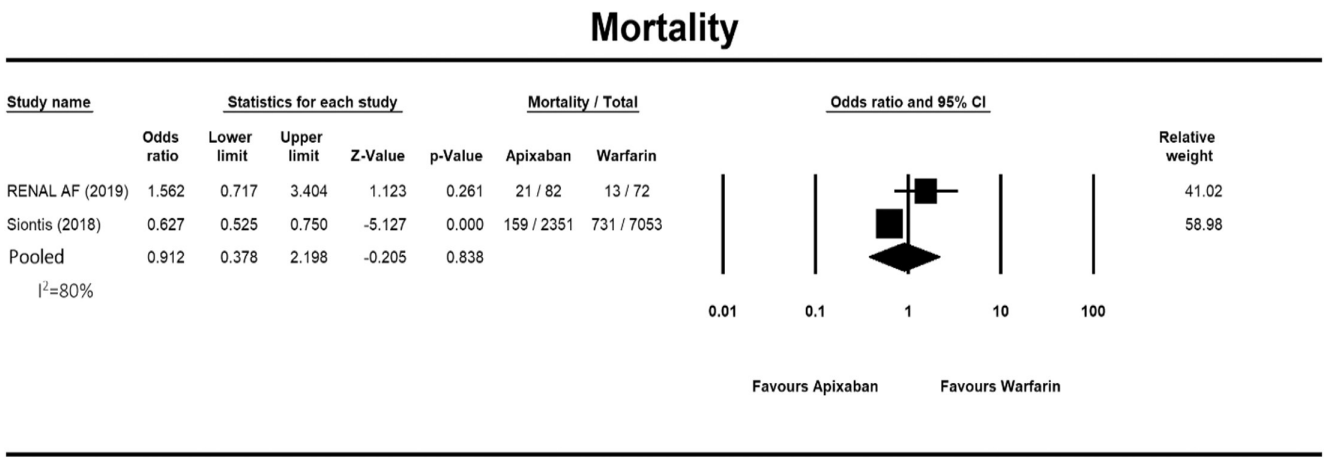


FIGURE 4 Risk of stroke or systemic embolism outcomes in dialyzed patients with atrial fibrillation apixaban versus warfarin.

bleeding was observed with apixaban compared with no anticoagulation (hazard ratio 2.74, 95% CI 1.37 to 5.47; $p = .004$). Apixaban was associated with reduction in all-cause mortality rates compared with no anticoagulation (hazard ratio, 0.58; 95% CI, 0.43 to 0.78), which the authors attributed to residual confounding.

4 | DISCUSSION

In our pooled analysis, apixaban was associated with an approximately 50% reduction in major bleeding and 40% reduction in intracranial and gastrointestinal bleeding compared to warfarin in



* Cochran Q = 5.01, P = 0.025; Tau= 0.577

FIGURE 5 Risk of all-cause mortality in dialyzed patients with atrial fibrillation apixaban versus warfarin.

patients with ESRD receiving dialysis. Apixaban was also associated with a 35% reduction in stroke or systemic embolism. In contrast, we found one study which showed no difference in stroke or systemic embolism between apixaban and placebo, but higher risk of fatal and intracranial bleeding. The number of studies examining all-cause mortality was too few to draw any definitive conclusions. Importantly, the inferences drawn are limited by both the quantity and quality of available studies highlighting the need for more data to address this important knowledge gap.

Clinical equipoise remains regarding stroke prevention in patients with AF and ESRD on dialysis. On one hand, ESRD requiring dialysis confers a markedly increased risk of stroke in patients with AF.[2,3] On the other hand, warfarin is associated with more major bleeding.[2,3,5] In a propensity-adjusted analysis of 10-year administrative data, Shah and colleagues showed that warfarin did not reduce stroke and was associated with a 44% increased bleeding risk compared to no anticoagulation.[6] In contrast, Olesen and colleagues found that warfarin did indeed reduce the risk of stroke by 54%, but it was similarly associated with a major (27%) risk of bleeding compared to no anticoagulation.[1,11] This conflicting data led to divergent clinical guidelines of the use of warfarin in patients with AF on dialysis.[9–11] In our current analysis, apixaban appeared to be superior to warfarin in reducing stroke and systemic embolism. However, our assessment of the comparison between apixaban and no OAC, although limited by the availability of a single study, did not show any significant difference between the two groups with regards to stroke and systemic embolism. Well-conducted clinical trials are needed to resolve this issue and perhaps should focus on patients at highest risk of stroke or systemic embolism in whom a net clinical benefit may be found.

One of the drawbacks of warfarin is the need to maintain patients within a narrow therapeutic range. Below the therapeutic range, warfarin is not effective for stroke protection, while the bleeding risk rises exponentially once the therapeutic range is exceeded.[18,19] Maintaining this therapeutic range is even more difficult in patients on dialysis.[19,20] Indeed, in the RENAL-AF trial, time in the therapeutic range was only 44% with an important percentage of patients in the subtherapeutic range. More frequent monitoring can enhance time in therapeutic range, but this time often remains below levels seen in the non-dialysis population.[21] Moreover, the polypharmacy prevalent in patients with ESRD can further complicate warfarin's efficacy and safety. In contrast to warfarin, apixaban does not require monitoring or dose adjustment, has 25% renal excretion, and is poorly dialyzable. Therefore, the more stable therapeutic levels of apixaban may partially explain the observed reduction in bleeding, including major bleeding as well as intracranial and gastrointestinal bleeding, compared to warfarin in patients on dialysis.[5] Based on these factors, the American Heart Association/American Congress of Cardiology and Heart Rhythm Society considered apixaban as reasonable in patients requiring dialysis, in contrast to all other non-vitamin K antagonists.[1] Importantly, the complexity of this issue has translated into clinical practice with significant heterogeneity of practice observed in clinician surveys.[22] Stroke-prevention studies that assessed the anticoagulation for patients with AF have uniformly excluded patients on dialysis; therefore, consensus is severely lacking in this area.

Compared to warfarin, the relative reductions of approximately 50% in major bleedings and 40% in gastrointestinal bleeding with apixaban in our meta-analysis were of a similar magnitude to those reported in the patients with normal kidney functions enrolled in the ARISTOTLE trial (43% and 58% reduction in major and gastrointestinal bleedings, respectively). In a subgroup analysis of 269 patients with creatinine clearance of 25–30 mL/min enrolled in the ARISTOTLE trial, Stanifer et al. observed a remarkable 66% reduction in risk of major bleeding with apixaban compared to warfarin. The consistent reductions in bleeding risk in our meta-analysis of dialysis patients as well as this ARISTOTLE CKD subgroup analysis may reflect the pharmacology of apixaban, with less renal excretion (25%) compared to warfarin's metabolites (92%). Bhatia and colleagues showed similar results in patients with stage 4 kidney disease and stage 5 disease not on dialysis.[23]

The observational study of Siontis et al. provided the most weight to our results, given that it was the largest included study. Nevertheless, the estimates of the other studies for stroke and

systemic embolism, major bleeding, intracranial bleeding, and gastrointestinal bleeding, were all in favor of apixaban. We did not observe any heterogeneity between the studies. Kuno and colleagues' network meta-analysis,[8] which did not include Siontis's study, did not show any stroke reduction with apixaban. Kuno et al. reported a 40% reduction in major bleeding with both doses of apixaban compared to warfarin in dialyzed patients.[8] The major limitation in the analysis of the analysis by Kuno et al. was the use of indirect comparisons in a network meta-analysis with only one study that directly assessed apixaban. Overall, both our findings and Kuno et al.'s study suggested a superior safety profile for apixaban compared to warfarin in dialysis patients with AF. A meta-analysis by Murtaza et al. had also examined the efficacy and safety of apixaban compared to warfarin in hemodialysis patients.[24] The main difference is that the analysis by Murtaza et al. only included four studies and importantly did not assess apixaban compared to no anticoagulation. Comparing apixaban to no anticoagulation is important given the equipoise with whether warfarin should be prescribed versus no anticoagulation.

Two ongoing trials may shed invaluable insights into the anticoagulation of patients with AF on dialysis. The Strategies for the Management of Atrial Fibrillation in patients Receiving Dialysis (SAFE-D) trial (NCT03987711) is randomizing 150 patients into three arms, warfarin or apixaban or no anticoagulation. In addition, in the Compare Apixaban and Vitamin-K Antagonists in Patients with Atrial Fibrillation and End-Stage Kidney Disease (AXADIA) trial recruitment was stopped early after enrolling 108 of a planned 222 patients on dialysis who were randomized to receive either low-dose apixaban or vitamin-K antagonist (NCT02933697).

Our meta-analysis has several limitations. First, the small number of studies pooled reflected the paucity of data in this high-risk patient population. Second, we could not evaluate separately the effects of the two different doses of apixaban. Third, because of the absence of patient-level data, we could not evaluate the effect of apixaban on diverse patient risk profiles. Imbalances in patients' characteristics may have exaggerated the observed safety benefit of apixaban. However, except for Reed et al.'s report, all other studies included older patients and more females in the apixaban arm. Therefore, the reduction in major bleeding with apixaban may be potentially more pronounced if the bleeding risks were more balanced between the two treatment arms. Fourth, except for Siontis et al.'s report, all other studies were of relatively short duration and consequently our meta-analysis is likely underpowered to detect differences in long-term mortality. Fifth, the analysis included observational studies, which can be influenced by selection and confounded by indication bias. This can also explain the magnitude of the effect sizes found. Sixth, the protocol was not registered on a protocol registration platform such as PROSPERO. Finally, only a very small minority of patients were on peritoneal dialysis (5%). Hence, the generalizability of our findings in patients on peritoneal dialysis is limited.

In conclusion, apixaban was associated with reductions in major, intracranial, and gastrointestinal bleedings as well as stroke and systemic embolism in dialysis patients with AF. Future randomized controlled studies are needed to confirm our findings and may elucidate which subgroup of dialyzed patients would derive the greatest clinical benefit with apixaban.

CONFLICT OF INTEREST STATEMENT

Dr. Mavrakanas reports personal fees from Daiichi Sankyo and Pfizer, outside the submitted work and received salary support from the Department of Medicine, McGill University, Montreal, Canada. Dr. Essebag has received honoraria from Bayer, Boehringer Ingelheim, BMS Pfizer, and Servier and is the recipient of a Clinical Research Scholar Award from the Fonds de recherche du Québec-Santé (FRQS). Dr Huynh has received significant research grants from Boehringer Ingelheim Canada, Bristol Myers Squibb Canada, Pfizer Canada, and Bayer Canada. The other authors have no relevant disclosures. There was no funding provided for this study.

ETHICS APPROVAL STATEMENT

N/A.

PATIENT CONSENT STATEMENT

N/A.

CLINICAL TRIAL REGISTRATION

N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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