Indian Pacing and Electrophysiology Journal 21 (2021) 221–226

Contents lists available at ScienceDirect

Indian Pacing and Electrophysiology Journal

journal homepage: www.elsevier.com/locate/IPEJ

Safety and Efficacy of Apixaban versus warfarin in patients with atrial fibrillation or Venous Thromboembolism and End-Stage renal disease on hemodialysis: A systematic review and meta-analysis

Ghulam Murtaza [a], Mohit K. Turagam [b], Jalaj Garg [c], Urooge Boda [d], Krishna Akella [a], Poonam Velagapudi [e], Andrea Natale [f], Rakesh Gopinathannair [a], Dhanunjaya Lakkireddy [a, *]

[a] Division of Cardiac Electrophysiology, The Kansas City Heart Rhythm Institute & Research Foundation, Overland Park, KS, USA
[b] Helmsley Electrophysiology Center, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[c] Division of Cardiology, Cardiac Arrhythmia Service, Medical College of Wisconsin, Milwaukee, WI, USA
[d] Department of Medicine, Overland Park Regional Medical Center, Overland Park, KS, USA
[e] Department of Cardiovascular Diseases, University of Nebraska Medical Center, Omaha, NE, USA
[f] Division of Cardiac Electrophysiology, St. David's Texas Cardiac Arrhythmia Institute, Austin, TX, USA

ARTICLE INFO

Article history:
Received 29 January 2021
Received in revised form
8 April 2021
Accepted 12 April 2021
Available online 15 April 2021

Keywords:
Apixaban
Warfarin
Dialysis
End-stage renal disease
Meta-analysis

ABSTRACT

Background: Warfarin is traditionally the drug of choice for stroke prophylaxis or treatment of venous thromboembolism in patients with end-stage renal disease (ESRD) on hemodialysis as data on apixaban use is scarce. We aimed to assess the safety and efficacy of Apixaban in patients with ESRD on hemodialysis when compared with warfarin.

Methods: A comprehensive literature search in PubMed, Google Scholar, and Cochrane databases from inception until Nov 25, 2019, was performed. Studies reporting clinical outcomes comparing Apixaban (2.5 mg BID or 5 mg BID) versus Warfarin in ESRD patients on hemodialysis were included. Mantel-Haenszel risk ratio (RR) random-effects model was used to summarize data.

Results: Four studies (three retrospective and one randomized) with a total of 9862 patients (apixaban = 2,547, warfarin = 7315) met inclusion criteria. The overall mean age was 66.6 ± 3.9 years and mean CHA2DS2-VASc score 4.56 ± 0.58. Apixaban was associated with lower rates of major bleeding (RR 0.53, 95% CI 0.45–0.64, $p < 0.0001$], gastrointestinal (GI) bleed (RR 0.65, 95% CI 0.55–0.76, $p < 0.0001$), intracranial bleed (RR 0.56, 95% CI 0.36–0.89, $p = 0.01$), and stroke/systemic embolism [RR 0.65, 95% CI 0.52–0.83, $p = 0.0004$] compared with warfarin in patients with ESRD on hemodialysis. There was no significant increased risk of all-cause mortality with the apixaban vs. warfarin (RR 0.90, 95% CI 0.41–1.96, $p = 0.78$).

Conclusion: Apixaban had an overall favorable risk-benefit profile, with significant reductions in ischemic stroke, major bleeding, and intracranial bleeding compared to Warfarin in ESRD patients on hemodialysis with non-valvular AF and/or venous thromboembolism.

1. Introduction

Warfarin has been the mainstay of treatment for deep venous thrombosis (DVT), pulmonary embolism, thromboembolic prophylaxis in atrial fibrillation (AF), and DVT prophylaxis post hip/knee replacement. The rise of direct oral antagonists (DOACs) in the last decade for the abovementioned conditions has led to a decrease in warfarin use. With the rising number of end-stage renal disease (ESRD) patients and associated increased bleeding and thromboembolic complications, the optimal anticoagulation strategy remains dismal in this patient population.

Besides, the landmark DOAC clinical trials excluded patients

* Corresponding author. Kansas City Heart Rhythm Institute (KCHRI) @ HCA MidWest, 12200 West 106th street, Overland Park Regional Medical Center, Overland Park, KS, 66215, USA.
E-mail address: dlakkireddy@gmail.com (D. Lakkireddy).
Peer review under responsibility of Indian Heart Rhythm Society.

https://doi.org/10.1016/j.ipej.2021.04.002

with severe renal dysfunction and ESRD, thus leading to European guidelines not recommending DOAC's in patients with severe renal impairment [1]. On the contrary, United States Federal Drug Administration approved the use of DOAC's (Apixaban, rivaroxaban, and dabigatran) in patients with chronic kidney disease (CKD, creatinine clearance 15–29 m ml/min), while only approved Apixaban in patients on hemodialysis. Although prior randomized study - ARISTOTLE demonstrated a favorable risk profile for Apixaban (vs. warfarin) for thromboembolic prophylaxis [2], the safety and efficacy of Apixaban (as compared to warfarin) in patients with ESRD on hemodialysis remains unclear. Warfarin has traditionally been used in this patient population; however, it is associated with fluctuating international normalized ratio (INR), drug-drug interaction, and increased risk of vascular calcifications. Therefore, we performed a systematic review and meta-analysis evaluating the safety and efficacy of Apixaban in comparison to warfarin in patients with end-stage renal disease on hemodialysis.

2. Methods

2.1. Search strategy

This systematic review and meta-analysis complied with the **M**eta-analysis **Of** **O**bservational **S**tudies in **E**pidemiology (MOOSE) guidelines [3].

The initial search strategy was developed by two authors (GM and MT). A systematic literature search was performed using PubMed, Google Scholar, and Cochrane databases from inception until Nov 27, 2019, for studies comparing Apixaban vs. Warfarin in ESRD patients on HD. The following keywords were used: *atrial fibrillation*, *dialysis, Apixaban, Warfarin, end-stage renal disease.*

2.2. Study selection and data extraction

Our systematic review's eligibility criteria included: 1) all studies reporting outcomes in ESRD patients comparing Apixaban vs. warfarin on HD; 2) studies that included human subjects 18 years of age or older; and 3) reported at least one clinical outcome. We included studies only in the English language. Case reports, editorials, systematic reviews, or studies without a comparator arm were excluded were from our analysis.

Two investigators (GM and MT) independently performed the literature search and screened all titles and full-text versions of all relevant studies that met study inclusion criteria. The data from the included studies were extracted using a standardized protocol and a data extraction form. Any discrepancies between the two investigators were resolved with a consultation with the senior investigator (DL). The following data were extracted from the included studies: age, gender, study population, duration of follow-up, history of atrial fibrillation, presence of liver disease, aspirin, or clopidogrel use, CHA_2DS_2-VASc score. The Newcastle Ottawa Risk assessment tool was used to appraise the quality of the included studies. We rated the quality of studies (good, fair, and poor) by awarding stars in each domain. A “good” quality score required 3 or 4 stars in the selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes. A “fair” quality score required two stars in the selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes. A “poor” quality score reflected 0 or 1 star(s) in selection, or 0 stars in comparability, or 0 or 1 star(s) in outcomes.

2.3. Outcomes

Efficacy outcome: The primary efficacy outcome was the prevention of systemic embolic events (composite of stroke and systemic embolism) (SEE).

Safety outcomes: The primary safety outcomes included major bleeding, gastrointestinal (GI) bleeding, intracranial bleeding, and all-cause mortality.

2.4. Statistical analysis

Statistical analysis was performed using Cochrane RevMan version 5.3 (Cochrane Collaboration, London, United Kingdom). Mantel-Haenszel risk ratio (RR) random-effects model (DerSimonian and Laird method) was used to summarize data between the two groups [4]. Higgins I-squared (I^2) statistic was used to assess the test of heterogeneity [5]. A value of I^2 of 0–25% represented insignificant heterogeneity, 26–50% represented low heterogeneity, 51–75% represented moderate heterogeneity, and more than 75% represented high heterogeneity. A two-tailed $p < 0.05$ was considered statistically significant.

3. Results

3.1. Search results

A total of 2203 articles were identified (Fig. 1) during the initial search, of which 245 articles were excluded as duplicates. An additional 1815 articles were excluded after the title and abstract review. Finally, four articles including 9862 patients (Apixaban = 2547 and Warfarin = 7315) were eligible for our analysis [6–9]. Table 1 summarizes the baseline characteristics of the included studies.

3.2. Study characteristics

This meta-analysis included four studies (all from the United States, three observational [7–9] and one randomized controlled trial (abstract form only) [6] comprising 9862 patients with a mean follow-up duration of 327.4 ± 32.7 days. Patients in the Apixaban arm were older than patients in the warfarin arm (67.04 ± 5.18 years vs. 66.14 ± 2.85 years, respectively, $p < 0.001$). The mean CHA2DS2-VASc score was 4.56 ± 0.58. The indication for anticoagulant in two studies was non-valvular AF [[6,7]], while in the other two studies, it was combined non-valvular AF and venous thromboembolism (VTE) [[4,5]]. Table 1 summarizes the study characteristics of the included trials.

The definition of major bleeding was defined per the International Society of Thrombosis and Hemostasis (ISTH) criteria [6–8]. In contrast, in one study, major bleeding was defined as any bleeding associated with critical site code, requiring blood transfusion or resulting in death [9]. Based on the Newcastle Ottawa Risk assessment tool, all studies were of good quality (Table 2).

3.3. Systemic embolic event

The data for SEE was available in three trials [4,6,7]. Apixaban was associated with lower SEE as compared to warfarin (3.31% vs 5.22%, respectively; RR 0.65, 95% CI 0.52–0.83, $p = 0.0004$). No significant heterogeneity was observed ($I^2 = 0\%$) (Fig. 3).

3.4. Major bleeding

The data for major bleeding was available in all four studies. Apixaban was associated with lower rates of major bleeding compared to warfarin (5.49% vs. 10.11%; RR 0.53, 95% CI 0.45–0.64, $p < 0.0001$, respectively]. No significant heterogeneity was observed ($I^2 = 8\%$) (Fig. 3).

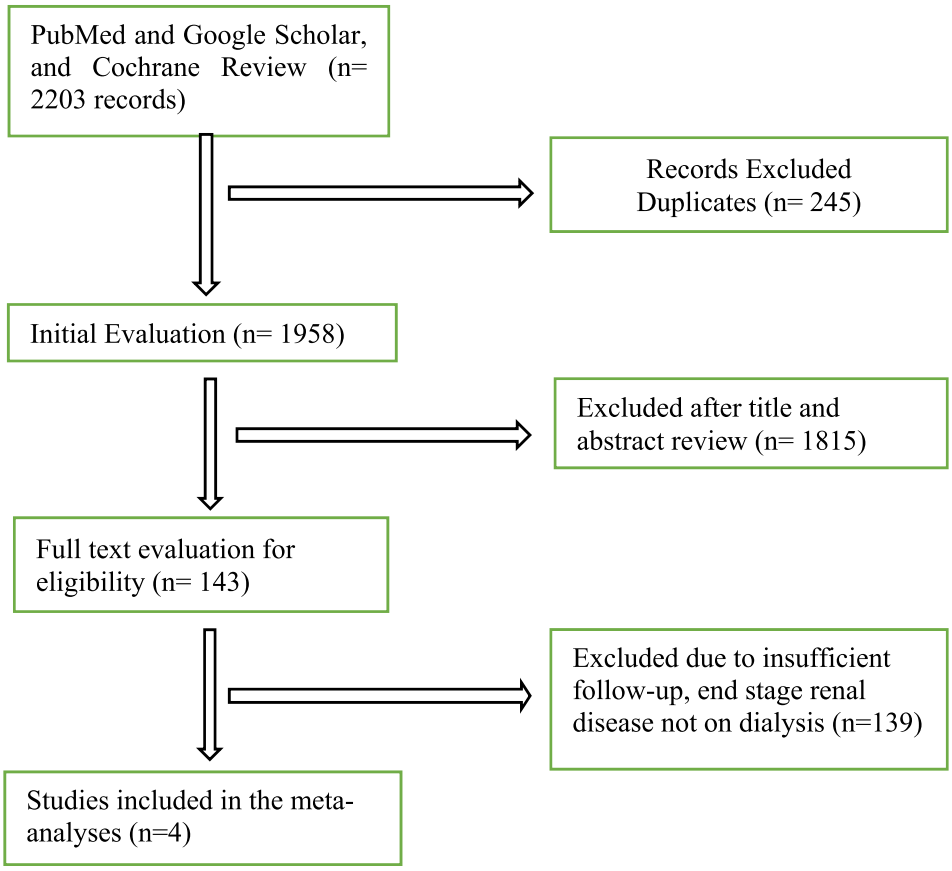


Fig. 1. Flow Diagram illustrating the systematic search of studies.

Table 1
Baseline characteristics of the studies included in our meta-analysis.

	Granger 2019		Reed 2018		Sarratt 2017		Siontis 2018	
Characteristics	*Apixaban*	*Warfarin*	*Apixaban*	*Warfarin*	*Apixaban*	*Warfarin*	*Apixaban*	*Warfarin*
Age (years)	69 (61–76)[a]	68 (60.5–72.5)[a]	59.4 ± 14.7	62.4 ± 14.4	70.9(60–81)[a]	66.5(53–80)[a]	68.87 ± 11.49	68.04 ± 11.90
Male (%)	58.5	69.4	51.40%	62%	50%	48.30%	54.40%	54.90%
Female (%)	41.5	30.6	48.60%	38%	50%	51.70%	45.60%	45.10%
# of patients in each group	82	72	74	50	40	140	2351	7053
Follow-up (days)	350.5	340.5	304.2	304.2	NR	NR	NR	NR
CHA_2DS_2VASc score	4(3–5)^	4(3–5)^	4.1 ± 1.2	4.0 ± 1.4	5(1–6)^	5(2–7)^	5.27 ± 1.77	5.14 ± 1.78
Paroxysmal AF	54.90%	55.60%	NR	NR	NR	NR	NR	NR
Persistent/Permanent AF	45.10%	44.40%	NR	NR	NR	NR	NR	NR
Prior clinically relevant bleeding	22%	19.40%	NR	NR	NR	NR	NR	NR
Liver disease	NR	NR	27%	16%	12.50%	6.70%	9.40%	10.30%
Aspirin or clopidogrel use	36.70%	45.70%	28.40%	36%	37.50%	44.20%	6.60%	7.00%
Indication for anticoagulant	AF (100%)	AF (100%)	AF (39.2%) VTE (60.8%)	AF (58%), VTE (42%)	VTE (100%)	VTE (100%)	AF (100%)	AF (100%)
Apixaban 2.5 mg BID	28.60%	NR	20.30%	NR	57.50%	NR	NR	NR
Apixaban 5 mg BID	71.40%	NR	79.70%	NR	42.50%	NR	NR	NR

Values are represented as % or n + SD; ^ = median (interquartile range).
[a] = median (range); AF = atrial fibrillation; NR = not reported.

Table 2
Risk of bias assessment of the studies included in the meta-analysis using the Newcastle-Ottawa Scale.

Study	Selection	Comparability	Outcome
Granger 2019	****	**	***
Reed 2018	***	**	**
Sarratt 2017	****	**	***
Siontis 2018	****	**	***

3.5. Gastrointestinal bleeding

The data for GI bleeding was available in all four studies. Apixaban was associated with lower rates of GI bleeding compared to warfarin (6.55% vs. 9.96%; RR 0.65, 95% CI 0.55–0.76, $p < 0.0001$). No significant heterogeneity was observed ($I^2 = 0\%$) (Fig. 3).

3.6. Intracranial bleeding

The data for intracranial bleeding was available in three studies [4,6,7]. Apixaban was associated with lower intracranial bleeding rates than Warfarin (0.87% vs. 1.57%; RR 0.56, 95% CI 0.36–0.89, p = 0.01). No significant heterogeneity was observed (I^2 = 0%) (Fig. 3).

3.7. All-cause mortality

The data for all-cause mortality was available in two studies [6,7]. No significant difference was observed between the two groups (7.39% vs 10.75%; RR 0.90, 95% CI 0.41–1.96, p = 0.78]. Significant heterogeneity was observed (I^2 = 84%) (Fig. 3).

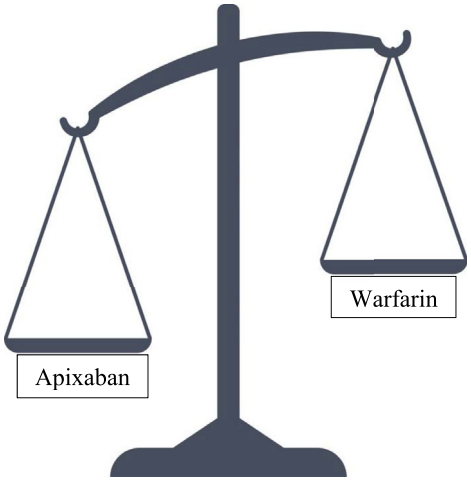
Publication bias: Publication bias could not be assessed because the number of studies in the meta-analysis was < 10.

4. Discussion

The main findings in this analysis were: a) risk of the systemic embolic event, major bleeding, gastrointestinal bleeding, and intracranial bleeding was significantly lower in patients with Apixaban as compared to warfarin; b) no significant difference in all-cause mortality was observed between the two groups (Fig. 2).

Stroke is the leading cause of morbidity and mortality in patients with atrial fibrillation. The complex interplay of the coagulation cascade in ESRD patients is a dynamic process, and a fine balance between the pro-coagulant and anticoagulant factors in these patients determine the increased risk of thrombosis and/or bleeding. Given the high prevalence of AF and VTE in patients with ESRD and increased overall bleeding risk, it is imperative to determine a safe anticoagulant with an overall low bleeding risk profile. In regard to the prevention of SEE, our study demonstrated that the use of oral anticoagulant (Apixaban) was associated with improved outcomes during the follow-up period as compared to warfarin. Our study results are intriguing and in line with the previously published RCT trial – ARISTOTLE trial (that demonstrated that Apixaban was superior to warfarin in preventing strokes and systemic emboli in patients with non-valvular AF) [2]. However, unlike our study, patients with ESRD on hemodialysis were excluded from the trial.

Patients with ESRD on hemodialysis are at increased risk of bleeding complications likely due to platelet dysfunction (impaired platelet adhesion/aggregation, uremic related platelet dysfunction, and altered Von-Willebrand factor) and underlying intrinsic vessel abnormality [10–12]. Warfarin use in patients with chronic kidney disease or ESRD on hemodialysis increases the risk of associated anticoagulant nephropathy, accelerated vascular calcification, and calciphylaxis [13,14], thus increasing the risk of bleeding. Apixaban, on the other hand, is only partially excreted by the kidneys (20–25%) and mostly metabolized by non-renal pathways (such as cytochrome P450, biliary and intestinal excretion) [15,16]. Because of high plasma protein binding, apixaban is not expected to be dialyzable. Therefore, FDA recommends dose adjustment (2.5 mg BID) in ESRD patients on hemodialysis with any one of the following indications - age ≥80 years or body weight ≤60 kg



Clinical Outcomes	Risk Ratio	95% Confidence Interval
Stroke	0.65	0.52 – 0.83
Major Bleeding	0.53	0.45 - 0.64
Gastrointestinal Bleeding	0.65	0.55 – 0.76
Intracranial Bleeding	0.56	0.36 – 0.89
All-cause mortality	0.90	0.41 – 1.96

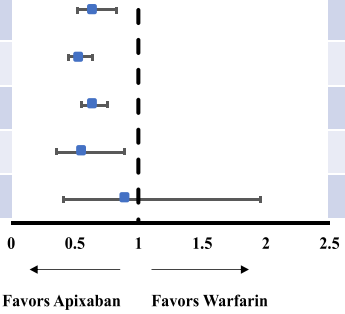


Fig. 2. Safety and efficacy of apixaban versus warfarin in patients with atrial fibrillation or venous thromboembolism and end-stage renal disease on hemodialysis.

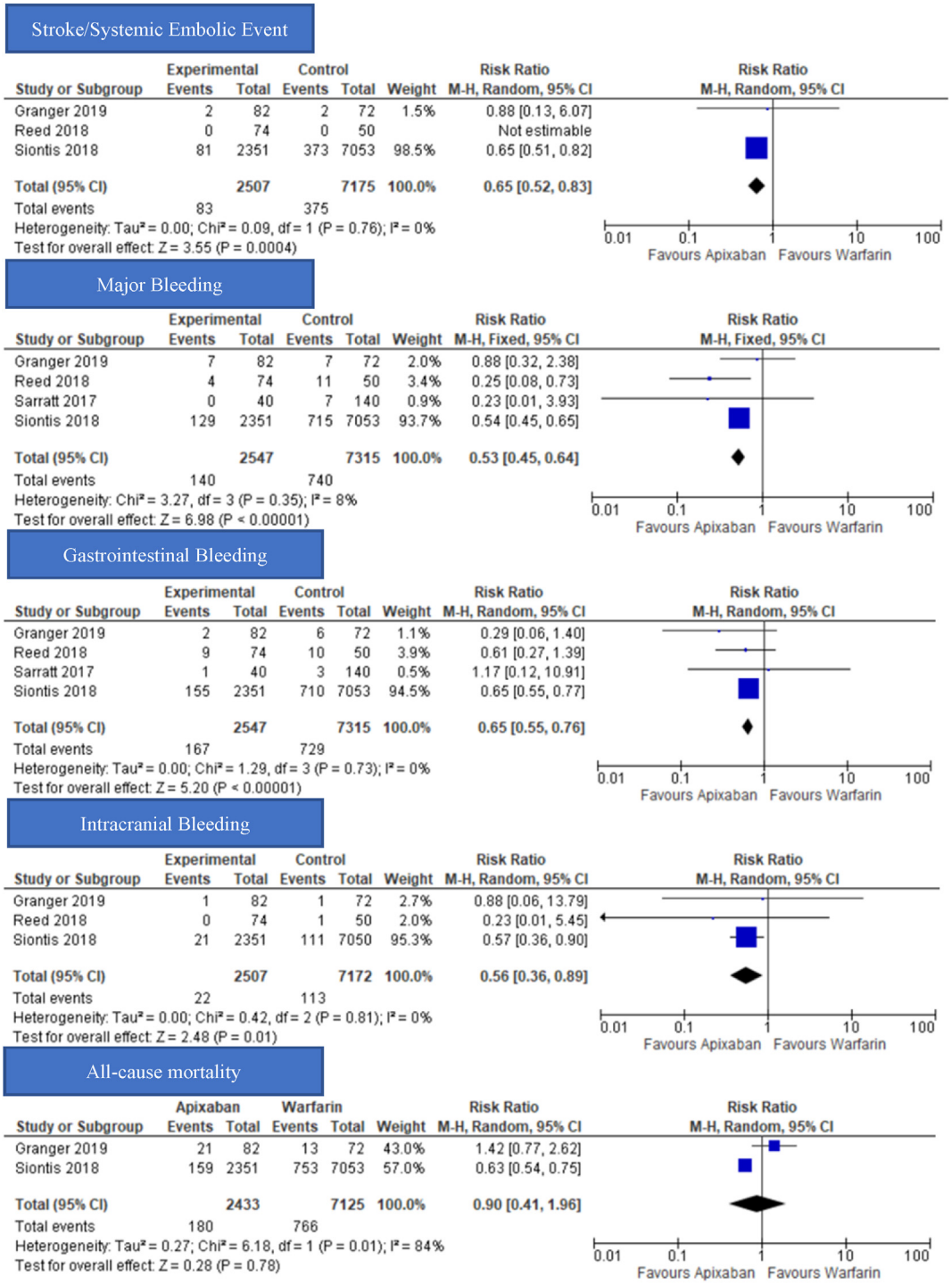


Fig. 3. Forest plots for individual clinical outcomes.

(although dosing recommendation is based on a small study) [17]. In our study, although a significant reduction in bleeding-related complications was observed with Apixaban as compared to warfarin (finding that echoes with ARISTOTLE trial), concluding appropriate drug dosing has been difficult due to differences in trial designs and lack of individual patient-level data comparing Apixaban 2.5 mg BID vs. 5 mg BID. Regardless, 64.5% of patients in our received 5 mg BID Apixaban (data limited to three trials).

Although our study results are in accordance with the recently published meta-analysis by Chokesuwattanaskul et al. [18], our study is unique as we only included patients with ESRD on hemodialysis in contrary to the latter. Since patients with ESRD are at increased risk of both ischemic and hemorrhagic stroke, our study's findings are intriguing, demonstrating a significant reduction in ischemic and hemorrhagic stroke with no increase in all-cause mortality as compared to warfarin. However, current evidence is

limited to studies with a small sample size. Future RCT with enough sample size might shed light on the true clinical benefit of this approach. There are two ongoing clinical trials to assess the beneficial effects of Apixaban in ESRD patients - (i) The AXADIA trial (NCT02933697) is an ongoing RCT enrolling 222 ESRD patients on hemodialysis comparing Phenprocoumon (vitamin K antagonist) vs. Apixaban in non-valvular AF, and (ii) The AVKDIAL trial will randomize 855 ESRD patients with non-valvular AF comparing safety and efficacy of oral anticoagulation vs. no anticoagulation.

4.1. Limitations

Our study has several important limitations. First, patient selection bias due to the small sample size and retrospective nature of the included studies (except one – being presented in abstract form only) could not be excluded. Second, studies included in our pooled analysis come from the United States, and hence findings of our study may not be generalized to patients outside North American and should be interpreted with caution. Third, subgroup analysis comparing low dose versus standard dose apixaban could not be performed as data was not available. Forth, included studies evaluated Apixaban and Warfarin for various indications, and the risk of bleeding or thromboembolism may vary among populations with different indications and underlying baseline characteristics. Fifth, patient-level data to perform information on INR management or time in therapeutic range (for patients treated with warfarin) was not available. Sixth, the results of our meta-analysis were primarily driven by Siontis et al., accounting together for more than two-thirds of the total study population. Seventh, publication bias could not be evaluated due to less than ten studies included in the pooled analysis.

5. Conclusion

Apixaban had an overall favorable risk-benefit profile, with significant reductions in ischemic stroke, major bleeding, and intracranial bleeding when compared to Warfarin in ESRD patients on hemodialysis with non-valvular AF and/or venous thromboembolism.

Funding source

None.

Declaration of competing interest

None.

Acknowledgments

None. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Camm AJ, Lip GY, De Caterina R, et al. Focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012 2012;33:2719–47.
[2] Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.
[3] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
[4] DerSimonian R, Laird N. Meta-analysis in clinical trials. Contr Clin Trials 1986;7:177–88.
[5] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343. d5928.
[6] AHA. Presentation slides: renal-AF-. https://www.acc.org/education-and-meetings/image-and-slide-gallery/media-detail?id=469e5bd88fff4d2bb8ec183e71521637; 2019. Last accessed 1/10/21.
[7] Reed D, Palkimas S, Hockman R, Abraham S, Le T, Maitland H. Safety and effectiveness of apixaban compared to warfarin in dialysis patients. Res Pract Thromb Haemost 2018;2:291–8.
[8] Sarratt SC, Nesbit R, Moye R. Safety outcomes of apixaban compared with warfarin in patients with end-stage renal disease. Ann Pharmacother 2017;51:445–50.
[9] Siontis KC, Zhang X, Eckard A, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. Circulation 2018;138:1519–29.
[10] Lai HM, Aronow WS, Kalen P, et al. Incidence of thromboembolic stroke and of major bleeding in patients with atrial fibrillation and chronic kidney disease treated with and without warfarin. Int J Nephrol Renovascular Dis 2009;2:33–7.
[11] Ghadban R, Flaker G, Katta N, Alpert MA. Anti-thrombotic therapy for atrial fibrillation in patients with chronic kidney disease: current views. Hemodial Int 2017;21(Suppl 2):S47–56.
[12] Reinecke H, Brand E, Mesters R, et al. Dilemmas in the management of atrial fibrillation in chronic kidney disease. J Am Soc Nephrol 2009;20:705–11.
[13] Danziger J. Vitamin K-dependent proteins, warfarin, and vascular calcification. Clin J Am Soc Nephrol 2008;3:1504–10.
[14] Holden RM, Sanfilippo AS, Hopman WM, Zimmerman D, Garland JS, Morton AR. Warfarin and aortic valve calcification in hemodialysis patients. J Nephrol 2007;20:417–22.
[15] Mavrakanas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML. Apixaban pharmacokinetics at steady state in hemodialysis patients. J Am Soc Nephrol 2017;28:2241–8.
[16] Harel Z, Sholzberg M, Shah PS, et al. Comparisons between novel oral anticoagulants and vitamin K antagonists in patients with CKD. J Am Soc Nephrol 2014;25:431–42.
[17] Wang X, Tirucherai G, Marbury TC, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. J Clin Pharmacol 2016;56:628–36.
[18] Chokesuwattanaskul R, Thongprayoon C, Tanawuttiwat T, Kaewput W, Pachariyanon P, Cheungpasitporn W. Safety and efficacy of apixaban versus warfarin in patients with end-stage renal disease: meta-analysis. Pacing Clin Electrophysiol 2018;41:627–34.