Review Article

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Apixaban in Dialysis Patients: A Review

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Introduction
Atrial Fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice, reportedly affecting up to 2% of the general population in the developed world [1,2]. In patients with chronic kidney disease (CKD), its prevalence ranges from 7% to 27% [3].

Significantly, the risk of developing AF increases with the stage of CKD [2]. Patients with end stage renal failure (ESRF) are at a greater risk of having a stroke compared with the general population [3-5]. Subsequently, the decision to anticoagulate these patients poses a therapeutic dilemma. Balancing the increased risk of stroke, is the increased risk of bleeding. Dialysis patients have a high risk of bleeding due to uremia induced platelet dysfunction [6].

Additional risk factors include repeated vascular access cannulations, dialysis membrane interactions, anticoagulant treatment with heparin during dialysis and higher than average blood pressures [6]. Warfarin is the anticoagulant of choice in such patients, but there is conflicting evidence supporting its use; with some studies reporting significant bleeding effects and no benefit from stroke prevention [7]. In the last few years, direct oral anticoagulants (DOACS) have emerged as an alternative therapy to warfarin [7].

Of these agents apixaban is the least renally excreted. As a result, there is increasing interest in using apixaban amongst dialysis patients for the management of AF and vascular thromboembolism (VTE) [2,3,6].

To date, the only published studies assessing the use of apixaban in dialysis patients have been pharmacokinetic (PK) and retrospective studies. As such, there are concerns about its safety and efficacy in dialysis patients [2,3].

Currently, there are 2 randomized controlled trials in development comparing warfarin and apixaban use in dialysis patients. Till the results of these trials are available, there will continue to be much debate.

Discussion
Apixaban is an oral factor X a inhibitor that is mainly excreted via hepatic metabolism through the actions of the liver enzyme CYP3A4. Approximately 25-28% is cleared via the urine [3,5,6,8,9]. Apixaban is the least renally excreted drug amongst all the DOACS, making it an ideal drug for use in patients with renal failure [3,6,10].

The ARISTOTLE trial, (Apixaban for reduction in stroke and other thromboembolic events in Atrial Fibrillation) was the first study to demonstrate superior efficacy of apixaban to warfarin and reduced mortality with apixaban. It was heralded as a breakthrough drug and an alternative to warfarin therapy [6,5].

In this study, 18,201 patients with non-valvular AF were randomized to receive either apixaban or warfarin. The dose of apixaban varied from 2.5 mg twice daily to 5 mg twice daily. 2.5 mg of Apixaban was administered to patients with 2 of the following criteria; creatinine between 1.5 and 2.5 mg/dL, age greater than 80 years, or body weight less than or equal to 60 kg [5].

Of significance, the study did not include patients with severe renal dysfunction as defined by creatinine greater than 2.5 g/dL, creatinine clearance of less than 25 ml/min and patients on hemodialysis [5]. Pre-specified secondary analyses, however included patients with mild moderate and severe renal impairment. Results of these analyses showed greater efficacy and reduced mortality with apixaban in patients with mild, moderate and severe CKD [5].

On further analysis it was observed that patients with moderate to severe CKD when compared to patients with mild CKD or normal renal functions, had a greater reduction in bleeding episodes with apixaban when compared to warfarin [5].

The results of these analyses encouraged the US (United States) Food and drug administration (FDA) to approve the use of apixaban 5 mg twice daily or 2.5 mg twice daily to patients with a creatinine clearance of greater than 25 ml/min, and at least 2 of the following criteria; creatinine at or above 1.5 mg/dL, age 80 or older, or body weight less than or equal to 60 kg [5].

In January 2014, the use of apixaban was extended to include patients with ESRF on hemodialysis. 5 mg twice daily was the recommended dose, with dose reduction to 2.5 mg twice daily in patients over the age of 80 or body weight less than 60 kg [5].

Despite this recommendation, there was debate on what was the safest and most effective dose of the drug. Dosage of apixaban in ESRF is still disputed. Several pharmacokinetic studies have been performed with the aim of identifying the safest dose for patients. The original recommended dosage of 5 mg twice daily was partially based on the pharmacokinetic study by Wang et.al. [11].

This study was an open label, parallel group single dose study that included 8 subjects with ESRF, matched against 8 subjects with preserved renal functions. A single oral dose of 5 mg was administered to healthy subjects and twice daily to subjects with ESRF, separated by 7 days; 2 hours before or on hemodialysis and immediately after a 4 hour hemodialysis session. The results of the study showed that post hemodialysis administration of 5 mg of Apixaban, resulted in a 36% increase in drug exposure compared with healthy subjects and normal renal function. Despite this result, the authors concluded that hemodialysis had limited impact on apixaban clearance [5-7].

Similar findings and conclusions were observed in the study by Chang and group. (Chang). In this comparative study, apixaban pharmacokinetics pharmacodynamics and safety were evaluated in subjects with varying degrees of renal impairment; mild, moderate and severe and healthy subjects who had preserved renal functions. A single oral dose of 10 mg was administered to subjects. Results of this study showed a 44% increase in drug exposure in patients with severe renal impairment [6].

The authors reported no adverse effects with apixaban and concluded that dose reduction was not required. Contrasting results were however seen in the study by Mavrakanas and group [1]. The pharmacokinetic study by Mavrakanas and group, was the first study to assess multiple dose administration of apixaban to patients on maintenance hemodialysis. Instead of comparing with healthy subjects, the study involved two groups of dialysis patients receiving different doses of apixaban.

In this study, 7 patients received apixaban at 2.5 mg twice daily for 8 days. Blood samples were collected before and after apixaban administration on days 1 and 8, which were nondialysis days. After a 5 day washout period, 5 patients received 5 mg of apixaban twice daily for 8 days. Significant findings from the study revealed that Apixaban at a dose of 2.5 mg twice daily resulted in a drug exposure level comparable to a standard dose of 5 mg twice daily in patients with preserved renal function [1].

Secondly, apixaban at 5 mg twice daily resulted in supratherapeutic levels. Mavrakanas and group were critical of the results of the studies by chang and wang, claiming that a single dose approach can be misleading due to confounders, citing interperson variability [1]. Furthermore, they suggest that multidosing reduces interperson variability [1]. As such, their recommendations were to use a dose of 2.5 mg twice daily in hemodialysis patients.

These pharmacokinetic studies have indicated that apixaban can be used in patients with ESRF on hemodialysis. Dosage is still uncertain. There are further questions that surround its efficacy and safety when compared to warfarin.

Patients with CKD or ESRF are at a greater risk of having a stroke compared to the general population [3,4,7]. Additionally, there is increased risk of bleeding. The study by Masson and group had shown that there was increased risk of intracerebral hemorrhage as opposed to ischemic stroke in patients with ESRF [4]. Furthermore, it is well recognized that patients with this bleeding risk require hospitalization [3].

It has been reported 14 to 20% of patients on dialysis, are hospitalized with major bleeding within 4 years of initiation of dialysis [3]. Moreover, gastrointestinal bleeding has been associated with warfarin use [3]. Consequently, the decision to anticoagulate these patients poses as a therapeutic dilemma for the clinician.

Current guidelines do not advocate the use of DOACS in patients with advanced CKD [3,7,10,12]. The 2014 ACC/AHA/HRS AF guidelines and the 2016 CHEST VTE guidelines recommend warfarin as the preferred anticoagulant for the ESRF population [12].

However, several studies have demonstrated increased risk of hemorrhagic stroke in AF patients receiving hemodialysis and taking warfarin. DOACS have been therefore considered in this setting [13].

Comparative studies assessing different anticoagulant therapy in patients with ESRF have been lacking, thus not allowing for confident recommendations for use of DOACS over traditional therapy [12]. Subsequently in the last 2 to 3 years retrospective studies have been done examining the safety and effectiveness of warfarin and apixaban. These comparative studies have supported the use of apixaban in patients with ESRF, with many seeing apixaban as an alternative to warfarin [8-10].

Results of these studies essentially showed less bleeding events

associated with apixaban compared with warfarin [8-10]. The results of these studies though, should be interpreted with caution as there were significant limitations identified. Major limitations that were recognized in these studies included their retrospective design and confounding factors that introduced bias. The data collection was dependent on accurate documentation in medical records and clinical interpretation [8-10].

In addition, capturing of patients with bleeding events may not have taken place during hospital admission, as said anticoagulation would have been withheld or discontinued. Furthermore, the sample size of these studies was small and underpowered to detect a difference in the primary outcome which was major bleeding [8-10].

The study performed by Steuber and group was a retrospective cohort study that aimed to identify variables associated with bleeding events in hospitalized patients taking apixaban with ESRF. Unlike the other studies, patients on warfarin were excluded [14].

Moreover, in contrast to previous studies comparing warfarin with

Author	Study design	Primary Endpoint	Findings
Wang et.al (2016) [11]	Open label, single-dose study, patients on HD on 5 mg bdn=8	N/A	36% increase in apixaban exposure in HD patients compared to matched controls
Chang et.al (2016) [16]	open label, single-dose study patients on HD on 10 mg od.	N/A	44% increase in apixaban exposure compared to matched controls
Reed et.al (2017) [10]	Retrospective cohort study single center 74 patients on Apixaban 50 patients warfarin n= 124	Bleeding events	Apixaban group fewer overall bleeding events than warfarin. (18.9% vs 42%) p=0.01 major bleeding events less frequent in apixaban than warfarin. (5.4% vs 22.0%)
Sarrat et.al (2017) [8]	Retrospective cohort study single center 40 patients on apixaban 120 patients on warfarin. n=160	Bleeding events	Apixaban group fewer bleeding events. 7 major bleeding events warfarin, 0 in apixaban p=0.34 (5.8% vs 12.5%) apixaban and warfarin non -major bleeding events. p=0.17
Schafer et.al (2017) [12]	Retrospective cohort Stage IV, V, HD patients n=604	Bleeding events -Primary outcome within 3/12 -Secondary outcome major bleeding Ischemic stroke Recurrence of VTE within 3-12 months	Apixaban and warfarin similar bleeding rates at 3 months Warfarin higher bleeding rates at more than 6 months
Chokesuwattanaskul et.al (2017) [13]	Meta-analysis Safety and efficacy of warfarin vs apixaban in patients with ESRF N=43850	N/A	Apixaban lower risk of bleeding CKD/ESRF; Pooled OR 0.42 (95% CI 0.28-0.61) Dialysis; Pooled OR 0.27 (95%CI 0.07-0.95)
Steuber et.al (2017) [14]	Retrospective cohort multi-center Correlational analysis and logistic regression to identify variables for bleeding. n=114	N/A	Bleeding events in 17 patients. Logistic regression; bleeding events increased by outpatient apixaban OR 13.07 (95% CI 1.54-110.54) Increased total daily dose of Apixaban OR =1.72 (95% CI 1.20-2.48) total HD sessions receiving apixaban OR =2.04 (95% CI 1.06-3.92)
Mavrakanas et.al (2017) [1]	open label comparative study in dialysis patients 2.5 vs 5 mg bd dosing n=12 (7 vs 5)	N/A	Apixaban 2.5 mg comparable to 5 mg bd in patients with preserved renal functions Apixaban 5 mg bd associated with supratherapeutic levels.
Stanton et.al (2017) [9]	Retrospective matched cohort Apixaban vs Warfarin 73 patients on apixaban 73 patients on warfarin n=146	Major Bleeding	No significant difference in occurrence/rate of bleeding Occurrence of stroke similar
Konstantinos et.al (2018) [17]	Retrospective cohort (USRDS data) 2351 patients on apixaban 23,172 patients on warfarin n=25,523	Stroke/systemic embolism Major bleeding Death	Apixaban associated with lower risk of major bleeding compared with warfarin. 19.7 vs 22.9 per 100 patient years. Apixaban not associated with reduced mortality. HR 0.85 (95 CI 0.71-1.01)
Garza-Mayers et.al (2018) [18]	Retrospective case series Apixaban use in ESRF patients with calciphylaxis n=20	N/A	Apixaban safe and alternative to warfarin in patients with ESRF and calciphylaxis. 3/20 patients with bleeding.

Table 1: Literature Review of Apixaban in Dialysis Patients.

apixaban, results of this study suggested increased risk of bleeding with apixaban. A weak correlation was observed for higher cumulative apixaban exposure, increased number of hemodialysis sessions whilst on apixaban and increased length of stay (LOS). Logistic regression of the data revealed that composite bleeding events were increased independently by continuation of apixaban in the outpatient setting, increased total daily use of apixaban and total dialysis sessions whilst receiving apixaban [14].

There were several limiting factors that were noted by the authors. These factors included a small sample size with a small patient population, which made the task of evaluating variables associated with increased bleeding risk difficult [14]. Additionally, the authors noted the presence of outliers which further influenced the risk of bleeding. Another limitation identified was the duration of the study. The study focused on inpatients only which made the duration of the study short. Also, the variables correlated with increased bleeding were observed up to hospital discharge only. As a result, the authors had argued that the bleeding rates were not able to be accurately measured in the study [14].

Compared with previous studies that compared warfarin with apixaban, Steuber and company concluded that apixaban use in ESRF patients should prompt concern to the treating clinician and that additional evaluation of its use in ESRF patients is needed [14]. There are 2 upcoming randomized controlled trials comparing warfarin and apixaban therapy in dialysis patients; AXADIA-AFNET 8 and RENAL-AF.

The AXADIA-AFNET 8 study is a prospective phase III b trial currently in progress in Germany. In this trial, a total of 222 patients will be randomized in an open labelled 1:1 design to receive apixaban 2.5 mg twice daily or dose adjusted warfarin therapy according to target INR;(2-3).

All patients are to be treated and followed up for a minimum of 6 months up to a maximum of 24 months. The primary outcome of the study is major or clinically relevant non-major bleeding or death of any cause. Secondary outcomes include stroke, endovascular weather and other thrombotic events [15].

The RENAL-AF trial is a prospective randomized openlabel end point trial which will be completely blinded. The primary objective of the study is comparing the safety of apixaban versus warfarin, regarding major bleeding or clinical relevant non-major bleeding in patients with non-valvular AF and ESRF. The primary outcome is International society of thrombosis and hemostasis (ISTH) major bleeding and clinically relevant non-major bleeding. Enrollment for the study has been completed. 155 patients have been enrolled into the study.

Conclusion

There is an increase in the use of Apixaban amongst patients with ESRF on hemodialysis. Although approved by the US FDA in 2014, there is much conjecture about its role and safety in dialysis patients. Several questions remain. Dosage remains an uncertainty with no definitive dose established, likewise the incidence rate of major bleeding events with apixaban in a large population over a period, is still a concern.

Results from AXADIA-AFNET8 and RENAL-AF are eagerly awaited. Till then, selection of anticoagulation should be individualized allowing for patient factors, to determine the decision whilst contemplating the risks and benefits of each agent.

References

1. Mavrakanas T, Samer C, Nessim S, et al. Apixaban pharmacokinetics at steady state in Hemodialy-sis Patients. J Am Soc Nephrol. 2017; 28: 2241-2248.
2. Stamellou E, Floege J. Novel oral anticoagulants in patients with Chronic Kidney Disease and Atrial Fibrillation. Nephrol Dial Transplant. 2018; 33: 1683-1689.
3. Bansal v, Herzog G, et al. Oral Anticoagulants to prevent stroke in non-valvular atrial fibrillation in patients with CKD stage 5D: An NKF-KDQI controversies Report. Am J Kidney Dis. 2017; 70: 859-868.
4. Masson P, Kelly P, Craig J, et al. Risk of stroke in patients with ESRD. Clin J Am Soc Nephrol. 2015; 10: 1585-1592.
5. Nishimura M, Hsu J. Non-Vitamin K Antagonists Oral Anticoagulants in Patients with Atrial Fibril-lation and End-Stage Renal Disease. Am J Cardiol. 2018; 121: 131-140.
6. Chan K, Giugliano R, Patel M, et al. Non-vitamin K Anticoagulant agents in patients with ad-vanced chronic kidney disease or on dialysis with AF. J Am Coll Cardiol.2016; 67: 2888-28899.
7. Bhatia HS, Hsu JC, Kim RJ. Atrial Fibrillation and Chronic Kidney Disease: A review of options for Therapeutic Anticoagulation to reduce thromboembolic risk. Clin cardiol. 2018; 10: 1395-1402.
8. Sarrat S, Nesbit R, Moyne R. Safety Outcomes with Apixaban compared with Warfarin in patients with End-Stage Renal Disease. Annals of Pharmacotherapy. 2017; 51: 445-450.
9. Stanton B, Barasch N, Tellor K, et al. Comparison of the safety and effectiveness of Apixaban ver-sus Warfarin in patients with severe renal impairment. Pharmacotherapy. 2017; 37: 412-419.
10. Reed D, Palkimas S, Hockman R, et al. Safety and effectiveness of Apixaban compared to warfarin in dialysis patients. Res Prac Thromb Haemost. 2018; 2: 291-298.
11. Wang X, Marbury T, Wang J, et al. Pharmacokinetics, pharmacodynamics and safety of Apixaban in subjects with End-Stage Renal Disease on Hemodialysis. J Clin Pharmacol. 2016; 56: 628-636.
12. Schafer J, Casey A, Dupre K, et al. Safety and Efficacy of Apixaban versus Warfarin in patients with Advanced Chronic Kidney Disease. Annals of Pharmacotherapy. 2018; 52: 1078-1084.
13. Chokesuwattanaskul R, Thongprayson C, Tanawattiwat T, et al. Safety and efficacy of apixaban versus warfarin in patients with end-stage renal disease: Meta-analysis. Pacing Clin Electrophysiol. 2018; 41: 627-634.
14. Steuber T, Schiltz D, Cairns A, et al. A Multicenter Analysis

of Factors associated with Apixaban-Related Bleeding in Hospitalized Patients with End-Stage Renal Disease on Hemodialysis. Annals of Pharmacotherapy. 2017; 51: 954-960.
15. Reinecke H, Jurgensmeyer S, Englebertz C, et al. Design and Rationale of a randomized controlled trial comparing apixaban to phenprocoumon in patients with atrial fibrillation and chronic hemodial-ysis; the AXADIA-AFNET 8 study. BMJ Open 2018; 10: 8.
16. Chang M, Yu Z, Wang J, et al. Effect of renal impairment on the pharmacokinetics, pharmacody-namics and safety of apixaban. J Clin Pharmacol 2016; 56: 647-645.
17. Konstantinos C, Zhang X, Eckard A, et al. Outcomes associated with Apixaban use in End-stage Kidney Disease Patients with Atrial Fibrillation in the United States. Circulation 2018; 138: 1519-1528.
18. Garza-Mayers A, Shah R, Sykes D, et al. The successful use of Apixaban in Dialysis patients who require anticoagulation: A retrospective analysis. Am J Nephrol. 2018; 48: 163-171.