Joanne Nadhem
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Outcomes Associated with Apixaban Use in Patients with End-Stage Kidney Disease and Atrial Fibrillation in the United States

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Funding	The national institute of the digestive and diabetes and kidney diseases through national institutes of health contract	
Background/ Objective(s)	**Background:** End stage kidney disease (ESKD) increases thromboembolic risk among patients with atrial fibrillation (AF), and AF has been associated with poor outcome in ESKD. Dialysis-dependent ESKD patients have been excluded from AF clinical trials with DOACs use and safety concerns have been rising with the use of Dabigatran and Rivaroxaban and yet no studies have been conducted for the use of Apixaban in this patients' population. **Study Objective:** This study is conducted to determine patters of apixaban use and the associated outcomes in dialysis dependent patients with ESKD and AF compared to warfarin.	
Methods		
Study design /enrollment	Retrospective cohort study consisted of 25523 patients, 23172 patients received warfarin, 2351 were prescribed Apixaban with 56% receiving 2.5 mg twice daily and 44% receiving standard dose of 5mg twice daily.	
Inclusion/ Exclusion Criteria	**Inclusion:** Continuous Medicare parts A B D enrollment, Medicare as primary insurer in the 12 months before the first anticoagulation prescription, patients with inpatient or outpatient international classification of the disease, patients with AF diagnosis within 1 years before the anticoagulation prescription, patients with intermittent hemodialysis or peritoneal dialysis, comparing of warfarin to apixaban only	**Exclusion:** Patients with mitral stenosis or heart valve replacement/repair procedure before the anticoagulation prescription, patients with repaired or bio prosthetic heart valves, patients with an anticoagulation prescription of 1 year to 30 days before their first AF diagnosis
Treatment arms/ intervention and follow up	**Treatment arms/intervention:** Patients were prescribed daily dose of warfarin, 1317 patients received 5mg twice a day dose of apixaban and 1034 patients were prescribed Apixaban 2.5 mg twice a day. **Follow-up:** Until the end of the study which is 5 years (December 31, 2015), or death or censoring	
Endpoints	**Primary endpoint:** Ischemic stroke or systemic embolism whichever occurred first, **Secondary endpoint:** major bleeding, gastrointestinal bleeding, intracranial bleeding, and death.	
Statistical Analysis	**Statistical analysis methods:** Prognostic score matching of (1:3) was used to account for the differences in patient characteristics effecting prescribing Apixaban over warfarin. Kaplan-Meier curve presented the survival free of an event between Apixaban and warfarin which was then compared to log-rank testing. Hazard rations and Cox regression analysis was used for each outcome associated between the prescribed anticoagulation and the time of event. Secondary analysis was preformed to exclude the patients that were originally prescribed warfarin then switched to apixaban.	
Results		
Baseline characteristics	**Baseline Characteristics (what does the average patient look like)** Age (68), Male (54.3%), White (66%), Hemodialysis (94.6%), Time on dialysis ≥ 3 years (49.4%), No Pre-ESKD nephrology care (47.1%), Hypertension comorbidity (99.6%), B-blockers as one of the baseline medications (41.7%)	
Results for each endpoint	**Primary outcomes:** the event rates for stroke/SE were 12.4 and 11.8 per 100 patient-years for the apixaban and warfarin groups respectively with no difference in survival free of stroke/SE between groups p=0.29 HR 0.88(0.69-1.12) **Secondary outcomes:** The event rates for major bleeding were 19.7 and 22.9 per 100 patient-years for the apixaban and warfarin groups respectively with HR 0.72 favoring	

	apixaban 95%CI: 0.59-0.87 p<0.001. Rest of outcomes were non-significantly different. In matched cohorts of apixaban 5 mg twice a day and warfarin, apixaban was associated with significant lower risk of incident stroke/SE (HR, 0.64; 95% CI, 0.42-0.97; P= 0.04), major bleeding (HR, 0.71; 95% CI, 0.53-0.95; P= 0.02), and death (HR, 0.63; 95% CI, 0.46-0.85; P= 0.03). In matched cohorts of apixaban 2.5 mg twice a day and warfarin, apixaban was associated with lower risk of major bleeding (HR, 0.71; 95% CI, 0.56-0.91; P= 0.007), and no significant differences in stroke/SE or death
Discussion/ interpretation	Prognostic testing was used to account for the differences in patient characteristics effecting prescribing Apixaban over warfarin. Statistically significant results of lower risk of major bleeding was associated with Apixaban use over warfarin. This finding is supported by many clinical trials and clinical practice that excluded the ESKD-dialysis patients, but with the finding from the study, this patient population can potentially benefit from the use of Apixaban, but future randomized trial should be conducted to investigate the benefits. When the standard dose of Apixaban (5mg twice daily) was compared to its reduced dose (2.5 mg twice daily), significantly lower Stroke/SE and death risks was obtained with the use of the standard dose. Upon these findings, the FDA has approved the standard dose of Apixaban for this group of patients. However, guidelines are waiting for future studies to be conducted until changes can be made.
Author's Conclusion	**Authors' Conclusion**: This study has provided significant results associated with safety and efficacy of Apixaban use over warfarin where significant reduction of major bleeding risk is associated with the standard dose of Apixaban 5mg twice daily, and significant reductions in thromboembolic risk and death rate when the standard dose was compared with the reduced dose. Further studies need to be conducted to further investigate these findings. This study provided significant results that should be taken under consideration when prescribing warfarin vs Apixaban. However, the nature of this study being a retrospective cohort makes it difficult for guidelines to make changes, but it can be useful for future randomized studies when conducted, given the favored outcomes of standard dose of Apixaban.
Critique	**Author's Strengths:** supported the findings with other trials and clinical practice, appropriate tastings were conducted, and p values provided, adjusted for the differences in baselines characteristics between groups, first study to include ESKD dialysis-dependent patients. **Author's limitations:** absence of observed bleeding rates between the two dosed groups suggestive of selective prescribing, study did not include a group not receiving any anticoagulants, minor bleeds were not included in the study, short follow up period because of the censoring, adherence rate was not measured between groups, unclear whether Apixaban was temporarily discontinues before dialysis, small number of peritoneal dialysis. **Study generalizability/applicability:** According to GoodRx, the lowest price patients have to pay for a 30-day supply of Apixaban is $472.81 compared to warfarin being $4 for a 30-day supply. The huge price difference can affect patient's preference. However, patients should be educated on the safety concerns associated with warfarin and the benefits of Apixaban over it which can significantly impact adherence. According to 2019 ACC/AHA/HRS guidelines, the use of warfarin or Apixaban might be reasonable in dialysis dependent patients with AF and further studies need to be conducted. The study did not result in many significant outcomes as desired. However, it can serve as a tool for future randomized studies to be conducted.