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

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### Abstract

**Background**—Patients with end-stage kidney disease (ESKD) on dialysis were excluded from clinical trials of direct oral anticoagulants for atrial fibrillation (AF). Recent data have raised concern regarding the safety of dabigatran and rivaroxaban, but apixaban has not been evaluated despite current labeling supporting its use in this population. The goal of this study was to

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determine patterns of apixaban use and its associated outcomes in dialysis-dependent ESKD patients with AF.

**Methods**—We performed a retrospective cohort study of Medicare beneficiaries included in the United States Renal Data System (October 2010 to December 2015). Eligible patients were those with ESKD and AF undergoing dialysis who initiated treatment with an oral anticoagulant. Due to the small number of dabigatran and rivaroxaban users, outcomes were assessed only in patients treated with apixaban or warfarin. Apixaban and warfarin patients were matched (1:3) based on prognostic score. Differences between groups in survival free of stroke or systemic embolism, major bleeding, gastrointestinal bleeding, intracranial bleeding, and death were assessed using Kaplan-Meier analyses. Hazard ratios (HR) and 95% confidence intervals (CI) were derived from Cox regression analyses.

**Results**—The study population consisted of 25,523 patients (45.7% women; age 68.2±11.9 years), including 2,351 patients on apixaban and 23,172 patients on warfarin. An annual increase in apixaban prescriptions was observed following its marketing approval in the end of 2012, such that 26.6% of new anticoagulant prescriptions in 2015 were for apixaban. In matched cohorts, there was no difference in the risks of stroke/systemic embolism between apixaban and warfarin (HR 0.88, 95% CI 0.69–1.12; P=0.29), but apixaban was associated with significantly lower risk of major bleeding (HR 0.72, 95% CI 0.59–0.87; P<0.001). In sensitivity analyses, standard dose apixaban (5 mg twice a day; n=1,034) was associated with significantly lower risks of stroke/systemic embolism and death as compared with either reduced dose apixaban (2.5 mg twice a day; n=1,317; HR 0.61, 95% CI 0.37–0.98, P=0.04 for stroke/systemic embolism; and HR 0.64, 95% CI 0.45–0.92, P=0.01 for death) or warfarin (HR 0.64, 95% CI 0.42–0.97, P=0.04 for stroke/systemic embolism; and HR 0.63, 95% CI 0.46–0.85, P=0.003 for death).

**Conclusions**—Among ESKD patients with AF on dialysis, apixaban use may be associated with lower risk of major bleeding compared with warfarin, with a standard 5 mg twice a day dose also associated with reductions in thromboembolic and mortality risk.

## Keywords

atrial fibrillation; anticoagulation; dialysis; stroke prevention; bleeding

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## Introduction

End-stage kidney disease (ESKD) increases thromboembolic risk among patients with atrial fibrillation (AF),<sup>1</sup> and AF has been associated with poor outcomes in ESKD.<sup>2, 3</sup> However, the prevention of AF-related morbidity in the dialysis-dependent ESKD population is challenging. Use of warfarin in dialysis patients may be associated with higher rates of bleeding compared with other populations and some observational studies have even questioned its overall effectiveness in preventing strokes in dialysis patients with AF.<sup>4, 5</sup> Thus, uncertainty remains regarding the optimal utilization of anticoagulation for stroke prophylaxis in ESKD patients with AF.

The direct oral anticoagulants (DOAC) have changed the landscape of stroke prevention in AF in the general population, and these drugs have been widely adopted in recent years.<sup>6, 7</sup> However, DOACs have varying degrees of renal clearance and their safety and effectiveness

in ESKD is uncertain. The pivotal trials that were the basis of the Food and Drug Administration (FDA) approval of DOACs in the United States did not enroll patients with ESKD.<sup>8–11</sup> Therefore, use of DOACs for AF in ESKD patients on dialysis is not endorsed by American or European professional guidelines, and warfarin remains the recommended agent for those considered suitable for anticoagulation.<sup>12–14</sup> Early data suggest, however, that off-label use of dabigatran and rivaroxaban in dialysis patients is occurring in routine clinical practice and may be associated with adverse outcomes.<sup>15</sup> No data regarding utilization of apixaban and its associated clinical outcomes exist to date. However, based on pharmacokinetic data, the FDA approved an updated labeling recommending standard dose apixaban in hemodialysis patients.

Accordingly, goals of the present study were to 1) characterize contemporary use of apixaban in patients with AF and ESKD undergoing dialysis in the United States, and 2) determine its associations with measures of clinical safety and effectiveness in this population as compared with warfarin.

## Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. This study was performed under the United States Renal Data System (USRDS) Coordinating Center contract with the NIH-NIDDK; research being performed as part of the contract has been approved by the University of Michigan Institutional Review Board. As data for the USRDS components are collected by federal mandate, there are no individual patient consent requirements.

### Data source and study population

The study population was derived from the USRDS, a national system that collects, analyzes, and distributes information about chronic kidney disease, including ESKD, in the United States. Among patients with ESKD included in USRDS, we used Medicare Part D prescription information to identify patients who were prescribed dabigatran, rivaroxaban, apixaban, or warfarin between October 2010 (coinciding with the initial approval of dabigatran) and December 2015. We restricted the population to patients with 1) continuous Medicare Parts A, B and D enrollment and 2) Medicare as primary insurer in the 12 months prior to the first anticoagulant prescription. Furthermore, we identified eligible patients with an inpatient or outpatient International Classification of Diseases, Revisions Ninth or Tenth (ICD-9 or ICD-10) diagnosis code for AF or atrial flutter<sup>16</sup> (collectively referred to as AF in this study) during the same period, excluding patients with mitral stenosis or heart valve replacement/repair procedure before the anticoagulant prescription in accordance with the 2014 ACC/AHA/HRS definition of “valvular” AF.<sup>12</sup> Even though the DOACs are emerging as safe and effective in patients with repaired or bioprosthetic heart valves,<sup>17</sup> we excluded these patients because data supporting their use in this population arose in or after 2015. Thus, these patients may have been more likely to receive warfarin rather than DOACs during the period of this study.

We only included patients with AF diagnosis within 1 year before the anticoagulant prescription and excluded patients with an anticoagulant prescription 1 year to 30 days before their first AF diagnosis in order to exclude anticoagulation prescriptions for indications other than AF. For example, patients with a remote diagnosis claim for AF that was isolated and non-recurrent (such as a peri-operative AF episode) may have been prescribed anticoagulation subsequently for another indication. The requirement for temporal proximity of the AF diagnosis and the anticoagulation start also increases the specificity of the diagnosis claims-based approach for definition of the AF cohort. Finally, we restricted the eligible population to patients who were on dialysis (intermittent hemodialysis or peritoneal dialysis) at the time of the anticoagulation prescription (see Supplementary Table 1 and Supplementary Figure 1 for further details on the cohort selection process).

Because we identified a small number of patients with dabigatran (n=260) and rivaroxaban (n=328) prescriptions and since the outcomes with the use of these medications in dialysis patients have been previously addressed,<sup>15</sup> we restricted our analyses only to comparisons of apixaban and warfarin.

### **Baseline variables**

Using the CMS-2728 ESKD Medical Evidence form, we documented characteristics of ESKD care, such as number of years on dialysis, duration of pre-ESKD nephrology care and type of medical coverage (private vs non-private). Comorbidities were ascertained based on ICD9 and ICD10 diagnosis codes from Medicare Parts A and B claims (1 inpatient or 2 outpatient claims within 1 year before the anticoagulation prescription) and the use of 16 classes of concomitant medications was documented by using Part D prescription information. Baseline medications were considered as concomitant if a patient had residual supply (based on fill date and available number of refills) at the time of the initial anticoagulation prescription. Of note, aspirin is not captured accurately in prescriptions claims because many patients obtain aspirin over the counter; therefore, use of aspirin was unavailable.

### **Follow-up and outcome definitions**

The date of the initial anticoagulation prescription was considered time 0 for this analysis. In order to maximize capture of new apixaban prescriptions, patients who were originally prescribed warfarin and then switched to apixaban were included only in the apixaban group with time 0 the date of the first apixaban prescription. Patients were followed until study end (December 31, 2015), or until death or censoring. Patients were censored at follow-up for the following reasons: expiration of anticoagulation prescription or >30-day gap between prescription refills (accounting for total days and number of refills supplied); discontinuation of dialysis because of kidney function recovery or kidney transplantation (unless a patient died within 21 days of dialysis discontinuation, in which case this was considered a death rather than censored event); switch from apixaban to warfarin or to a different DOAC; lapse of Medicare Part A, B, or D enrollment, or lapse of Medicare as primary payer status; incidence of a heart valve diagnosis or procedure code any time after time 0.

We assessed the following incident outcomes after time 0 using inpatient claims in the primary or secondary diagnosis position: ischemic stroke or systemic embolism (SE), whichever occurred first; major bleeding; gastrointestinal (GI) bleeding; intracranial bleeding; and death. Bleeding was considered major when it was associated with a critical site code (such as intracranial), need for blood product transfusion based on a procedure code during the same admission, or death.<sup>18, 19</sup> Further details on diagnosis codes and outcomes definitions are provided in Supplementary Table 1.

### Statistical analysis

We report the overall number of eligible dialysis patients with AF prescribed anticoagulants and we present trends of new apixaban prescriptions per year relative to dabigatran, rivaroxaban, and warfarin over the study period. Categorical variables are reported as frequencies and percentages, whereas continuous variables are reported as means and standard deviations.

In order to account for differences in patient characteristics that may affect the decision to prescribe apixaban rather than warfarin, we constructed matched cohorts for apixaban and warfarin. Matching was based on the prognostic score,<sup>20</sup> the outcome-based analog of the propensity score. For each patient, a score is computed that reflects outcome risk as a function of the adjustment covariates (and independent of treatment status). We used prognostic score matching given its straightforward implementation in regression modeling.<sup>21, 22</sup> For a given outcome, the prognostic score was obtained from a regression model that included all available baseline variables (Table 1) and was fit to patients in the warfarin group (i.e., control group cohort). Each apixaban patient was then matched to 3 warfarin patients using nearest neighborhood caliper matching with a caliper equal to 0.1 of the standard deviation of the prognostic score. Survival free of an event in the matched apixaban and warfarin groups was represented with Kaplan-Meier curves and compared with log-rank testing, treating death as competing outcome. For each outcome, we calculated hazard ratios (HR) and 95% confidence intervals (CI) from univariable Cox regression analyses for the association between the prescribed anticoagulant and the time to event in the matched apixaban and warfarin cohorts. Anticoagulant group was the only predictor variable in these analyses. All outcome analyses were “on treatment” as patients were censored if they switched from apixaban to warfarin or to another DOAC.

The main analysis was performed in prognostic-score matched cohorts. In a secondary analysis, the comparison between apixaban and warfarin for the outcomes of interest was also performed with multivariable Cox regression analysis in the overall (unmatched) apixaban and warfarin cohorts. All baseline variables listed in Table 1 were included as covariates in that multivariable model. In addition, because some patients in the apixaban group may have been originally prescribed warfarin and then switched to apixaban, we performed a sensitivity analysis that excluded these patients from the apixaban group.

Analyses were performed in R Statistical Software version 3.4.1 (Foundation for Statistical Computing, Vienna, Austria) and Stata version 14.1 (StataCorp, College Station, TX).  $P < 0.05$  was considered statistically significant.

## Subgroup and dose-specific analyses

We performed pre-specified subgroup analyses for the comparisons of apixaban vs warfarin defined by the following variables: age ( $\geq 75$  or  $<75$  years), sex, diabetes mellitus, history of cerebrovascular accident (CVA), history of major bleeding, obesity, dialysis modality, and possible interacting medications.<sup>23</sup> In an exploratory and pre-specified sensitivity analysis, we investigated the comparative associations of the standard (5 mg) apixaban dose and the reduced (2.5 mg) dose. Similarly to the main analysis, each dose-specific apixaban cohort was matched separately to a warfarin cohort (apixaban:warfarin 1:3) using a prognostic score for each outcome.

In the subgroup and dose-specific analyses, association estimates were obtained from univariable Cox regression analyses with anticoagulant drug exposure as the only predictor variable. The association estimates between each subgroup and between the “apixaban 5 mg vs warfarin” and “apixaban 2.5 mg vs warfarin” analyses for each outcome were compared using interaction testing based on the Cochran’s Q heterogeneity statistic. Due to the multiple tested comparisons, a P-value of  $<0.05$  (rather than the more common  $P<0.10$  for this test) was considered statistically significant, i.e. indicating that the associations of apixaban as compared with warfarin are different in the examined treatment groups. Further, we also performed a direct comparison of the two doses restricted to the apixaban patients by fitting a multivariable Cox regression model including the apixaban dose as a predictor variable along with age, sex, prior CVA, and prior major bleeding as covariates.

## Results

### Study population and trends of DOAC use

A total of 26,111 patients with ESKD on dialysis and a diagnosis of AF were prescribed an oral anticoagulant during the study period. A detailed description of the cohort selection process is shown in Supplementary Figure 1. In 2013, shortly after the approval of apixaban for patients with AF in the United States, there was a significant increase in the number of new DOAC prescriptions per year, predominantly apixaban, with a corresponding decline in warfarin use (Figure 1). As a result, 26.6% of new anticoagulation prescriptions in 2015 were for apixaban. Overall, 2,939 patients (11.3% of anticoagulated patients) received a DOAC, with apixaban being the most commonly prescribed DOAC, followed by rivaroxaban and dabigatran. Further analysis and reporting of results in this study focuses on the 25,523 patients who were prescribed apixaban ( $n=2,351$ , 9.2%) or warfarin ( $n=23,172$ , 90.8%).

The mean age of the study population was  $68.2\pm 11.9$  years and 13,852 (54.3%) patients were male (Table 1). A minority of patients underwent peritoneal dialysis ( $n=1,377$ ; 5.4%), while the rest were on hemodialysis. A total of 8,461 (33.2%) patients had prior CVA and 2,536 (9.9%) patients had prior major bleeding. The mean CHA<sub>2</sub>DS<sub>2</sub>VASc score was  $5.2\pm 1.8$ .

## Outcomes

Supplementary Table 2 shows the baseline characteristics of the apixaban and warfarin cohorts after matching was performed based on prognostic scores specific to each outcome, whereas the distributions of the prognostic scores before and after cohort matching are shown in Supplementary Figure 2. In addition, Supplementary Tables 3–4 demonstrate that the baseline characteristics and event rates of the warfarin group in the study years 2010–2012 were not different from those in the period 2013–2015 (i.e. the period coinciding with the start and uptake of apixaban prescriptions).

In the matched cohorts of apixaban (n=2,351) and warfarin (n=7,053), the rates of censoring due to expiration of the prescription or >30-day gap between prescriptions were high in both the apixaban and warfarin groups (62.4% and 72.5%, respectively). The majority of these censorings occurred in the first 12 months after the prescription (60.9% and 66.4%, respectively), whereas another 5.6% and 8.9% of patients in the apixaban and warfarin groups, respectively, died in the first 12 months. The average time on apixaban was 105 days and the average time on warfarin was 157 days before death or censoring.

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 (log-rank P=0.29, Figure 2). In Cox regression analyses treating death as competing risk, the HR (95% CI) for apixaban versus warfarin was 0.88 (0.69–1.12; P=0.29) for stroke/SE (Table 2). The event rates for major bleeding were 19.7 and 22.9 per 100 patient-years for the apixaban and warfarin groups, respectively (HR 0.72 favoring apixaban, 95% CI 0.59–0.87; P<0.001). In addition, there was a non-significant trend towards less GI bleeding in the apixaban group (HR 0.86, 95% CI 0.72–1.02; P=0.09). No significant difference between the two groups was detected for intracranial bleeding (3.1 and 3.5 per 100 patient-years for apixaban and warfarin, respectively) with imprecise association estimate (HR 0.79, 95% CI 0.49–1.26; P=0.32). Finally, apixaban was associated with a non-significant trend towards reduced mortality risk (HR 0.85, 95% CI 0.71–1.01; P=0.06). Similar results were produced when analysis was performed with multivariable Cox regression modeling in the overall (unmatched) apixaban and warfarin cohorts (Supplementary Table 5). Results were also similar when 580 (24.7%) patients who were originally prescribed warfarin and then switched to apixaban were excluded from the apixaban group (Supplementary Table 6).

Results of pre-defined subgroup analyses were generally consistent with the main analysis across outcomes. We did not detect any significant differences in the associations of apixaban vs warfarin in any of the subgroups (Supplementary Table 7).

## Apixaban dosing

In the apixaban group, 1,034 (44%) patients were prescribed the standard dose (5 mg twice a day) and 1,317 (56%) patients were prescribed the reduced dose (2.5 mg twice a day). Characteristics of patients prescribed the standard and the reduced apixaban doses are shown in Supplementary Table 8.

The number of events and the event rates for each outcome in the matched cohorts of the dose-specific apixaban analyses are shown in Supplementary Table 9. In matched cohorts of apixaban 5 mg twice a day and warfarin, apixaban was associated with statistically significantly lower risks 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;  $P=0.003$ ). 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;  $P=0.007$ ), but there were no differences for stroke/SE (HR 1.11, 95% CI 0.82–1.50;  $P=0.49$ ) or death (HR 1.07, 95% CI 0.87–1.33;  $P=0.52$ ). Neither standard nor reduced apixaban doses were associated with significant differences for GI bleeding or intracranial bleeding as compared with warfarin (Figure 3). Differences of association estimates in the dose-specific analyses of apixaban versus warfarin were statistically significant for stroke/SE and death, indicating greater benefit for these outcomes with the standard as compared with the reduced apixaban dose (p-for-interaction 0.035 for stroke/SE and 0.005 for death). There was no difference between the two doses for major bleeding (p-for-interaction 0.99), GI bleeding (p-for-interaction 0.32) or intracranial bleeding (p-for-interaction 0.14).

In multivariable Cox regression analyses restricted to patients receiving apixaban and including dose as a predictor variable, the standard dose of apixaban was associated with lower risks of stroke/SE (HR 0.61, 95% CI 0.37–0.98;  $P=0.04$ ) and death (HR 0.64, 95% CI 0.45–0.92;  $P=0.01$ ) compared with the reduced dose. There were no differences for major bleeding, GI bleeding, or intracranial bleeding between doses (Supplementary Table 10).

## Discussion

In this observational study of >25,000 dialysis patients with AF from the nationwide USRDS, we found that DOACs were increasingly utilized despite a paucity of evidence on their safety and effectiveness in this population. This increase was largely driven by a sharp rise in prescriptions for apixaban since its approval in late 2012. Furthermore, we demonstrate for the first time in an ESKD population that apixaban use (unlike other DOACs) was associated with lower risks of major bleeding compared with warfarin even though the absolute rates of bleeding were high in both groups. Apixaban 5 mg twice a day, but not the 2.5 mg twice a day dose, was also associated with lower risks of thromboembolism and death compared with warfarin, while there was no difference in the lowering of major bleeding risk between the 2 doses. Discontinuation rates were high and about two thirds of patients in each group were no longer taking the anticoagulant 12 months after the initial prescription.

For decades, warfarin has been the mainstay of thromboembolic stroke prevention in dialysis patients with AF considered eligible for anticoagulation. However, dialysis patients are at increased risk of treatment-related bleeding likely due to underlying platelet dysfunction and warfarin may not confer a thromboembolic risk reduction of the same magnitude as in non-ESKD patients.<sup>4, 5</sup> The DOACs were shown to have more favorable bleeding risk profile compared with warfarin in clinical trials and in real-world analyses in non-ESKD patients, so there is reason to anticipate that these benefits may extend to those with ESKD.<sup>8–10, 24, 25</sup> However, they have varying degrees of renal clearance and there are no data from



randomized trials regarding their outcomes in ESKD patients. Nevertheless, a study utilizing the Fresenius Medical Care North America ESKD database reported that some dialysis patients received off-label dabigatran or rivaroxaban shortly after their marketing approval in the US, and their use in this population was associated with poor outcomes.<sup>15</sup>

In contrast to dabigatran and rivaroxaban, apixaban is less dependent on renal elimination (~27%) and is labeled for use in ESKD. In the seminal Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, apixaban was associated with lower risks of stroke, bleeding and death compared with warfarin. However, ESKD patients were excluded from ARISTOTLE.<sup>10</sup> The only evidence to guide use of apixaban in ESKD stems from a pharmacokinetic study where 8 hemodialysis patients and 8 normal subjects were administered apixaban 5 mg resulting in comparable maximum blood concentrations and anti-factor Xa activity. This study was too small to assess safety or effectiveness outcomes.<sup>26</sup> Based on pharmacokinetic data alone, the FDA approved an updated dosing recommendation for apixaban 5 mg twice daily in ESKD hemodialysis patients. The 2014 AHA/ACC/HRS AF guidelines do not make a recommendation for or against apixaban in ESKD patients<sup>12</sup> while the respective European guidelines recommend against DOACs in this setting.<sup>13, 14</sup> Despite the paucity of data and guideline recommendations, we observed a steep rise in apixaban prescriptions shortly after its approval such that it accounted for ~25% of new anticoagulation prescriptions for ESKD patients in 2015.

This study is the first investigation of the potential safety and effectiveness of apixaban in ESKD patients on dialysis. In our main analysis comprising any apixaban dose, apixaban users had almost 30% reduced risk of major bleeding as compared with a matched cohort of warfarin-treated patients. The benefit associated with apixaban use in reducing major bleeding events is consistent with the findings of the ARISTOTLE trial of non-ESKD patients with AF, both in terms of the direction and magnitude of effect (HR 0.69, 95% CI 0.60–0.80, for apixaban vs warfarin in ARISTOTLE).<sup>10</sup> Further, a secondary analysis of ARISTOTLE demonstrated that although bleeding rates were higher among patients with kidney dysfunction, the relative risk reduction of major bleeding with apixaban versus warfarin was greater among the patients in the lowest eGFR category (< 30 mL/min, non-ESKD).<sup>27</sup> Thus, the comparative safety of apixaban may be more pronounced in patients with more advanced kidney dysfunction. Apixaban appears to be safer across the spectrum of kidney function categories, possibly owing to its predominantly non-renal elimination. The results of the current analysis are in contradistinction to the bleeding-related morbidity and mortality attributed to dabigatran and rivaroxaban in a previous analysis of hemodialysis patients,<sup>15</sup> suggesting that the increased bleeding risk in ESKD is not a drug class effect for all DOACs.

In secondary dose-specific analyses, the standard apixaban 5 mg dose was associated with a significant risk reduction of thromboembolism as compared with warfarin. In contrast, the reduced apixaban 2.5 mg dose was not associated with a lower risk of thromboembolism as compared with warfarin. The finding of lower thromboembolic risk with the standard apixaban dose has been a consistent finding in the ARISTOTLE trial<sup>10</sup> and in real-world practice settings.<sup>25</sup> In accordance with pharmacokinetic data, these findings suggest that

ESKD alone is not a sufficient indication for dose reduction of apixaban.<sup>26</sup> Interestingly, the standard apixaban dose was associated with a lower mortality risk compared with warfarin. Lower mortality with the standard apixaban dose compared with warfarin has been reported in ARISTOTLE (where 95.3% of patients received the standard dose) and in an observational study,<sup>28</sup> whereas another observational study did not show mortality difference with that dose.<sup>29</sup> In contrast, reduced-dose apixaban has been associated with higher mortality compared with warfarin.<sup>30</sup> It is possible that the survival benefit with standard-dose apixaban over warfarin in our study reflects the lower thromboembolic and bleeding risks with that dose. However, due to the observational nature of this analysis, residual confounding from selective prescribing of the reduced dose in patients with higher perceived bleeding risk cannot be ruled out and the absence of an observed difference in the bleeding rates between the low-dose and standard-dose apixaban groups may be suggestive of such selective prescribing. The indications for dose reduction of apixaban in patients undergoing dialysis require further research.

Despite the favorable outcomes with apixaban as compared with warfarin, there is uncertainty regarding the net benefit of anticoagulation for stroke prevention in dialysis patients with AF. Older observational data suggested that warfarin may be ineffective in reducing strokes in hemodialysis patients and may even increase mortality<sup>31</sup> – although recent studies have questioned this observation.<sup>32</sup> Our analysis did not include a group of patients not receiving any anticoagulants and it was not designed to address the question of anticoagulation versus no anticoagulation. Such a retrospective comparison of on-treatment versus untreated groups carries significant risks of confounding that statistical adjustments or cohort matching may not eliminate completely. However, it should also be noted that bleeding rates were high even in the apixaban group. In particular, the intracranial bleeding rate of 3.1 per 100 patient-years is strikingly high in comparison to the rate of 0.33 per 100 patient-years in ARISTOTLE. Further, censoring due to expiration of anticoagulation prescription or >30-day gap between prescriptions was frequent even in the apixaban group resulting in overall short periods of treatment. Notably, the short follow-up periods until censoring or death in our cohort are consistent with the only other study examining the use of DOACs (dabigatran and rivaroxaban) in dialysis patients where the average times on dabigatran, rivaroxaban, and warfarin were 168 days, 106 days, and 175 days, respectively.<sup>15</sup> This may reflect the poor tolerability of any type of anticoagulation in this population, which can also manifest as nuisance bleeding, rather than major bleeding. Minor bleeding was not captured in this analysis, but it was recently reported to be as high as 20% in a general anticoagulated population.<sup>33</sup> Minor bleeding may be even more common and problematic in dialysis patients who require vascular access for dialysis several times weekly. Poor adherence may have also led to high rates of censoring due to >30-day gaps in prescriptions. The real-world adherence to anticoagulants is generally poor even with DOACs.<sup>34, 35</sup> The above issues further highlight the complexities of decision-making and net benefit assessment regarding anticoagulation in dialysis patients with AF. Future clinical trials are therefore needed to assess whether focusing on stroke reduction using apixaban or warfarin is worth the elevated risks of bleeding in this specific setting.

Other limitations of this analysis merit consideration. First, we did not have information on body weight at the time of apixaban prescription to determine the extent of inappropriate

dose reduction of apixaban, which may have contributed to the lack of thromboembolic reduction benefit compared with warfarin in that subgroup.<sup>19</sup> Second, due to the claims-based nature of our data, we could not determine the rates of adherence in the apixaban group or the time in therapeutic range in the warfarin group. In addition, we could not determine which non-oral anticoagulants were administered during dialysis or whether apixaban was routinely discontinued temporarily before a dialysis session. Finally, this analysis included only a small number of peritoneal dialysis patients. Outcomes of warfarin therapy may be superior in peritoneal dialysis compared with hemodialysis.<sup>36</sup>

In conclusion, apixaban is increasingly utilized among patients with ESKD on dialysis and AF in the United States and now accounts for more than a quarter of new anticoagulant prescriptions in this population. Apixaban may be associated with superior safety and effectiveness outcomes in this population as compared with warfarin. While both the standard and reduced apixaban doses were associated with lower major bleeding risks compared with warfarin, only the standard 5 mg dose was associated with reduced thromboembolic events and mortality. These findings require further investigation and confirmation in randomized controlled trials.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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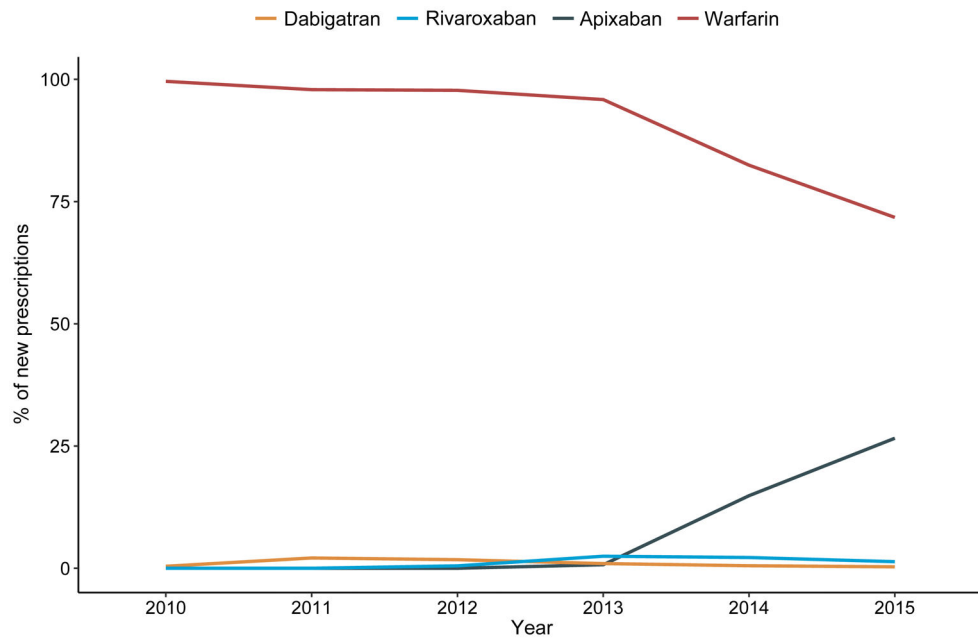
### **Clinical Perspective**

#### **What is new?**

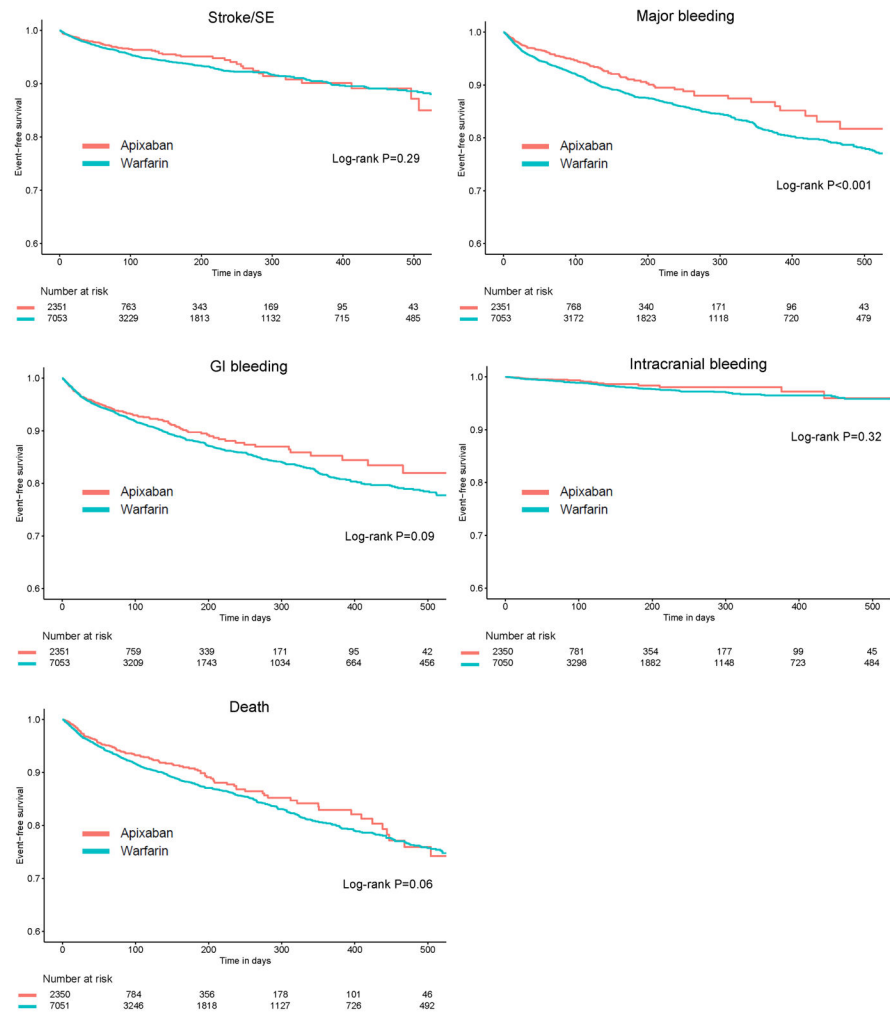
- The outcomes of apixaban use in dialysis patients are unknown.
- In this retrospective, prognostic score matched analysis of Medicare beneficiaries with end-stage kidney disease on dialysis and atrial fibrillation (AF), apixaban was associated with lower rates of major bleeding compared with warfarin, whereas there was no difference in stroke or systemic embolism.
- Patients on standard dose apixaban (5 mg) had lower rates of stroke and death compared with those on reduced dose apixaban (2.5 mg).

#### **What are the clinical implications?**

- Apixaban may be associated with superior safety and comparable effectiveness outcomes as warfarin in dialysis patients with AF.
- These findings require confirmation in randomized trials.

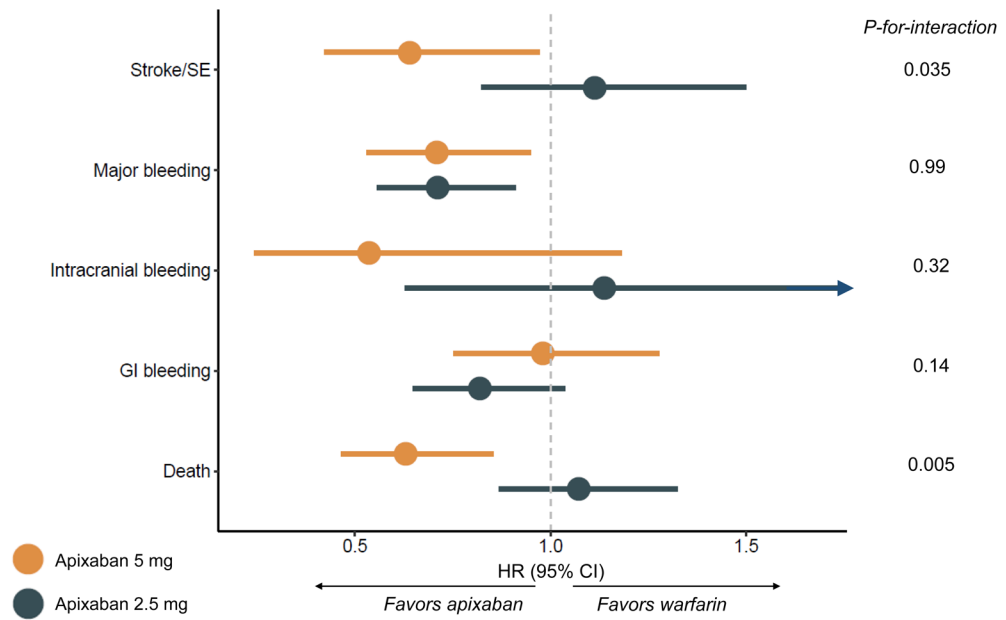


**Figure 1.** Trends in new oral anticoagulant prescriptions in AF patients with ESKD on dialysis in the United States (2010–2015).



**Figure 2.** Kaplan-Meier survival curves for the apixaban group and a prognostic-score matched warfarin cohort for stroke/SE, major bleeding, GI bleeding, intracranial bleeding and death.





**Figure 3.** Association estimates from dose-specific comparisons of apixaban versus warfarin. Hazard ratios and 95% confidence intervals are derived from Cox regression analyses in prognostic score-matched cohorts of apixaban 2.5 mg and apixaban 5 mg doses to warfarin. Abbreviations: SE, systemic embolism; GI, gastrointestinal; HR, hazard ratio; CI, confidence interval

**Table 1**

## Baseline characteristics in the overall eligible population

| Variable                    | Overall (n=25,523) | Apixaban (n=2,351) | Warfarin (n=23,172) |
|-----------------------------|--------------------|--------------------|---------------------|
| <i>Demographics</i>         |                    |                    |                     |
| Age (yrs)                   | 68.22 (11.89)      | 68.87 (11.49)      | 68.15 (11.93)       |
| Male                        | 13,852 (54.3)      | 1,280 (54.4)       | 12,572 (54.3)       |
| Race                        |                    |                    |                     |
| White                       | 16,837 (66.0)      | 1,595 (67.8)       | 15,242 (65.8)       |
| Black                       | 7,458 (29.2)       | 604 (25.7)         | 6,854 (29.6)        |
| Other                       | 1,228 (4.8)        | 152 (6.5)          | 1,076 (4.6)         |
| <i>Nephrology care</i>      |                    |                    |                     |
| Dialysis modality           |                    |                    |                     |
| Hemodialysis                | 24,146 (94.6)      | 2,216 (94.3)       | 21,930 (94.6)       |
| Peritoneal dialysis         | 1,377 (5.4)        | 135 (5.7)          | 1,242 (5.4)         |
| Time on dialysis            |                    |                    |                     |
| <1 year                     | 7,196 (28.2)       | 656 (27.9)         | 6,540 (28.2)        |
| 1 to <2 years               | 2,949 (11.6)       | 240 (10.2)         | 2,709 (11.7)        |
| 2 to <3 years               | 2,759 (10.8)       | 256 (10.9)         | 2,503 (10.8)        |
| 3 years                     | 12,619 (49.4)      | 1,199 (51.0)       | 11,420 (49.3)       |
| Private insurance           | 3,898 (15.3)       | 416 (17.7)         | 3,482 (15.0)        |
| Pre-ESKD nephrology care    |                    |                    |                     |
| None                        | 12,010 (47.1)      | 1,012 (43.0)       | 10,998 (47.5)       |
| <6 months                   | 2,842 (11.1)       | 283 (12.0)         | 2,559 (11.0)        |
| 6 to <12 months             | 4,374 (17.1)       | 422 (17.9)         | 3,952 (17.1)        |
| 12 months                   | 6,297 (24.7)       | 634 (27.0)         | 5,663 (24.4)        |
| <i>Comorbidities</i>        |                    |                    |                     |
| Hypertension                | 25,421 (99.6)      | 2,342 (99.6)       | 23,079 (99.6)       |
| Cerebrovascular event*      | 8,461 (33.2)       | 778 (33.1)         | 7,683 (33.2)        |
| Diabetes                    | 19,121 (74.9)      | 1,773 (75.4)       | 17,348 (74.9)       |
| Congestive heart failure    | 19,827 (77.7)      | 1,868 (79.5)       | 17,959 (77.5)       |
| SCD/VA                      | 3,339 (13.1)       | 279 (11.9)         | 3,060 (13.2)        |
| Peripheral arterial disease | 11,521 (45.1)      | 1,084 (46.1)       | 10,437 (45.0)       |
| Smoking                     | 9,797 (38.4)       | 978 (41.6)         | 8,819 (38.1)        |
| Hypothyroidism              | 461 (1.8)          | 90 (3.8)           | 371 (1.6)           |
| Liver disease               | 2,580 (10.1)       | 221 (9.4)          | 2,359 (10.2)        |
| Obesity                     | 5,526 (21.7)       | 590 (25.1)         | 4,936 (21.3)        |
| Venous thromboembolism      | 4,658 (18.3)       | 279 (11.9)         | 4,379 (18.9)        |
| Cancer                      | 3,848 (15.1)       | 330 (14.0)         | 3,518 (15.2)        |
| Anemia                      | 25,336 (99.3)      | 2,334 (99.3)       | 23,002 (99.3)       |

| Variable                                    | Overall (n=25,523) | Apixaban (n=2,351) | Warfarin (n=23,172) |
|---|--------------------|--------------------|---------------------|
| Myocardial infarction                       | 6,850 (26.8)       | 632 (26.9)         | 6,218 (26.8)        |
| Sleep apnea                                 | 5,399 (21.2)       | 550 (23.4)         | 4,849 (20.9)        |
| Prior major bleeding                        | 2,536 (9.9)        | 217 (9.2)          | 2,319 (10.0)        |
| Prior gastrointestinal bleeding             | 2,966 (11.6)       | 249 (10.6)         | 2,717 (11.7)        |
| CHA <sub>2</sub> DS <sub>2</sub> VASc score | 5.24 (1.79)        | 5.27 (1.77)        | 5.24 (1.79)         |
| <i>Baseline medications</i>                 |                    |                    |                     |
| Statin                                      | 6,174 (24.2)       | 553 (23.5)         | 5,621 (24.3)        |
| Non-statin lipid lowering                   | 649 (2.5)          | 44 (1.9)           | 605 (2.6)           |
| ACEi  | 3,195 (12.5)       | 213 (9.1)          | 2,982 (12.9)        |
| Angiotensin receptor blocker                | 1,474 (5.8)        | 156 (6.6)          | 1,318 (5.7)         |
| Beta-blocker                                | 10,645 (41.7)      | 925 (39.3)         | 9,720 (41.9)        |
| Calcium channel blocker                     | 5,946 (23.3)       | 530 (22.5)         | 5,416 (23.4)        |
| Diuretic                                    | 2,329 (9.1)        | 214 (9.1)          | 2,115 (9.1)         |
| Other antihypertensive                      | 3,689 (14.5)       | 332 (14.1)         | 3,357 (14.5)        |
| Antiarrhythmics                             | 5,616 (22.0)       | 538 (22.9)         | 5,078 (21.9)        |
| Antianginal vasodilator                     | 2,365 (9.3)        | 206 (8.8)          | 2,159 (9.3)         |
| Antiplatelet <sup>‡</sup>                   | 1,866 (7.3)        | 154 (6.6)          | 1,712 (7.4)         |
| NSAIDs                                      | 357 (1.4)          | 32 (1.4)           | 325 (1.4)           |
| Insulin                                     | 3,419 (13.4)       | 283 (12.0)         | 3,136 (13.5)        |
| Non-insulin diabetes drug                   | 1,320 (5.2)        | 126 (5.4)          | 1,194 (5.2)         |
| Proton pump inhibitor                       | 5,036 (19.7)       | 408 (17.4)         | 4,628 (20.0)        |
| Antidepressant                              | 3,787 (14.8)       | 307 (13.1)         | 3,480 (15.0)        |

Categorical variables are shown as n (%). Continuous variables are shown as mean (standard deviation).

None of the listed variables had a standardized mean difference >0.2 between the apixaban and warfarin groups.

\* Seven (0.3%) patients in the apixaban group and 57 (0.2%) patients in the warfarin group had hemorrhagic events. All other patients had ischemic events.

<sup>‡</sup> Clopidogrel (94.4%), prasugrel (2%), ticagrelor (1.7%), dipyridamole (1.7%) and ticlopidine (0.2%).

Abbreviations: ESKD, end-stage kidney disease; SCD/VA, sudden cardiac death/ventricular arrhythmia; ACEi, angiotensin converting enzyme inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; SMD, standardized mean difference

**Table 2**

Event rates and association estimates from Cox regression analyses in prognostic score-matched cohorts of apixaban and warfarin

|                       | Overall | Apixaban | Warfarin | HR (95% CI)      | p-value |
|-----------------------|---------|----------|----------|------------------|---------|
| Stroke/SE             |         |          |          |                  |         |
| N patients            | 9,404   | 2,351    | 7,053    |                  |         |
| N events              | 454     | 81       | 373      | 0.88 (0.69–1.12) | 0.29    |
| Event rate per 100 PY | 11.9    | 12.4     | 11.8     |                  |         |
| Major bleeding        |         |          |          |                  |         |
| N patients            | 9,404   | 2,351    | 7,053    |                  |         |
| N events              | 844     | 129      | 715      | 0.72 (0.59–0.87) | <0.001  |
| Event rate per 100 PY | 22.3    | 19.7     | 22.9     |                  |         |
| GI bleeding           |         |          |          |                  |         |
| N patients            | 9,404   | 2,351    | 7,053    |                  |         |
| N events              | 865     | 155      | 710      | 0.86 (0.72–1.02) | 0.09    |
| Event rate per 100 PY | 23.4    | 23.8     | 23.4     |                  |         |
| Intracranial bleeding |         |          |          |                  |         |
| N patients            | 9,400   | 2,350    | 7,050    |                  |         |
| N events              | 132     | 21       | 111      | 0.79 (0.49–1.26) | 0.32    |
| Event rate per 100 PY | 3.4     | 3.1      | 3.5      |                  |         |
| Death                 |         |          |          |                  |         |
| N patients            | 9,404   | 2,351    | 7,053    |                  |         |
| N events              | 912     | 159      | 753      | 0.85 (0.71–1.01) | 0.06    |
| Event rate per 100 PY | 24.7    | 23.7     | 24.9     |                  |         |

Abbreviations: PY, patient-years; HR, hazard ratio; CI, confidence interval

Association estimates are derived from univariable Cox regression analyses with drug exposure (apixaban or warfarin) as the only predictor variable. HR<1 favors apixaban.