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## Retrospective Cohort Study

## Effectiveness and safety of apixaban and rivaroxaban vs warfarin in patients with atrial fibrillation and chronic kidney disease

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Mehalingam V, India**Received:** May 19, 2023**Peer-review started:** May 19, 2023**First decision:** July 19, 2023**Revised:** July 26, 2023**Accepted:** September 26, 2023**Article in press:** September 26, 2023**Published online:** December 25, 2023**Sylvie Perreault**, Faculty of Pharmacy, University of Montreal, Quebec, Montreal H3C3J7, Canada**Laurie-Anne Boivin Proulx**, Department of Cardiology, Faculty of Medicine, University of Ottawa Heart Institute, Ontario, Ottawa K1Y4W7, Canada**Aurélie Lenglet**, Department of Pharmacy, Amiens-Picardie Hospital University Center, Amiens 80000, France**Aurélie Lenglet**, Faculty of Pharmacy, MP3CV Laboratory, UR7545, University of Picardie Jules Verne, Amiens 80000, France**Ziad A Massy**, Division of Nephrology, University of Paris Ouest -Versailles-Saint-Quentin-en-Yvelines (UVSQ), Villejuif, France., AP-HP Ambroise-Paré Hospital, Boulogne Billancourt/Paris 92104, France**Marc Dorais**, StatSciences Inc., Notre-Dame-de-l'Île-Perrot, Quebec, Montreal J7W 3K8, Canada**Corresponding author:** Sylvie Perreault, BPharm, MSc, PhD, Professor, Faculty of Pharmacy, University of Montreal, No. 2940 Chemin de Polytechnique, Quebec, Montreal H3C3J7, Canada. [sylvie.perreault@umontreal.ca](mailto:sylvie.perreault@umontreal.ca)**Abstract****BACKGROUND**

Randomized controlled trials (RCTs) of direct oral anticoagulants (DOACs) included a low proportion of atrial fibrillation (AF) patients with chronic kidney disease (CKD), and suggested that DOACs are safe and effective in patients with mild-to-moderate CKD. In a metaanalysis of RCTs and observational studies, DOACs were associated with better efficacy (*vs* warfarin) in early CKD and had similar efficacy and safety profiles in patients with stages IV-V CKD. But few studies have provided data on the safety and effectiveness of each DOAC *vs* warfarin in patients with stage III CKD. The effectiveness and safety of DOACs in those patients are still subject to debate.

**AIM**

To assess and compare the effectiveness and safety of apixaban and rivaroxaban *vs* warfarin in this patient population.

## METHODS

A cohort of patients with an inpatient or outpatient code for AF and stage III CKD who were newly prescribed apixaban and rivaroxaban was created using the administrative databases from the Quebec province of Canada between 2013 and 2017. The primary effectiveness outcome was a composite of ischemic stroke, systemic embolism, and death, whereas the primary safety outcome was a composite of major bleeding within a year of DOAC *vs* warfarin initiation. Treatment groups were compared in an under-treatment analysis using inverse probability of treatment weighting and Cox proportional hazards.

## RESULTS

A total of 8899 included patients filled out a new oral anticoagulation therapy claim; 3335 for warfarin and 5564 for DOACs. Compared with warfarin, 15 mg and 20 mg rivaroxaban presented a similar effectiveness and safety composite risk. Apixaban 5.0 mg was associated with a lower effectiveness composite risk [Hazard ratio (HR) 0.76; 95% confidence interval (CI): 0.65-0.88] and a similar safety risk (HR 0.94; 95%CI: 0.66-1.35). Apixaban 2.5 mg was associated with a similar effectiveness composite (HR 1.00; 95%CI: 0.79-1.26) and a lower safety risk (HR 0.65; 95%CI: 0.43-0.99). Although, apixaban 5.0 mg was associated with a better effectiveness (HR 0.76; 95%CI: 0.65-0.88), but a similar safety risk profile (HR 0.94; 95%CI: 0.66-1.35). The observed improvement in the effectiveness composite for apixaban 5.0 mg was driven by a reduction in mortality (HR 0.61; 95%CI: 0.43-0.88).

## CONCLUSION

In comparison with warfarin, rivaroxaban and apixaban appear to be effective and safe in AF patients with stage III CKD.

**Key Words:** Atrial fibrillation; Chronic kidney disease; Direct oral anticoagulant; Effectiveness; Safety; Warfarin

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**Core Tip:** Compared to warfarin, rivaroxaban and apixaban appear to be effective and safe in atrial fibrillation patients with stage III chronic kidney disease (CKD) in real world. Rivaroxaban 15 mg and 20 mg presented a similar effectiveness and safety composite risk. However, apixaban 2.5 mg might even have a better safety profile than warfarin, while apixaban 5.0 mg might have a better effectiveness profile than warfarin, to a reduction in deaths. Appropriately sized randomized controlled trials are needed to confirm these findings in stage III CKD patients.

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## INTRODUCTION

Patients with chronic kidney disease (CKD) often develop atrial fibrillation (AF) at a rate of more than twice that of the general population[1-3]. Because patients with both AF and CKD have a greater risk of systemic embolism and bleeding events, an effective therapy is challenging[4-6]. For patients with non-valvular AF (NVAf) requiring oral anticoagulation therapy (OAC), medical evidence suggests treatment with a direct oral anticoagulant (DOAC) over warfarin, including patients with stage I-IV CKD[7]. Despite these recommendations, warfarin remains the OAC of choice for most AF patients [8] as well as AF patients with moderate to severe CKD[9].

Although the randomized controlled trials (RCTs) of DOACs included a low proportion of AF patients with CKD, the results suggested that DOACs are safe and effective in patients with mild-to-moderate CKD (stages I-III CKD, using Cockcroft-Cault formula)[10-13]. In a meta-analysis of observational studies and RCTs, DOACs were found to be more effective (*vs* warfarin) in early CKD and had similar efficacy and safety profiles in patients with CKD stages IV-V as well as patients on dialysis[14]. Recent population-based studies of AF patients with CKD have also examined the effectiveness and safety of DOACs *vs* warfarin[15-22]. However, few of these studies examined the safety and effectiveness of individual DOACs *vs* warfarin, nor did they examine the impact of varying doses in patients with stage III CKD with respect to stroke, systemic embolic events, major bleeding, or death[16,23]. Therefore, we attempted to evaluate and compare the efficacy and safety of various DOACs, including low-dose rivaroxaban (15 mg once per day), standard-dose rivaroxaban (20 mg once per day), low-dose apixaban (2.5 mg twice per day), and standard-dose apixaban (5.0 mg twice per day) *vs* warfarin in AF patients with stage III CKD.

## MATERIALS AND METHODS

We analyzed several Quebec health care claims databases, in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[24]. The need for informed consent was waived by the local institutional research committee (University of Montreal, Montreal, Quebec, Canada). The study protocol complied with the ethical guidelines of the 1975 declaration of Helsinki and was approved by the institutional research committee of the University of Montreal.

### Data sources

We assembled a cohort of inpatients or outpatients using the Med-Echo administrative databases (hospital discharge reports), medical services of the Régie de l'Assurance Maladie du Québec (RAMQ), and RAMQ public drug plans, all databases administered by the RAMQ[25-28]. The databases were linked *via* encrypted health insurance numbers. Information from these databases provided a complete picture of hospital admissions, medical services, and medication used, if the patient was still living in the Quebec province.

### Population

We identified adult patients with AF from January 1, 2013, to December 31, 2017. AF was detected by searching for the international classification of diseases, 9<sup>th</sup> revision (ICD-9) codes 427.3, 427.31, or 427.32, or the international classification of diseases, 10<sup>th</sup> revision (ICD-10) code I48[29,30]. The first instance of AF coding was used to determine eligibility. The cohort was subsequently restricted to patients who filled a new prescription for rivaroxaban (15 mg or 20 mg once daily), apixaban (2.5 or 5.0 mg twice daily) or warfarin within a year of AF diagnosis. Few patients had a new prescription of either dabigatran or edoxaban, so they were not included in our analysis. The date of the first OAC claim was defined as the date of cohort entry. New OAC users were defined as those not exposed to any OACs in the year prior to the claim index date. Patients were also required to have had pharmacy coverage for at least 12 mo and enrollment in a drug health insurance plan for at least one year before cohort entry.

We also excluded patients with a code for any condition or procedure that might have impacted the choice of OAC and duration of treatment at discharge: Cardiac valve replacement or valve procedures in the five years before cohort entry; end-stage CKD (meaning being on dialysis), kidney transplant, dialysis, or coagulation deficiency in the three years before cohort entry; medical procedures (including cardiac catheterization, stent, coronary artery bypass grafting, cerebrovascular, or defibrillator) in the three months before cohort entry; deep vein thrombosis or orthopedic surgery in the six months before cohort entry.

Lastly, the cohort was restricted to patients with stage III CKD by using the algorithm 2 to identify CKD G3-5ND, and then applying the exclusion of CKD G4-5ND by using the algorithm 3 (as defined by a composite variable covering the ICD code, drug use, and consultations with a nephrologist, as identified in the administrative databases). The composite variable has been validated, with reference to medical chart reviews of older adults with CKD [the algorithm used for estimated glomerular filtration rate (eGFR) definition], and has presented good positive predictive values[31].

### Exposure

Treatment with an OAC was checked against the prescription fulfillment dates and the number of days of medication supplied for each fill. Exposure to treatment was considered in all analyses. We consider a gap of less than 30 d between the end of a treatment period and a new fill corresponded to continuous treatment. Patients were censored when they discontinued a treatment, switched to another OAC, or to another dose level. Allowing a gap in treatment of up to 30 d is reasonable because of the DOACs' short half-life. Taking this definition into account, the adherence rate over the 12-mo assessment period was at least 92% for all included patients. The patient's OAC exposure and censored status were updated every 30 d.

### Outcomes

The primary effectiveness outcome was a composite of ischemic stroke or systemic embolism (SE) and all-cause mortality. The primary safety outcome was a composite of major bleeding, defined as either intracranial hemorrhage, gastrointestinal bleeding, or major bleeding from other sites. The individual components of the safety and effectiveness outcomes were evaluated in a secondary analysis.

We identified the outcomes by screening the ICD-9 or ICD-10 codes for the primary diagnosis on inpatient claims (Supplementary Table 1). In earlier validation studies, these codes performed relatively well and gave positive predictive values of over 80%[32,33].

### Patient demographics and clinical characteristics

We documented demographic variables upon cohort entry and determined the associated morbidities from the inpatient and outpatient ICD-9 and ICD-10 diagnostic codes recorded in the three years preceding the cohort entry[30-32]. Next, we used the patients' characteristics and associated comorbidities to calculate the CHADS<sub>2</sub> score (Supplementary Tables 2 and 3)[34] and the modified HAS-BLED score (Supplementary Tables 2 and 4). The comorbidity burden was scored with the Charlson-Deyo Comorbidity Index[35,36]. A frailty score was also calculated from the modified elders risk assessment in the two years preceding cohort entry[37,38]. Lastly, we assessed all drug prescriptions filled in the two weeks preceding the cohort entry.

## Statistical analyses

Descriptive statistics were used to summarize the demographic and clinical characteristics of patients, according to the type of OAC used. The follow-up periods and the level of adherence were reported as the mean with standard deviation (SD) or the median with interquartile range. The adherence to treatment in the year of follow-up was calculated by dividing the total number of days of treatment by 365. When the dispensing periods overlapped, the full length of each filled claim was accounted for, and the start date of the second claim was shifted to the end of the previous claim.

For the main analyses of the primary effectiveness and safety composites in an on-treatment, we used an inverse probability of treatment weighting (IPTW) approach to account for differences in patient characteristics between treatment groups[39,40]. Four IPTW cohorts were created: (1) Rivaroxaban 15 mg *vs* warfarin; (2) rivaroxaban 20 mg *vs* warfarin; (3) apixaban 2.5 mg *vs* warfarin; and (4) apixaban 5.0 mg *vs* warfarin. We then used a multivariable logistic regression model to estimate the observed probability (according to propensity score matching) of being in the treatment group (rivaroxaban 15 mg, rivaroxaban 20 mg, apixaban 2.5 mg, and apixaban 5.0 mg), based on all the baseline covariates, and the impact of temporal trends accounted for in the analysis by including the date of cohort entry in the IPTW matching. By approximating the randomization used in RCTs, the IPTW approach establishes a pseudo-population, balances the treatment groups according to the covariates included in the model, and thus minimizes the impact of confounding biases in observational studies. All weights were stabilized by multiplying the IPTW weight by the marginal probability of being in the treatment group. Descriptive statistics were also used to summarize the baseline characteristics of each IPTW cohort. For baseline characteristics, only absolute standardized differences of 10% or more between the unadjusted cohort and the IPTW-adjusted cohort were considered meaningful[39]. We reported the outcomes per 100 person-years for each treatment in each IPTW population. Hazard ratios (HRs) with 95% CIs associated were estimated using Cox proportional hazards models for each of the four IPTW cohorts described above.

Patients were censored at the time of enrollment if they were in a non-governmental drug coverage plan, admitted to a long-term care facility, admitted to the hospital (for more than two weeks), or in the case of a safety or effectiveness endpoint or death (whichever occurred first). The patient's OAC exposure and censored status were updated every 30 d.

For the sensitivity analyses of the primary effectiveness and safety composites, we first estimated Cox proportional HRs for outcomes in an intent-to-treat analyses in which we removed the censoring criteria of drug discontinuation or switching, so that all patients were followed up for 365 d unless they were censored for another reason. We used an IPTW approach to account for differences in patient characteristics between treatment groups. We reported the outcomes per 100 person-years for each treatment in each IPTW population. HRs and 95% CIs associated were estimated using Cox proportional hazards models for each of the four IPTW cohorts described above.

Secondly, we provided a negative control outcomes analyses using the risk of diabetes complications (primary code of hospitalization (ICD-9: 250.1-250.9, 357.2, 366.41; ICD-10: E10-E14 excluding E10.9, E11.9, E12.9, E13.0, E14.9). Lastly, we calculated an E-value to assess the impact of unmeasured confounding[41]. The E-value indicates how strongly an unmeasured confounder would have to be associated with use of apixaban 2.5 mg, or apixaban 5.0 mg *vs* warfarin and the outcomes to reduce the observed effect to the null, depending on the measured covariates. All analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC). A biomedical statistician performed statistical review of the study.

## RESULTS

A total of 8899 included AF patients with stage III CKD filled a new OAC prescription: 3335 for warfarin, 744 for the 15-mg dose of rivaroxaban, 1064 for 20-mg rivaroxaban, 1674 for 2.5-mg apixaban, and 2082 for 5.0-mg apixaban (Figure 1). The frequency of warfarin prescriptions decreased over time and was associated with a concomitant increase in DOAC prescription (Figure 2). As of 2017, apixaban 5.0 mg was the most commonly initiated drug.

### Demographic and clinical characteristics

The patients' unadjusted characteristics are summarized in Supplementary Tables 5-8. Compared with warfarin users, rivaroxaban 15 mg users were slightly younger (mean  $\pm$  SD age: 83.0  $\pm$  8.5 *vs* 82.6  $\pm$  7.8, respectively) and had a lower mean  $\pm$  SD Charlson-Deyo Comorbidity index (6.1  $\pm$  3.4 *vs* 5.3  $\pm$  3.5, respectively), a lower mean  $\pm$  SD CHADS<sub>2</sub> score (3.1  $\pm$  1.2 *vs* 2.8  $\pm$  1.2, respectively) and a lower mean  $\pm$  SD HAS-BLED score of 3.6  $\pm$  1.3 *vs* 3.2  $\pm$  1.3, respectively. Compared with users of warfarin, rivaroxaban 20 mg users were younger (mean  $\pm$  SD age: 83.0  $\pm$  8.5 *vs* 74.2  $\pm$  9.2, respectively) and had a lower mean  $\pm$  SD Charlson-Deyo Comorbidity index (6.1  $\pm$  3.4 *vs* 4.7  $\pm$  3.5, respectively), a lower mean  $\pm$  SD CHADS<sub>2</sub> score (3.1  $\pm$  1.2 *vs* 2.3  $\pm$  1.2, respectively), and a lower mean  $\pm$  SD HAS-BLED score (3.6  $\pm$  1.3 *vs* 2.7  $\pm$  1.3, respectively). Compared with warfarin users, apixaban 2.5 mg users were older (mean  $\pm$  SD age: 83.0  $\pm$  8.5 *vs* 86.5  $\pm$  6.3, respectively), had a lower mean  $\pm$  SD Charlson-Deyo Comorbidity index (6.1  $\pm$  3.4 *vs* 5.4  $\pm$  3.3, respectively), a similar mean  $\pm$  SD CHADS<sub>2</sub> score of 3.1  $\pm$  1.2 *vs* 3.0  $\pm$  1.1, respectively), and a similar mean  $\pm$  SD HAS-BLED score of 3.6  $\pm$  1.3 *vs* 3.3  $\pm$  1.3, respectively. And, compared with users of warfarin, apixaban 5.0 mg users were also younger (mean  $\pm$  SD age: 83.0  $\pm$  8.5 *vs* 78.0  $\pm$  8.4, respectively), and had a lower mean  $\pm$  SD Charlson-Deyo Comorbidity index (6.1  $\pm$  3.4 *vs* 5.1  $\pm$  3.5, respectively), a lower mean  $\pm$  SD CHADS<sub>2</sub> score (3.1  $\pm$  1.2 *vs* 2.6  $\pm$  1.2, respectively), and a lower mean  $\pm$  SD HAS-BLED score (3.6  $\pm$  1.3 *vs* 3.0  $\pm$  1.3, respectively). As shown in Table 1, demographic and clinical characteristics of cohorts of new OAC users with stage III CKD after IPTW from 2013 to 2017 are well balanced.



**Total of patients in RAMQ database**

Extraction criteria: All patients aged 18 and older who received a diagnosis of atrial fibrillation (AF) (medical claim or hospitalization) between 2005 and 2017	353841
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**Inclusion criteria**

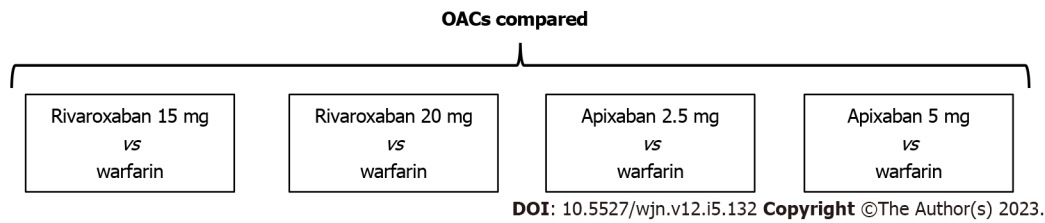
Diagnosis of AF (medical claim or hospitalization) between 2013 and 2017	119169	(Excluded) (234672)
At least one dispensation of oral anticoagulant (warfarin or DOAC) within the year following the AF diagnosis. The date of the first anticoagulant dispensation was defined as the claim index date	65329	(53840)
Complete coverage by the RAMQ drug plan for the year preceding the claim index date	65254	(75)
No warfarin and no DOAC in the year preceding the claim index date	49945	(15309)

**Exclusion criteria**

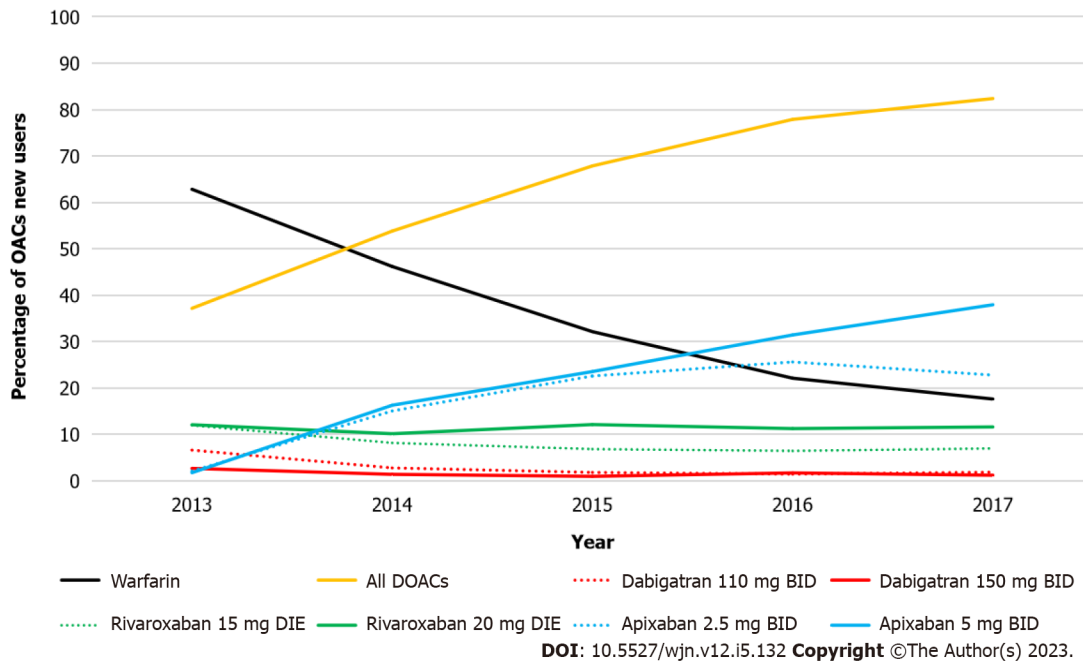
No valvular replacement/procedures in the 5 years preceding the claim index date	47685	(Excluded) (2260)
No end-stage renal disease or dialysis (for a minimal period of 3 continuous mo) in the 3 years preceding the claim index date	47498	(187)
No kidney transplant in the 3 years preceding the claim index date	47494	(4)
No coagulation deficiency in the 3 years preceding the claim index date	47480	(14)
No hip/knee/pelvis fracture in the 6 wk preceding the claim index date	46509	(971)
No catheterization, coronary cerebrovascular or defibrillator procedures during the 3 mo preceding the claim index date	41652	(4857)
No absence of chronic kidney disease stage III	9308	(32344)

**Among the 9308 patients**

Number of users of:	
Warfarin:	3335
Dabigatran 110 mg:	263
Dabigatran 150 mg:	146
Rivaroxaban 15 mg:	744
Rivaroxaban 20 mg:	1064
Apixaban 2.5 mg:	1674
Apixaban 5 mg:	2082



**Figure 1 Study flow chart.** No patients in the cohort received edoxaban, and patients using dabigatran were excluded for the low sample size between 2011-2017. DOAC: Direct oral anticoagulant; RAMQ: Régie d'Assurance Maladie du Québec.



**Figure 2 Changes in oral anticoagulant prescriptions from 2010 to 2017.** DOACs: Direct oral anticoagulants; OAC: Oral anticoagulant.

**Cumulative incidence in the IPTW cohorts**

As shown in Table 1 and Supplementary Tables 5-8, there were no significant differences in baseline characteristics between the IPTW treatment groups. In Figures 3 and 4, we show the cumulative incidence curves for the effectiveness and safety composite outcomes in the IPTW in an on-treatment analysis. The follow-up times and levels of adherence are shown in Supplementary Tables 9 and 10.

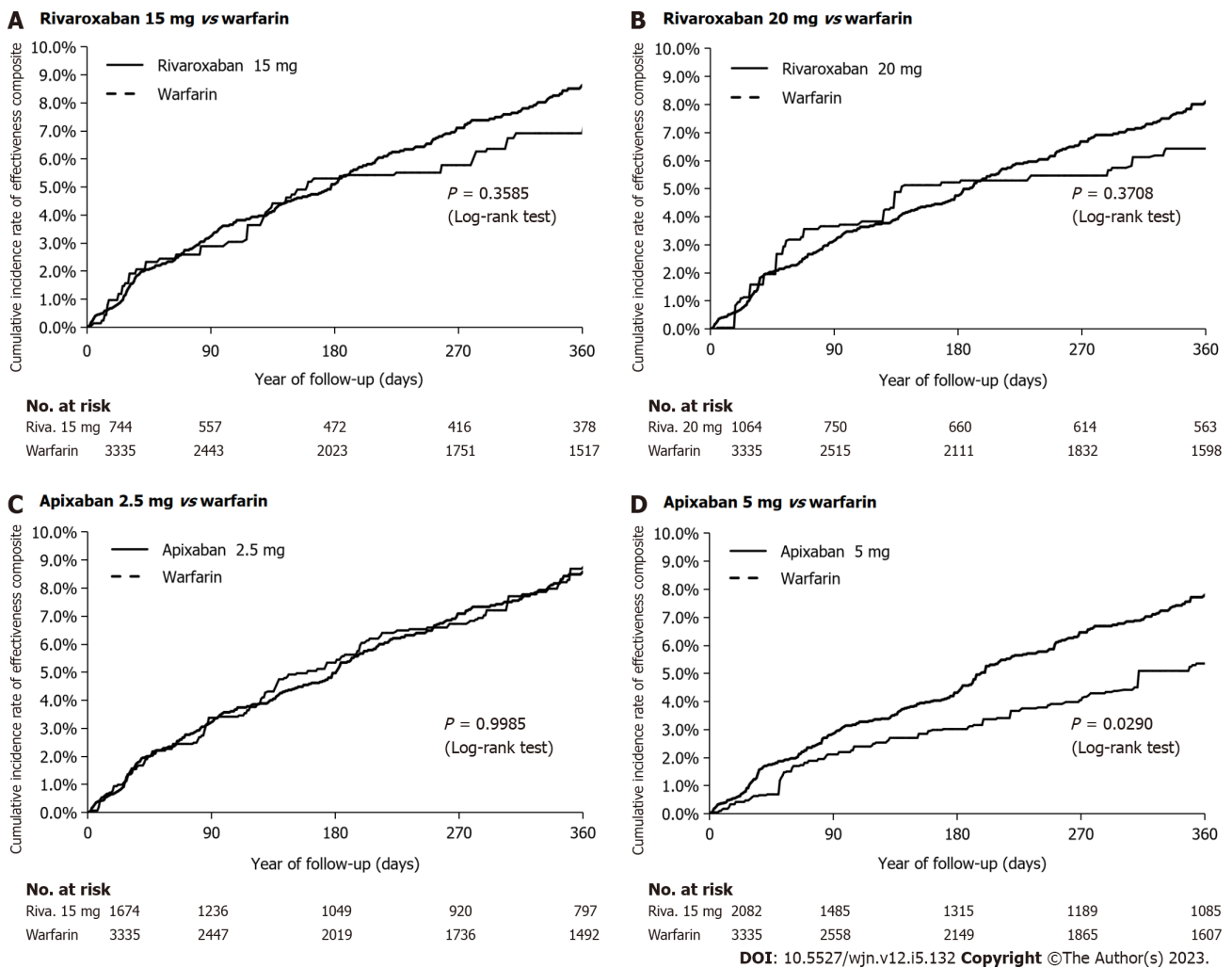
**HRs for effectiveness and safety outcomes in the IPTW cohorts**

The annual rates and HRs for the primary analyses of the safety and effectiveness composites in the IPTW treatment groups in an on-treatment are shown in Supplementary Table 11. With warfarin as the reference group, we found rivaroxaban 15 mg and 20 mg had a similar effectiveness composite (HR 0.84; 95%CI: 0.60-1.18 and HR 0.83; 95%CI: 0.61-1.13, respectively) (Figure 5); and similar safety profile (HR 1.13; 95%CI: 0.70-1.83 and HR 1.29; 95%CI: 0.84-1.95, respectively). Apixaban 2.5 mg was similarly effective (HR 1.00; 95%CI: 0.79-1.26), but had a better safety profile (HR 0.65; 95%CI: 0.43-0.99), while apixaban 5.0 mg was associated with a better effectiveness (HR 0.76; 95%CI: 0.65-0.88), but a similar safety profile (HR 0.94; 95%CI: 0.66-1.35). A reduction in mortality (HR 0.61; 95%CI: 0.43-0.88) accounted for the observed improvement in the effectiveness composite for apixaban 5.0 mg.

**Sensitivity analyses**

The annual rates and HRs for the analyses of the effectiveness and safety composites in the IPTW treatment groups in an intent-to-treat are shown in Supplementary Table 12. Under intent-to-treat analyses, rivaroxaban 20 mg presented a better effectiveness composite (HR 0.79; 95%CI: 0.65-0.96), and the observed improvement in the effectiveness composite was due to a reduction in mortality (HR 0.72; 95%CI: 0.58-0.91) (Figure 6). Those point estimates are in relation to those observed in the IPTW treatment groups in an on-treatment, and the level of significance is linked to an increase of the number of events, particularly among those in the warfarin group.

As shown in Table 2, warfarin and DOACs had a similar rate of hospitalization per 100 person-years for diabetes complications, with no significant HRs. As we expected, all groups had similar results. In Table 3, we found the E-value closest to boundary 1 for the effectiveness composite and apixaban 5.0 mg vs warfarin was 1.53; hence, we suspect an



**Figure 3** Cumulative rate of the primary effectiveness outcome after inverse probability of treatment weighting in an on-treatment analysis. A: Rivaroxaban 15 mg vs warfarin; B: Rivaroxaban 20 mg vs warfarin; C: Apixaban 2.5 mg vs warfarin; D: Apixaban 5 mg vs warfarin.

unmeasured confounder occurring 1.53 times more frequently in patients receiving apixaban 5.0 mg than in patients receiving warfarin, thus increasing the rate of safety composite events by a factor of 1.53. The high E-values indicate that the statistically significant results are robust with regards to unmeasured confounding factors.

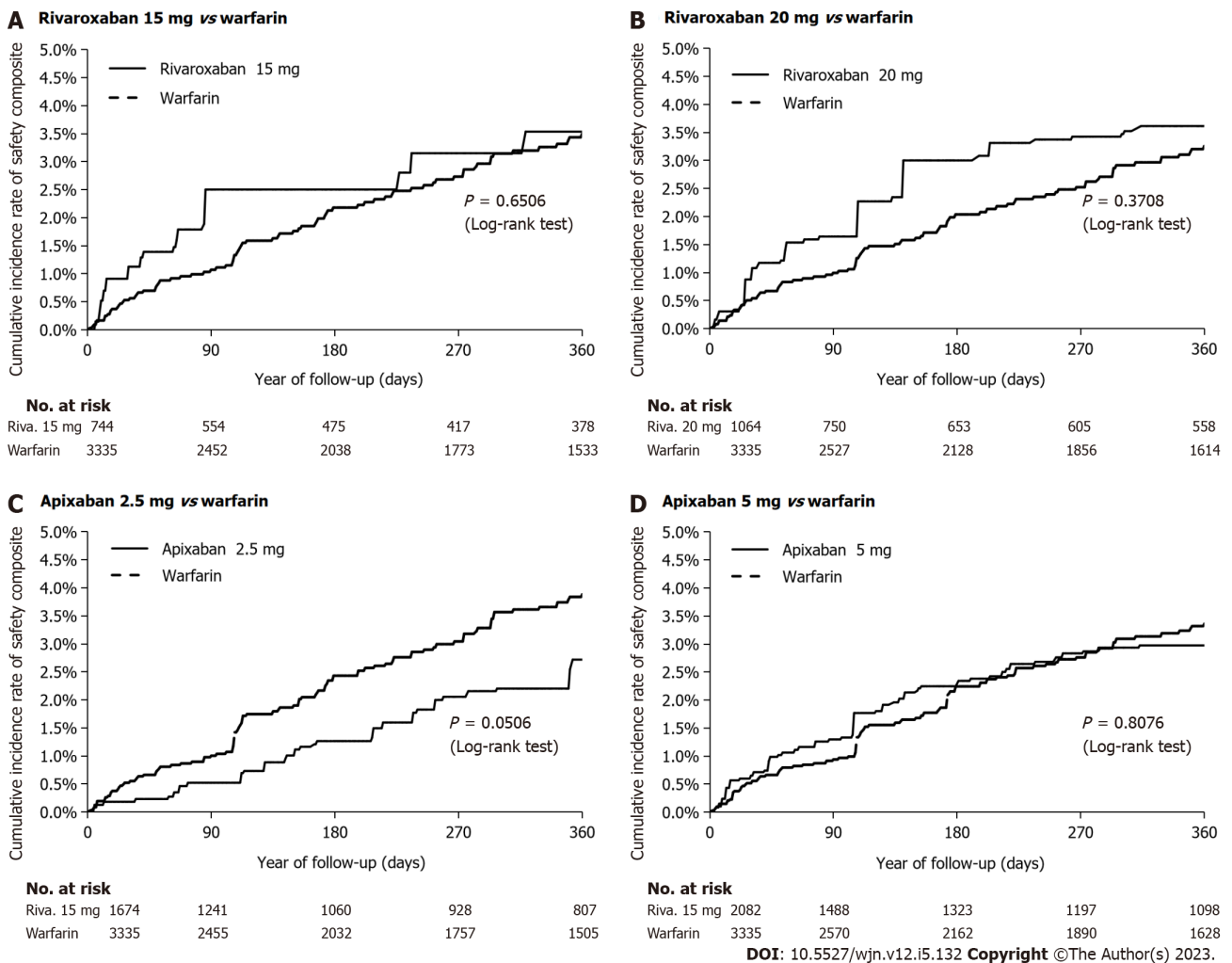
## DISCUSSION

The results of our cohort analysis provided several insights relevant to clinical practice. Firstly, DOAC prescription increased substantially over time, whereas warfarin prescription fell concomitantly. Nevertheless, over 10% of AF patients with stage III CKD were still being prescribed warfarin in 2017. Secondly, relative to warfarin, rivaroxaban appears to be safe and effective in AF patients with stage III CKD. Apixaban 2.5 mg might even have better safety profiles than warfarin; and for apixaban 5.0 mg, this difference in effectiveness was mainly driven by a reduction in deaths.

The increase in DOAC prescription is in line with the latest AF guidelines from the Canadian society of cardiology and European society of cardiology, which recommend DOAC therapy over warfarin for patients with NVAf and stage III CKD[7,42]. This recommendation is based on a sub-analysis of AF RCTs, which demonstrated that along with the DOACs' logistic advantages vs dose-adjusted warfarin, these drugs are no worse or even better than warfarin for reducing the risk of AF-associated stroke or SE in AF patients with stage III CKD, with a lower or similar major bleeding risk[10-13]. A meta-analysis of RCTs and observational trials of AF patients with CKD showed that DOACs can provide a significant reduction in stroke/SE (HR 0.81; 95%CI: 0.68-0.97) and a nonsignificant reduction in major bleeding (HR 0.87; 95%CI: 0.69-1.05) in stage III CKD, when compared with warfarin[14].

Very little data exists regarding the effectiveness and safety of individual DOACs and the impact of various doses on patients with stage III CKD. Most of the existing data comes from observational studies[15-21]. Data from a sub-analysis of the Aristotle trial demonstrated that apixaban can effectively reduce the occurrence of stroke, major bleeding, and mortality compared to that of warfarin among patients with impaired renal function ( $\leq 50$  mL/min), when using creatinine-based estimates of GFR[13]. Wetmore *et al*[23] examined Medicare data from 22739 AF patients with stage III-





**Figure 4** Cumulative rate of the primary safety outcome after inverse probability of treatment weighting in an on-treatment analysis. A: Rivaroxaban 15 mg vs warfarin; B: Rivaroxaban 20 mg vs warfarin; C: Apixaban 2.5 mg vs warfarin; D: Apixaban 5 mg vs warfarin.

IV CKD and found that apixaban reduced stroke/SE (HR 0.70; 95% CI: 0.51-0.96) and risk of major bleeding (HR 0.47; 95% CI: 0.37-0.59). Using electronic health record data, Fu *et al*[43] examined the safety and effectiveness of rivaroxaban vs warfarin in 555 stage III CKD AF patients and found a similar risk of stroke (HR 0.60; 95% CI: 0.23-1.56) and major bleeding (HR 0.73; 95% CI: 0.38-1.41). A subanalysis of the ROCKET-AF trial found that rivaroxaban 20 mg daily had a better efficacy profile in patients with a creatinine clearance (CrCl) of 50 mL/min or more but that rivaroxaban 15 mg daily had a similar efficacy profile in patients with a CrCl of 30-49 mL/min; the safety profile was similar for both CrCl categories[44]. Nonetheless, dose adjustment yielded results consistent with the overall trial, when compared with dose-adjusted warfarin[11]. Wetmore *et al*[23] found that in AF patients with stage III-IV CKD, rivaroxaban was associated with similar risks of stroke/SE (HR 0.80; 95% CI: 0.54-1.17) and major bleeding (HR 1.05; 95% CI: 0.85-1.30). However, the investigators did not report data on the effectiveness and safety of each dose level of DOAC vs warfarin in stage III CKD AF patients specifically.

Likewise, very few published studies have examined the impact of DOAC therapy vs warfarin on mortality, and also per specific dose. Makani *et al*[17] examined electronic health record data on 21733 AF patients with CKD and found that DOACs reduce the risk of all-cause mortality for all CKD classes. When examining individual DOACs in an on-treatment analysis, Wetmore *et al*[23] found a reduction in mortality for apixaban (HR 0.90; 95% CI: 0.84-0.96) but not for rivaroxaban (HR 0.95; 95% CI: 0.88-1.02) or dabigatran (HR 0.92; 95% CI: 0.84-1.01). These results might be explained by the fact that DOACs are associated with a lower incidence of renal adverse outcomes in patients with mild-to-moderate CKD, including declined renal function, a doubling in the serum creatinine level, or acute kidney injury[45]. Moreover, warfarin treatment is associated with an elevated risk of vascular and cardiac valve calcification[46-48], which in turn is associated with greater cardiovascular morbidity and mortality rates[49].

The present study has several strengths. First, it is one of the few large, real-world comparative studies of the effectiveness, safety, and mortality rates associated with individual DOACs and their dose levels vs warfarin. Second, we analyzed the single-payer health care claims database across the province of Quebec. Given that: (1) Most such clinical events result in an administrative claim, and (2) few patients in the province travel outside of Quebec for medical treatment, the study may likely have captured the vast majority of clinically significant events; which might not have been the case in previous single-hospital or single-insurer studies. Third, we performed IPTW cohorts by accounting for

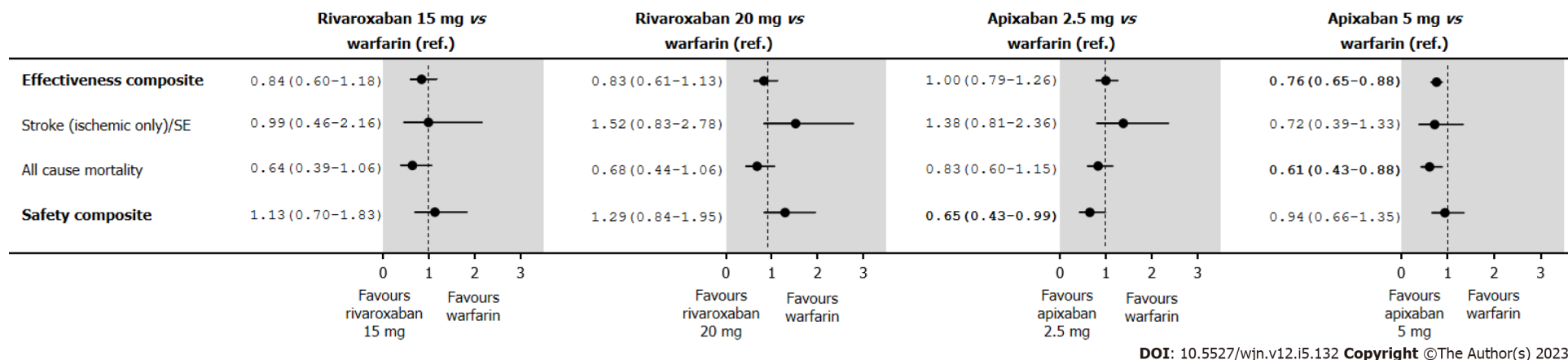


Figure 5 Hazard ratios (95% confidence interval) of effectiveness and safety outcomes in an on-treatment after inverse probability of treatment weighting of new oral anticoagulant users with stage III chronic kidney disease. SE: Systemic embolism.

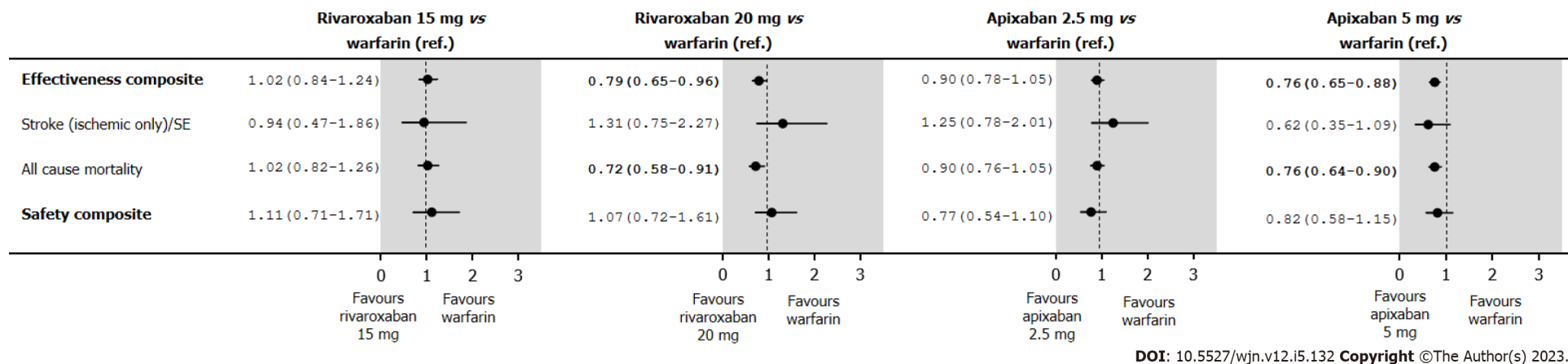


Figure 6 Hazard ratios (95% confidence interval) of effectiveness and safety outcomes in an intent-to-treat after inverse probability of treatment weighting of new oral anticoagulant users with stage III chronic kidney disease. SE: Systemic embolism.

**Table 1 Demographic and clinical characteristics of cohorts of new oral anticoagulation therapy users with stage III chronic kidney disease after inverse probability of treatment weighting from 2013 to 2017 (mean ± SD, %)**

	IPTW warfarin and rivaroxaban 15 mg		IPTW warfarin and rivaroxaban 20 mg		IPTW warfarin and apixaban 2.5 mg		IPTW warfarin and apixaban 5.0 mg	
	Warfarin (n = 3335)	Rivaroxaban 15 mg (n = 744)	Warfarin (n = 3335)	Rivaroxaban 20 mg (n = 1064)	Warfarin (n = 3335)	Apixaban 2.5 mg (n = 1674)	Warfarin (n = 3335)	Apixaban 5.0 mg (n = 2082)
Age (yr)	82.9 ± 8.6	82.8 ± 7.7	80.1 ± 10.8	79.1 ± 8.2	84.3 ± 8.3	84.5 ± 7.2	80.4 ± 10.2	80.2 ± 7.8
Female sex	56.5	56.5	54.8	52.3	58.2	59.0	54.3	53.9
CHA <sub>2</sub> DS <sub>2</sub> -VASc	4.1 ± 1.4	4.1 ± 1.3	3.9 ± 1.5	3.9 ± 1.5	4.2 ± 1.4	4.2 ± 1.3	3.9 ± 1.5	3.8 ± 1.3
CHADS <sub>2</sub> score	3.0 ± 1.2	3.0 ± 1.2	2.8 ± 1.3	2.9 ± 1.2	3.0 ± 1.2	3.0 ± 1.1	2.9 ± 1.3	2.8 ± 1.1
HAS-BLED score	3.5 ± 1.3	3.5 ± 1.3	3.3 ± 1.5	3.4 ± 1.4	3.5 ± 1.3	3.5 ± 1.2	3.3 ± 1.4	3.3 ± 1.2
Charlson-Deyo Comorbidity Index	5.9 ± 3.4	6.0 ± 3.6	5.7 ± 3.5	5.9 ± 3.6	5.9 ± 3.4	5.8 ± 3.2	5.7 ± 3.5	5.7 ± 3.4
Frailty score	18.6 ± 6.2	18.6 ± 5.9	17.7 ± 6.7	17.6 ± 6.3	18.8 ± 6.2	18.8 ± 5.8	17.7 ± 6.6	17.5 ± 6.1
Comorbidities (including the index hospitalization and the three years prior to cohort entry)								
Hypertension	86.2	86.5	83.9	85.2	86.9	86.9	84.5	84.0
Coronary artery disease	64.7	65.1	62.0	62.7	64.1	62.5	61.2	58.4
Acute myocardial infarction	21.1	20.3	18.9	17.5	20.9	20.9	18.8	15.8
Chronic heart failure	56.2	56.7	53.4	54.2	56.1	56.6	53.3	53.6
Cardiomyopathy	7.9	8.3	7.7	8.7	7.4	7.1	8.2	7.8
Other cardiac dysrhythmias	18.8	19.0	17.8	16.4	19.2	19.4	18.2	18.0
Valvular heart disease	26.1	27.1	24.9	24.6	25.7	25.6	23.5	22.3
Stroke/TIA	16.9	17.2	16.0	17.3	16.8	16.1	15.9	15.0
Peripheral vascular disease	27.7	27.5	26.6	25.9	27.3	26.2	25.6	23.2
Dyslipidemia	54.4	53.3	54.2	55.8	53.9	54.0	55.5	53.8
Diabetes	45.1	46.1	46.4	49.9	43.1	42.7	47.3	46.9
Major bleeding	38.5	38.3	37.0	39.3	38.3	37.0	36.2	34.8
Major intracranial bleeding	3.7	3.7	3.5	5.7	3.9	3.5	4.2	3.8
Major gastrointestinal bleeding	8.3	9.5	7.9	7.7	8.7	8.1	7.9	7.9
Other sites of major bleeding	32.0	30.9	30.9	32.4	31.8	31.2	29.8	28.8
Liver disease	2.6	2.8	2.9	2.9	2.5	2.4	2.7	2.5
Chronic obstructive pulmonary disease/asthma	44.0	44.2	46.0	49.7	42.2	42.1	44.5	45.3
Depression	11.8	11.5	12.2	11.8	11.7	11.4	12.1	11.9
Medical procedures (three years prior to cohort entry)								
Cardiac catheterization	5.0	5.4	5.2	5.3	5.0	4.9	6.4	6.4
Percutaneous coronary intervention-stent	4.1	3.9	3.8	4.1	3.8	4.0	4.1	4.0
Coronary artery bypass grafting	0.6	0.5	0.8	0.7	0.5	0.5	1.2	1.2
Implantable cardiac device	0.1	0.1	< 0.1	< 0.1	< 0.1	0.0	< 0.1	0.0

Medications (two weeks prior to cohort entry)								
Statin	51.0	51.2	51.1	52.9	50.0	47.9	50.6	50.4
Antiplatelet	8.7	8.5	8.1	8.9	8.3	7.4	8.1	7.9
Low-dose ASA	35.3	35.5	34.8	35.2	35.6	34.9	33.9	33.4
Proton pump inhibitors	49.7	49.6	47.8	46.9	50.0	49.1	46.4	44.7
NSAIDs	0.9	0.9	1.3	1.6	0.9	1.0	1.2	1.2
Digoxin	9.3	10.6	9.1	10.1	9.2	9.0	8.9	8.7
Amiodarone	9.6	9.3	8.6	6.1	9.3	9.8	8.8	8.0
Antidepressants	10.5	10.1	10.4	10.5	10.6	10.3	10.2	10.4
Beta-blockers	62.5	63.1	61.4	61.1	63.8	62.8	62.4	62.5
Calcium channel blockers	42.9	42.6	41.9	39.8	42.7	43.2	41.4	41.0
Inhibitors of the renin-angiotensin system	37.5	36.9	38.1	38.5	38.0	36.5	38.0	38.3
Diuretics	60.5	60.3	61.4	61.0	61.0	60.8	60.3	60.4
Loop diuretics	56.2	55.8	57.0	54.4	56.4	56.7	55.4	56.3
Antidiabetics	27.4	28.0	28.7	30.3	26.5	25.8	29.2	29.3
Health medical services (one year prior to cohort entry)								
Consultations with specialist physicians	1.2 ± 2.4	1.2 ± 1.9	1.2 ± 2.5	1.2 ± 2.3	1.2 ± 2.4	1.2 ± 2.2	1.2 ± 2.6	1.2 ± 1.8
Consultations with family physicians	1.3 ± 3.3	1.3 ± 2.8	1.2 ± 3.1	1.2 ± 2.5	1.3 ± 3.4	1.4 ± 3.0	1.2 ± 3.2	1.2 ± 2.6
Emergency visits	3.4 ± 3.1	3.4 ± 2.9	3.4 ± 3.4	3.5 ± 3.0	3.4 ± 3.1	3.5 ± 2.9	3.4 ± 3.3	3.3 ± 2.8
Health hospital services (three years prior to cohort entry)								
All-cause hospital admission	2.5 ± 2.1	2.5 ± 2.0	2.5 ± 2.4	2.6 ± 2.2	2.4 ± 2.0	2.5 ± 1.9	2.5 ± 2.3	2.4 ± 2.0

ASA: Acetylsalicylic acid; CKD: Chronic kidney disease; IPTW: Inverse probability of treatment weighting; NSAIDs: Nonsteroidal anti-inflammatory drugs; OAC: Oral anticoagulant; TIA: Transient ischemic attack.

**Table 2 Sensitivity analysis of negative controls after inverse probability of treatment weighting in an on-treatment analysis**

	Incident rate of rivaroxaban 15 mg 100 PY (95%CI)	Incident rate of warfarin 100 PY (95%CI)	HR (95%CI) <sup>1</sup>	P value
Diabetes complications	1.1 (0.2-2.0)	1.1 (0.6-1.5)	1.02 (0.40-2.60)	0.96
	Incident rate of rivaroxaban 20 mg 100 PY (95%CI)	Incident rate of warfarin 100 PY (95%CI)	HR (95%CI) <sup>1</sup>	P value
Diabetes complications	1.5 (0.6-2.4)	1.0 (0.6-1.5)	1.48 (0.72-3.06)	0.29
	Incident rate of apixaban 2.5 mg 100 PY (95%CI)	Incident rate of warfarin 100 PY (95%CI)	HR (95%CI) <sup>1</sup>	P value
Diabetes complications	0.8 (0.3-1.3)	1.2 (0.8-1.7)	0.66 (0.31-1.41)	0.28
	Incident rate of apixaban 5.0 mg 100 PY (95%CI)	Incident rate of warfarin 100 PY (95%CI)	HR (95%CI)	P value
Diabetes complications	0.7 (0.2-1.1)	1.4 (0.9-1.9)	0.49 (0.24-1.02)	0.06

A significant value is for  $P < 0.05$  vs warfarin.

<sup>1</sup>For the negative control, we assessed the risk of diabetic complications (ICD-9: 250.1-250.9, 357.2, and 366.41; ICD-10: E10-E14 excluding E10.9, E11.9, E12.9, E13.0, and E14.9).

CI: Confidence interval; HR: Hazard ratio; PY: Person-years.

**Table 3 E-values for significant comparisons in an on-treatment analysis after inverse probability of treatment weighting of new oral anticoagulant users with stage III chronic kidney disease**

	Hazard ratio (95%CI)	E value corresponding to the CI bound closest to 1	E value for hazard ratio point estimate <sup>1</sup>
Apixaban 2.5 mg <i>vs</i> warfarin			
Safety composite	0.65 (0.43-0.99)	1.11	2.45
Apixaban 5.0 mg <i>vs</i> warfarin			
Effectiveness composite	0.76 (0.65-0.88)	1.53	1.96
All-cause mortality	0.61 (0.43-0.88)	1.53	2.66

<sup>1</sup>E-value for hazard used the point estimate instead of the bound closest to 1.  
CI: Confidence interval.

confounding effects in our primary analysis and we provided several sensitivity analyses.

Our study also had some limitations. First, observational studies of administrative data are subject to confounding bias by unadjusted factors, such as the severity of AF, the exact eGFR, the international normalized ratio, body weight, over-the-counter prescriptions, and ethnicity. Second, use of administrative claims depends on comprehensive, accurate coding and recording of all diagnoses, drugs, and procedures. Third, it might not be possible to generalize our results to younger patients, or patients treated with other DOACs (dabigatran and edoxaban). Fourth, the effect sizes for individual safety and effectiveness outcomes were small. Fifth, we could not use time spent in the therapeutic range to assess the appropriateness of warfarin dosing, since our database did not record the international normalized ratio. Finally, our study did not include exact eGFR values; however, we estimated eGFR using an algorithm known to be valid in older adults[31].

## CONCLUSION

In this observational study of new OAC users with AF and stage III CKD, we found that rivaroxaban is safe and effective relative to warfarin but if CrCl is between 30-49 mL/min, we need to reduce the dose to 15 mg. Apixaban 2.5 mg might even have a better safety profile than warfarin, while apixaban 5.0 mg might have a better effectiveness profile than warfarin, including a reduction in deaths. Appropriately sized RCTs are needed to confirm these findings in stage III CKD patients.

## ARTICLE HIGHLIGHTS

### Research background

The effectiveness and safety of apixaban and rivaroxaban in patients with atrial fibrillation (AF) and stage III chronic kidney disease (CKD) are not well established.

### Research motivation

Few studies have evaluated the safety and efficacy of individual direct oral anticoagulants *vs* warfarin, nor have they established how dose selection impacts patients with AF and stage III CKD with respect to the incidence of stroke/systemic embolism (SE), major bleeding, and death.

### Research objectives

We assessed and compared the effectiveness and safety of standard-dose rivaroxaban, low-dose rivaroxaban, standard-dose apixaban, and low-dose apixaban *vs* warfarin in a representative group of patients with AF and stage III CKD.

### Research methods

A cohort of new users of apixaban, rivaroxaban or warfarin in AF patients and stage III CKD was created using administrative databases. We defined the effectiveness as a composite of stroke, SE or death; safety was defined as a composite of major bleeding within 1-year of follow-up. Comparisons were under treatment analysis using inverse probability of treatment weighting and Cox models.

### Research results

Rivaroxaban 15 mg and 20 mg were associated with a similar efficacy and safety composite risk *vs* warfarin. Apixaban 5.0 mg was linked with decreased effectiveness composite risk [hazard ratio (HR) 0.76; 0.65-0.88] and a similar safety risk



(HR 0.94; 0.66-1.35), compared with apixaban 2.5 mg, which was associated with a similar effectiveness composite (HR 1.00; 0.79-1.26) and a lower safety risk (HR 0.65; 0.43-0.99).

### Research conclusions

This observational study of new users of rivaroxaban and apixaban find that both appear to be safe and effective compared to warfarin in patients with AF and stage III CKD. Apixaban 2.5 mg might even have a better safety profile than warfarin, while apixaban 5.0 mg might have a better effectiveness profile than warfarin, to a reduction in deaths.

### Research perspectives

The research perspective should be an appropriately sized randomized controlled trials to confirm these findings in AF patients with stage III CKD.

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## FOOTNOTES

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