Comparative Effectiveness and Safety of Direct Oral Anticoagulants versus Warfarin in Patients with Atrial Fibrillation and Stage III Chronic Kidney Disease

Sylvie Perreault[1], Laurie-Anne Boivin-Proulx[2], Aurélie Lenglet[3], Ziad Massy[4], and Marc Dorais[5]

[1]University of Montreal
[2]University of Montreal Hospital Centre Research Centre
[3]Jules Verne University of Picardie
[4]Paris-Saclay University (PSU) and University of Paris Ouest -Versailles-Saint-Quentin-en-Yvelines (UVSQ)
[5]Statsciences

August 30, 2022

Abstract

Aim: The effectiveness and safety of direct oral anticoagulants (DOACs) in atrial fibrillation (AF) patients with stage III chronic kidney disease (CKD) are still subject to debate. We therefore assessed and compared the effectiveness and safety of DOACs vs. warfarin in this population. Methods: A cohort of patients with an inpatient or outpatient code for AF and stage III CKD who were newly prescribed an oral anticoagulant (OAC) was created using 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 on-treatment analysis using inverse probability of treatment weighting and Cox proportional hazards. Results. A total of 8,899 included patients filled a new OAC claim: 3,335 for warfarin and 5,564 DOACs. Compared with warfarin, rivaroxaban 15 mg and 20 mg 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), whereas 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). Conclusion: In comparison with warfarin, rivaroxaban and apixaban appear to be effective and safe in AF patients with stage III CKD.

Introduction

The prevalence of atrial fibrillation (AF) is two to three times higher in patients with chronic kidney disease (CKD) than in the general population.[1-3] This results in a major therapeutic challenge because patients with CKD and AF have an elevated risk of both systemic thromboembolic events and bleeding.[4-6]Today's practice guidelines recommend treatment with a direct oral anticoagulant (DOAC) rather than warfarin, when oral anticoagulation therapy (OAC) is indicated in patients with non-valvular atrial fibrillation (NVAF) – including those with stage I-IV CKD.[7] Despite the broad dissemination of these guidelines, warfarin remains the OAC of choice in a high proportion of AF patients in general[8] and AF patients with moderate or severe CKD in particular.[9]

Although the landmark 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 metanalysis of RCTs and observational studies, DOACs were associated with better efficacy (relative to warfarin) in early CKD and had similar efficacy and safety profiles in patients with stages IV-V CKD as well as patients on dialysis.[14] Recent population-based studies have also examined the effectiveness and safety of DOACs vs. warfarin in AF patients with CKD.[15-22] However, few of these studies provided data on (i) the safety and effectiveness of each individual DOAC vs. warfarin, or (ii) the impact of dose selection in patients with stage III CKD on the incidence of stroke, systemic thromboembolic events, bleeding, and death.[16,23] We therefore decided to assess and compare the effectiveness and safety of standard-dose rivaroxaban (20 mg once daily), low-dose rivaroxaban (15 mg once daily), standard-dose apixaban (5.0 mg twice daily), low-dose apixaban (2.5 mg twice daily) and warfarin in a representative cohort of AF patients with stage III CKD.

Methods

We analyzed several Quebec healthcare claims databases, in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) 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 still living in the Quebec province.

Population

We identified adult patients (aged 18 or over) with AF from January 1, 2013, to December 31, 2017. AF was detected by searching for the International Classification of Diseases, 9th Revision (ICD-9) codes 427.3, 427.31 or 427.32, or the International Classification of Diseases, 10th 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 and so 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 months and enrolment 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, as defined by a composite variable covering the ICD code, drug use, and consultations with a nephrologist (as identified in the administrative databases). This 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 had a positive predictive value ranging from 94.5% to 97.7%).[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 that a gap of less than 30 days between the end of a treatment period and a new fill corresponded to continuous treatment. Patients were censored when they discontinued a treatment or switched to another OAC or to another dose level. Allowing a gap in treatment of up to 30 days is reasonable because of the DOACs' short half-life. Taking account of this definition, the adherence rate over the 12-month assessment period was at least 92% for all included patients. The patient's OAC exposure and censored status were updated every 30 days.

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 S1). 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 $CHADS_2$ score (Supplementary Tables S2 and S3) and the modified HAS-BLED score (Supplementary Tables S2 and S4). The comorbidity burden was scored with the Charlson-Deyo Comorbidity Index.[34,35] A frailty score was also calculated from the modified Elders Risk Assessment in the two years preceding cohort entry.[36,37] 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 95% confidence interval (CI) or the median with interquartile range (IQR). 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.[38,39] Four IPTW cohorts were created: (i) rivaroxaban 15 mg vs. warfarin; ii) rivaroxaban 20 mg vs. warfarin; (iii) apixaban 2.5 mg vs. warfarin; (iv) 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 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.[38]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 enrolment in a non-governmental drug coverage plan, admission to a long-term care facility, hospital admission (for more than two weeks), the occurrence of a safety or effectiveness endpoint or death (whichever occurred first). The patient's OAC exposure and censored status were updated every 30 days.

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 days 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.[40] 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).

Results

A total of 8,899 included AF patients with stage III CKD filled a new OAC prescription: 3,335 for warfarin, 744 for rivaroxaban 15 mg, 1,064 for rivaroxaban 20 mg, 1,674 for apixaban 2.5 mg, and 2,082 for apixaban 5.0 mg (Figure 1). The frequency of warfarin prescription decreased over time and was associated with a concomitant increase in DOAC prescription (Figure 2). In 2017, the most frequently initiated drug was apixaban 5.0 mg.

Demographic and Clinical Characteristics

The patients' unadjusted characteristics are summarized in Supplementary Tables S5-S8. Compared with warfarin users, rivaroxaban 15 mg users were lightly younger (mean ± standard deviation [SD] age: 83.0 ± 8.5 vs. 82.6 ± 7.8, respectively) and had a lower mean ± SD Charlson-Deyo Comorbidity Index (6.1 ± 3.4 vs. 5.3 ± 3.5, respectively), a lower mean ± SD $CHADS_2$ score (3.1 ± 1.2 vs. 2.8 ± 1.2, respectively) and a lower mean ± SD HAS-BLED score (3.6 ± 1.3 vs. 3.2 ± 1.3, respectively). Compared with warfarin users, rivaroxaban 20 mg users were younger (mean ± SD age: 83.0 ± 8.5 vs. 74.2 ± 9.2, respectively) and had a lower mean ± SD Charlson-Deyo Comorbidity Index (6.1 ± 3.4 vs. 4.7 ± 3.5, respectively), a lower mean ± SD $CHADS_2$ score (3.1 ± 1.2 vs. 2.3 ± 1.2, respectively) and a lower mean ± SD HAS-BLED score (3.6 ± 1.3 vs. 2.7 ± 1.3, respectively). Compared with warfarin users, apixaban 2.5 mg users were older (mean ± SD age: 83.0 ± 8.5 vs. 86.5 ± 6.3, respectively) and had a lower mean ± SD Charlson-Deyo Comorbidity Index (6.1 ± 3.4 vs. 5.4 ± 3.3, respectively), a similar mean ± SD $CHADS_2$ score (3.1 ± 1.2 vs. 3.0 ± 1.1, respectively) and a similar mean ± SD HAS-BLED score (3.6 ± 1.3 vs. 3.3 ± 1.3, respectively). And, compared with warfarin users, apixaban 5.0 mg users were also younger (mean ± SD age: 83.0 ± 8.5 vs. 78.0 ± 8.4, respectively) and had a lower mean ± SD Charlson-Deyo Comorbidity Index (6.1 ± 3.4 vs. 5.1 ± 3.5, respectively), a lower mean ± SD $CHADS_2$ score (3.1 ± 1.2 vs. 2.6 ± 1.2, respectively) and a lower mean ± SD HAS-BLED score (3.6 ± 1.3 vs. 3.0 ± 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.

Cumulative Incidence in the IPTW Cohorts

As shown in Table 1 and Supplementary Tables S5-S8, there were no significant differences in baseline characteristics between the IPTW treatment groups. Figures 3A and 3B 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 S9-S10.

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 S11 and Figure 4 (HRs only). With warfarin as the reference group, rivaroxaban 15 mg and 20 mg were associated with a similar effectiveness composite (HR 0.84; 95% CI 0.60–1.18 and HR 0.83; 95% CI 0.61–1.13, respectively); 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 associated with a similar effectiveness (HR 1.00; 95% CI 0.79–1.26), but better safety (HR 0.65; 95% CI 0.43–0.99) profile, while apixaban 5.0 mg was associated with a better effectiveness (HR 0.76; 95% CI 0.65–0.88), but a similar safety risk (HR 0.94; 95% CI 0.66–1.35) profile. 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).

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 S12 and Figure 5 (HRs only). Under intent-to-treat analyses, rivaroxaban 20 mg present a better effectiveness composite (HR 0.79; 95% CI 0.65–0.96), and the observed improvement in the effectiveness composite was driven by a reduction in mortality (HR 0.72; 95% CI 0.58–0.91). 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, the rate per 100 person-years of hospitalization for diabetes complications were similar for warfarin and DOACs, with no significant HRs. As expected, the results were similar in all the groups. As shown in Table 3, the E-value closest to boundary 1 for the effectiveness composite and apixaban 5.0 mg vs. warfarin was 1.53; hence, the HR that this effectiveness composite could be explained by an unmeasured confounder occurred 1.53 times more frequently in patients receiving apixaban 5.0 mg than in patients receiving warfarin, and thus increased 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 of relevance 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 effective and safe in AF patients with stage III CKD, but if creatinine clearance rate (CrCl) is between 30–49 mL/min, we need to reduce the dose at 15 mg. 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.[7,41] 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 in 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 are associated with 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]

There are few data on the effectiveness and safety of each individual DOAC and the impact of dose selection in patients with stage III CKD specifically, and mostly of the available information has been derived from observational studies.[15-21] A sub-analysis of the ARISTOLE trial's data showed that apixaban reduced the

rate of stroke and mortality relative to warfarin (regardless of the patient's level of renal function); however, the safety and effectiveness of apixaban vs. warfarin were not assessed specifically in stage III CKD patients.[13] Wetmore *et al* . examined Medicare data from 22,739 AF patients with stage III-IV CKD and found that apixaban was associated with a reduction in stroke/SE (HR 0.70; 95% CI 0.51–0.96) and in the major bleeding risk (HR 0.47; 95% CI 0.37–0.59).[23] Using electronic health record data, Fu*et al* . 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).[42] A sub-analysis of the ROCKET-AF trial found that rivaroxaban 20 mg daily had a better efficacy profile in patients with a 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.[43] Nonetheless, dose adjustment yielded results consistent with the overall trial, when compared with dose-adjusted warfarin.[11] Wetmore *et al* . 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).[23] 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, there are few published data on the impact of DOAC therapy vs. warfarin on mortality, and also per specific dose. Makani *et al.*examined electronic health record data on 21,733 AF patients with CKD and found that DOACs reduce the risk of all-cause mortality for all CKD classes.[17] When examining individual DOACs in an on-treatment analysis, Wetmore *et al.* 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).[23] This 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 a decline renal function, a doubling in the serum creatinine level, or acute kidney injury.[44] Moreover, warfarin treatment is associated with an elevated risk of vascular and cardiac valve calcification,[45-47] which in turn is associated with greater cardiovascular morbidity and mortality rates.[48]

The present study had several strengths. Firstly, it is one of the few large, real-world comparative studies of the effectiveness, safety and mortality rates associated with individual DOACs and dose levels vs. warfarin. Secondly, we analyzed the province-wide, single-payer Quebec healthcare claims database. Given that (i) most important clinical events would have resulted in an administrative claim and (ii) few patients seek medical services outside of the Quebec province, it is likely that nearly all clinically significant events were captured; this might not have been the case in previous single-hospital or single-insurer studies. Thirdly, we performed IPTW cohorts to account for confounding effects in our primary analysis and we provided several sensitivity analyses.

Our study also had some limitations. Firstly, this observational study of administrative data might have been subject to confounding bias by unadjusted factors (e.g. the severity of AF, the exact eGFR, the international normalized ratio, body weight, over-the-counter prescriptions, and ethnicity). Secondly, administrative claims data depend on the exhaustive, accurate recording and coding of diagnoses, procedures, and drugs. Thirdly, it might not be possible to generalize our results to younger patients, patients treated with other DOACs (dabigatran and edoxaban). Fourthly, the effect sizes for individual safety and effectiveness outcomes were small. Fifthly, time spent in the therapeutic range could not be used to assess the appropriateness of warfarin dosing, since the international normalized ratio was not recorded in our database. Lastly, we did not have the exact eGFR value; however, the algorithm used to estimate the eGFR is known to be valid in older adults.[31]

Conclusions

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 at 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, to a reduction in deaths. Appropriately sized RCTs are needed to confirm these findings in stage III CKD patients.

Acknowledgements

We thank the *Regie de l'assurance maladie du Quebec* (RAMQ) and Quebec Health Ministry for assistance with data management and the*Commission d'acces a l'information* for authorizing the study.

Conflict of Interest Statement

The authors do not have any conflicts of interest to disclose.

Funding Information

The study was funded by the *Reseau quebecois de recherche sur les medicaments* (RQRM).

Data Availability Statement

All relevant data analysed in this study are provided in main article and its supporting information. Due to the nature of this research, the data used for this study cannot be shared according to the*Commission d'acces a l'information* agreements, so supporting data is not available.

References

1. Ananthapanyasut W, Napan S, Rudolph EH, et al. Prevalence of atrial fibrillation and its predictors in nondialysis patients with chronic kidney disease. *Clin J Am Soc Nephrol.* 2010;5(2):173-181. doi: 10.2215/CJN.03170509.

2. Soliman EZ, Prineas RJ, Go AS, et al. Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC). *Am Heart J.* 2010;159(6):1102-1107. doi: 10.1016/j.ahj.2010.03.027.

3. Baber U, Howard VJ, Halperin JL, et al. Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study.*Circ Arrhythm Electrophysiol.* 2011;4(1):26-32. doi: 10.1161/CIRCEP.110.957100.

4. Mitsuma W, Matsubara T, Hatada K, et al. Clinical characteristics of hemodialysis patients with atrial fibrillation: The RAKUEN (Registry of atrial fibrillation in chronic kidney disease under hemodialysis from Niigata) study. *J Cardiol.* 2016;68(2):148-155. doi: 10.1016/j.jjcc.2015.08.023.

5. Bonde AN, Lip GY, Kamper AL, et al. Renal Function and the Risk of Stroke and Bleeding in Patients With Atrial Fibrillation: An Observational Cohort Study. *Stroke.* 2016;47(11):2707-2713. doi: 10.1161/strokeaha.116.014422.

6. Providencia R, Marijon E, Boveda S, et al. Meta-analysis of the influence of chronic kidney disease on the risk of thromboembolism among patients with nonvalvular atrial fibrillation. *Am J Cardiol.*2014;114(4):646-653. doi: 10.1016/j.amjcard.2014.05.048.

7. Andrade JG, Aguilar M, Atzema C, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. *Can J Cardiol.* 2020;36(12):1847-1948. doi: 10.1016/j.cjca.2020.09.001.

8. Marzec LN, Wang J, Shah ND, et al. Influence of Direct Oral Anticoagulants on Rates of Oral Anticoagulation for Atrial Fibrillation.*J Am Coll Cardiol.* 2017;69(20):2475-2484. doi: 10.1016/j.jacc.2017.03.540.

9. Haas S, Camm AJ, Bassand JP, et al. Predictors of NOAC versus VKA use for stroke prevention in patients with newly diagnosed atrial fibrillation: Results from GARFIELD-AF. *Am Heart J.*2019;213:35-46. doi: 10.1016/j.ahj.2019.03.013.

10. Bohula EA, Giugliano RP, Ruff CT, et al. Impact of Renal Function on Outcomes With Edoxaban in the ENGAGE AF-TIMI 48 Trial.*Circulation.* 2016;134(1):24-36. doi: 10.1161/CIRCULATIONAHA.116.022361.

11. Fox KAA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J.* 2011;32(19):2387-2394. doi: 10.1093/eurheartj/ehr342.

12. Hijazi Z, Hohnloser SH, Oldgren J, et al. Efficacy and Safety of Dabigatran Compared With Warfarin in Relation to Baseline Renal Function in Patients With Atrial Fibrillation. *Circulation.*2014;129(9):961-970. doi: 10.1161/CIRCULATIONAHA.113.003628.

13. Hohnloser SH, Hijazi Z, Thomas L, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J.* 2012;33(22):2821-2830. doi: 10.1093/eurheartj/ehs274.

14. Chen H-Y, Ou S-H, Huang C-W, et al. Efficacy and Safety of Direct Oral Anticoagulants vs Warfarin in Patients with Chronic Kidney Disease and Dialysis Patients: A Systematic Review and Meta-Analysis. *Clin Drug Investig.* 2021;41(4):341-351. doi: 10.1007/s40261-021-01016-7.

15. Di Lullo L, Tripepi G, Ronco C, et al. Safety and effectiveness of rivaroxaban and warfarin in moderate-to-advanced CKD: real world data. *J Nephrol.* 2018;31(5):751-756. doi: 10.1007/s40620-018-0501-7.

16. Siontis KC, Zhang X, Eckard A, et al. Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States. *Circulation.*2018;138(15):1519-1529. doi: 10.1161/CIRCULATIONAHA.118.035418.

17. Makani A, Saba S, Jain SK, et al. Safety and Efficacy of Direct Oral Anticoagulants Versus Warfarin in Patients With Chronic Kidney Disease and Atrial Fibrillation. *Am J Cardiol.* 2020;125(2):210-214. doi: 10.1016/j.amjcard.2019.10.033.

18. Schafer JH, Casey AL, Dupre KA, Staubes BA. Safety and Efficacy of Apixaban Versus Warfarin in Patients With Advanced Chronic Kidney Disease. *Ann Pharmacother.* 2018;52(11):1078-1084. doi: 10.1177/1060028018781853.

19. Coleman CI, Kreutz R, Sood NA, et al. Rivaroxaban Versus Warfarin in Patients With Nonvalvular Atrial Fibrillation and Severe Kidney Disease or Undergoing Hemodialysis. *Am J Med.* 2019;132(9):1078-1083. doi: 10.1016/j.amjmed.2019.04.013.

20. Loo SY, Coulombe J, Dell'Aniello S, Brophy JM, Suissa S, Renoux C. Comparative effectiveness of novel oral anticoagulants in UK patients with non-valvular atrial fibrillation and chronic kidney disease: a matched cohort study. *BMJ Open.* 2018;8(1):e019638. doi: 10.1136/bmjopen-2017-019638.

21. Shin JI, Secora A, Alexander GC, et al. Risks and Benefits of Direct Oral Anticoagulants across the Spectrum of GFR among Incident and Prevalent Patients with Atrial Fibrillation. *Clin J Am Soc Nephrol.* 2018;13(8):1144-1152. doi: 10.2215/CJN.13811217.

22. Liabeuf S, Laville SM, Bieber B, et al. Prescription of Direct Oral Anticoagulants to Patients With Moderate-to-Advanced CKD: Too Little or Just Right? *Kidney Int Rep.* 2021;6(9):2496-2500. doi: 10.1016/j.ekir.2021.06.004.

23. Wetmore JB, Roetker NS, Yan H, Reyes JL, Herzog CA. Direct-Acting Oral Anticoagulants Versus Warfarin in Medicare Patients With Chronic Kidney Disease and Atrial Fibrillation. *Stroke.*2020;51(8):2364-2373. doi: 10.1161/STROKEAHA.120.028934.

24. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. *Int J Surg.* 2014;12(12):1495-1499. doi: 10.1016/j.ijsu.2014.07.013.

25. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. *J Clin Epidemiol.* 1995;48(8):999-1009. doi: 10.1016/0895-4356(94)00234-h.

26. Eguale T, Winslade N, Hanley JA, Buckeridge DL, Tamblyn R. Enhancing pharmacosurveillance with systematic collection of treatment indication in electronic prescribing: a validation study in Canada. *Drug Saf.* 2010;33(7):559-567. doi: 10.2165/11534580-000000000-00000.

27. Wilchesky M, Tamblyn RM, Huang A. Validation of diagnostic codes within medical services claims. *J Clin Epidemiol.*2004;57(2):131-141. doi: 10.1016/S0895-4356(03)00246-4.

28. Tamblyn R, Reid T, Mayo N, McLeod P, Churchill-Smith M. Using medical services claims to assess injuries in the elderly: sensitivity of diagnostic and procedure codes for injury ascertainment. *J Clin Epidemiol.* 2000;53(2):183-194. doi: 10.1016/s0895-4356(99)00136-5.

29. Humphries KH, Jackevicius C, Gong Y, et al. Population rates of hospitalization for atrial fibrillation/flutter in Canada. *Can J Cardiol.* 2004;20(9):869-876. doi:

30. Perreault S, Shahabi P, Cote R, et al. Rationale, design, and preliminary results of the Quebec Warfarin Cohort Study. *Clin Cardiol.* 2018. doi: 10.1002/clc.22948.

31. Roy L, Zappitelli M, White-Guay B, Lafrance JP, Dorais M, Perreault S. Agreement Between Administrative Database and Medical Chart Review for the Prediction of Chronic Kidney Disease G category. *Can J Kidney Health Dis.* 2020;7:2054358120959908. doi: 10.1177/2054358120959908.

32. Blais C LL, Hamel D, Brown K, Rinfret S, Cartier R, Giguere M, Carroll C, Beauchamp C, Bogaty P. Evaluation des soins et surveillance des maladies cardiovasculaires de sante publique du Quebec et de L'institut national d'excellence en sante et services sociaux.*Gouvernement du Quebec, Institut national de sante publique , Institut national d'excellence en sante et des services sociaux.*2012:1-9. doi:

33. Levy AR, Tamblyn RM, Fitchett D, McLeod PJ, Hanley JA. Coding accuracy of hospital discharge data for elderly survivors of myocardial infarction. *Can J Cardiol.* 1999;15(11):1277-1282. doi:

34. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.*1992;45(6):613-619. doi: 10.1016/0895-4356(92)90133-8.

35. D'Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson comorbidity index with administrative data bases.*J Clin Epidemiol.* 1996;49(12):1429-1433. doi: 10.1016/s0895-4356(96)00271-5.

36. Crane SJ, Tung EE, Hanson GJ, Cha S, Chaudhry R, Takahashi PY. Use of an electronic administrative database to identify older community dwelling adults at high-risk for hospitalization or emergency department visits: the elders risk assessment index. *BMC Health Serv Res.*2010;10:338. doi: 10.1186/1472-6963-10-338.

37. Fillion V, Sirois MJ, Gamache P, Guertin JR, Morin SN, Jean S. Frailty and health services use among Quebec seniors with non-hip fractures: a population-based study using adminsitrative databases.*BMC Health Serv Res.* 2019;19(1):70. doi: 10.1186/s12913-019-3865-z.

38. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies.*Stat Med.* 2015;34(28):3661-3679. doi: 10.1002/sim.6607.

39. Allan V, Ramagopalan SV, Mardekian J, et al. Propensity score matching and inverse probability of treatment weighting to address confounding by indication in comparative effectiveness research of oral anticoagulants. *J Comp Eff Res.* 2020;9(9):603-614. doi: 10.2217/cer-2020-0013.

40. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med.*2017;167(4):268-274. doi: 10.7326/M16-2607.

41. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society

of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J.* 2021;42(5):373-498. doi: 10.1093/eurheartj/ehaa612.

42. Fu CM, Li LC, Lee YT, Wang SW, Hsu CN. Apixaban vs. Warfarin in Atrial Fibrillation Patients With Chronic Kidney Disease. *Front Cardiovasc Med.* 2021;8. doi: 10.3389/fcvm.2021.752468.

43. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *N Engl J Med.*2011;365(10):883-891. doi: 10.1056/NEJMoa1009638.

44. Yao X, Tangri N, Gersh BJ, et al. Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation. *J Am Coll Cardiol.*2017;70(21):2621-2632. doi: 10.1016/j.jacc.2017.09.1087.

45. Koos R, Mahnken AH, Muhlenbruch G, et al. Relation of oral anticoagulation to cardiac valvular and coronary calcium assessed by multislice spiral computed tomography. *Am J Cardiol.*2005;96(6):747-749. doi: 10.1016/j.amjcard.2005.05.014.

46. Shea MK, O'Donnell CJ, Hoffmann U, et al. Vitamin K supplementation and progression of coronary artery calcium in older men and women.*Am J Clin Nutr.* 2009;89(6):1799-1807. doi: 10.3945/ajcn.2008.27338.

47. Schurgers LJ, Aebert H, Vermeer C, Bultmann B, Janzen J. Oral anticoagulant treatment: friend or foe in cardiovascular disease?*Blood.* 2004;104(10):3231-3232. doi: 10.1182/blood-2004-04-1277.

48. Elango K, Javaid A, Khetarpal BK, et al. The Effects of Warfarin and Direct Oral Anticoagulants on Systemic Vascular Calcification: A Review.*Cells.* 2021;10(4):773. doi: 10.3390/cells10040773.

Table 1. Demographic and clinical characteristics of cohorts of new OAC users with stage III CKD after IPTW from 2013 to 2017.

	IPTW warfa
	Warfarin (n=
Age (mean ± SD)	82.9 ± 8.6
Female sex (%)	56.5
CHA_2DS_2-VASc	4.1 ± 1.4
$CHADS_2$ score (mean ± SD)	3.0 ± 1.2
HAS-BLED score (mean ± SD)	3.5 ± 1.3
Charlson-Deyo Comorbidity Index (mean ± SD)	5.9 ± 3.4
Frailty score (mean ± SD)	18.6 ± 6.2
Comorbidities (including the index hospitalization and the three years prior to cohort entry)	**Comorbiditi**
Hypertension (%)	86.2
Coronary artery disease (%)	64.7
Acute myocardial infarction (%)	21.1
Chronic heart failure (%)	56.2
Cardiomyopathy (%)	7.9
Other cardiac dysrhythmias (%)	18.8
Valvular heart disease (%)	26.1
Stroke/transient ischemic attack (%)	16.9
Peripheral vascular disease (%)	27.7
Dyslipidemia (%)	54.4
Diabetes (%)	45.1
Major bleeding (%)	38.5
Major intracranial bleeding (%)	3.7
Major gastrointestinal bleeding (%)	8.3
Other sites of major bleeding (%)	32.0
Liver disease (%)	2.6

	IPTW warfa
Chronic obstructive pulmonary disease/asthma	44.0
Depression (%)	11.8
Medical procedures (three years prior to cohort entry)	**Medical pro**
Cardiac catheterization (%)	5.0
Percutaneous coronary intervention – stent (%)	4.1
Coronary artery bypass grafting (%)	0.6
Implantable cardiac device (%)	0.1
Medications (two weeks prior to cohort entry)	**Medications**
Statin (%)	51.0
Antiplatelet (%)	8.7
Low-dose acetylsalicylic acid (%)	35.3
Proton pump inhibitors (%)	49.7
Nonsteroidal anti-inflammatory drugs (%)	0.9
Digoxin (%)	9.3
Amiodarone (%)	9.6
Antidepressants (%)	10.5
Beta-blockers (%)	62.5
Calcium channel blockers (%)	42.9
Inhibitors of the renin-angiotensin system (%)	37.5
Diuretics (%)	60.5
Loop diuretics (%)	56.2
Antidiabetics (%)	27.4
Health medical services (one year prior to cohort entry)	**Health medi**
Consultations with specialist physicians (mean ± SD)	1.2 ± 2.4
Consultations with family physicians (mean ± SD)	1.3 ± 3.3
Emergency visits (mean ± SD)	3.4 ± 3.1
Health hospital services (three years prior to cohort entry)	**Health hosp**
All-cause hospital admission (mean ± SD)	2.5 ± 2.1

CKD, chronic kidney disease; IPTW, inverse probability of treatment weighting; OAC, oral anticoagulant; SD, standard deviation.

Table 2. Sensitivity analysis of negative controlsafter 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[a] (95% CI)	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[a] (95% CI)	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[a] (95% CI)	P-value

	Incident rate of rivaroxaban 15 mg 100 PY (95% CI)	Incident rate of warfarin 100 PY (95% CI)	HR[a] (95% CI)	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[a] (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

CI, confidence interval; HR, hazard ratio; PY, person-years.[a] 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).

Table 3. E-values for significant comparisons in an on-treatment analysis after IPTW of new OAC users with stage III CKD.

	Hazard ratio (95% CI)	E-value corresponding to the CI bound *closest to*
Apixaban 2.5 mg vs. warfarin	**Apixaban 2.5 mg vs. warfarin**	**Apixaban 2.5 mg vs. warfarin**
Safety composite	0.65 (0.43 – *0.99*)	1.11
Apixaban 5.0 mg vs. warfarin	**Apixaban 5.0 mg vs. warfarin**	**Apixaban 5.0 mg vs. warfarin**
Effectiveness composite	0.76 (0.65 – *0.88*)	1.53
All-cause mortality	0.61 (0.43 – *0.88*)	1.53

CI, confidence interval; CKD, chronic kidney disease; IPTW, inverse probability of treatment weighting; OAC, oral anticoagulant.

Figure Legends

Figure 1. Study flow chart[a].

AF, atrial fibrillation; DOAC, direct oral anticoagulant; RAMQ,*Régie de l'assurance maladie du Québec* .[a] No patients in the cohort received edoxaban between 2011 and 2017.

Figure 2. Changes in OAC prescriptions from 2010 to 2017.

BID, twice daily; DIE, once daily; DOACs, direct oral anticoagulants; OAC, oral anticoagulant.

Figure 3A. Cumulative rate of the primary effectiveness outcome after inverse probability of treatment weighting in an on-treatment analysis.

Figure 3B. Cumulative rate of the primary safety outcome after inverse probability of treatment weighting in an on-treatment analysis.

Figure 4. Hazard ratios (95% CI) of effectiveness and safety outcomes in an on-treatment after IPTW of new OAC users with stage III

CKD.

CI, confidence interval; CKD, chronic kidney disease; IPTW, inverse probability of treatment weighting; OAC, oral anticoagulant; SE, systemic embolism.

Figure 5. Hazard ratios (95% CI) of effectiveness and safety outcomes in an intent-to-treat after IPTW of new OAC users with

stage III CKD.

CI, confidence interval; CKD, chronic kidney disease; IPTW, inverse probability of treatment weighting; OAC, oral anticoagulant; SE, systemic embolism.