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Cardiovascular and Bleeding Outcomes with Anticoagulants across Kidney Disease Stages: Analysis of a National US Cohort

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Keywords
Direct oral anticoagulant · Anticoagulation · Warfarin · Chronic kidney disease · Safety

Abstract
Background: While direct oral anticoagulants (DOACs) are considered safe among patients without chronic kidney disease (CKD), the evidence is conflicting as to whether they are also safe in the CKD and end-stage kidney disease (ESKD) population. In this observational cohort study, we examined whether DOACs are a safe alternative to warfarin across CKD stages for a variety of anticoagulation indications. ***Methods:*** Individuals on DOACs or warfarin were identified from OptumLabs® Data Warehouse (OLDW), a longitudinal dataset with de-identified administrative claims, from 2010 to 2017. Cox models with sensitivity analyses were used to assess the risk of cardiovascular disease and bleeding outcomes stratified by CKD stage. ***Results:*** Among 351,407 patients on anticoagulation, 45% were on DOACs. CKD stages 3–5 and ESKD patients comprised approximately 12% of the cohort. The most common indications for anticoagulation were atrial fibrillation (AF, 44%) and venous thromboembolism (VTE, 23%). DOACs were associated with a 22% decrease in the risk of cardiovascular outcomes (HR 0.78, 95% CI: 0.77–0.80, $p < 0.001$) and a 10% decrease in the risk of bleeding outcomes (HR 0.90, 95% CI: 0.88–0.92, $p < 0.001$) compared to warfarin after adjustment. On stratified analyses, DOACs maintained a superior safety profile across CKD stages. Patients with AF on DOACs had a consistently lower risk of cardiovascular and bleeding events than warfarin-treated patients, while among other indications (VTE, peripheral vascular disease, and arterial embolism), the risk of cardiovascular and bleeding events was the same among DOAC and warfarin users. ***Conclusion:*** DOACs may be a safer alternative to warfarin even among CKD and ESKD patients.

Introduction

Direct oral anticoagulant (DOAC) medications have transformed the treatment of venous thromboembolism (VTE) and have also been shown to decrease stroke risk with superior side effect profiles compared to warfarin in

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patients with atrial fibrillation (AF) since their first approval by the Food and Drug Administration (FDA) in 2010 [1–7]. In the absence of chronic kidney disease (CKD), DOAC therapy is preferred over warfarin as it eliminates the need for continuous international normalized ratio monitoring, reduces dietary restrictions on patients with regard to oral vitamin K intake, and most importantly, is a safe and effective alternative to warfarin [8, 9]. Moreover, DOAC therapy combined with aspirin has been shown to reduce the risk of cardiovascular events [10]. Unsurprisingly, DOACs have become cornerstones for treatment of AF and VTE in DOAC-eligible patients based on most recent guidelines [11, 12].

In CKD patients, DOACs theoretically confer another advantage over warfarin because they do not inhibit the vitamin K-dependent g-carboxylation activation of matrix Gla proteins, important inhibitors of vascular calcification [13, 14]. However, DOAC randomized clinical trials excluded patients with advanced CKD, and only apixaban, with its lower degree of renal clearance, has been approved for use in dialysis patients based on a single-dose pharmacokinetic study involving 8 hemodialysis patients [15]. Currently, the other 3 DOACs approved for use in the USA (rivaroxaban, edoxaban, and dabigatran) are not recommended in dialysis patients, given the lack of evidence from clinical trials [11]. Furthermore, findings regarding safety and efficacy of DOACs from large retrospective nondialysis CKD and dialysis cohorts of patients have been conflicting [16–18]. To better understand the risks of anticoagulation in the CKD population, we conducted a comparative analysis and examined cardiovascular and major bleeding outcomes with warfarin versus DOAC therapy in non-CKD, pre-dialysis CKD, and end-stage kidney disease (ESKD) patients on dialysis across a range of anticoagulation indications not limited to AF.

Methods

Study Population and Data Source

This study used de-identified administrative claims data from the OptumLabs® Data Warehouse (OLDW), which includes medical and pharmacy claims, laboratory results, and enrollment records for commercial and Medicare Advantage (MA) enrollees. The database contains longitudinal health information on over 200 million enrollees and patients, representing a diverse mix of ages, ethnicities, and geographical regions across the USA [19, 20]. New users of anticoagulant medication (either DOACs or warfarin) between October 1, 2010 and September 30, 2017 were identified via pharmacy claims with the first prescription date defined as the index anticoagulant date. DOACs included apixaban (30%), rivaroxaban (59%), edoxaban (0.1%), and dabigatran (10%). Betrixaban, which was FDA-approved in 2017, was excluded from this study. New users had to have been continuously enrolled in their healthcare plan without an enrollment gap longer than 45 days and be free of any anticoagulant prescriptions for at least 1 year prior to the index anticoagulant prescription date (online suppl. Fig. 1; see www.karger.com/doi/10.1159/0005514753 for all online suppl. material).

We excluded patients who had ambiguous birth dates or gender, were younger than 18 years, had anticoagulation treatment before October 1, 2010, or were reported to be on both DOAC and warfarin on the index treatment date (online suppl. Fig. 2). As this study involved analysis of pre-existing, de-identified data, it was exempt from institutional review board approval at the University of California, Irvine Medical Center, and the Tibor Rubin Veterans Affairs Medical Center.

Demographic and Clinical Data Ascertainment

Patient characteristics (including age, sex, and race) were obtained from OLDW. Comorbidities (acute kidney disease, diabetes, myocardial infarction (MI), congestive heart failure (CHF), ischemic stroke, hemorrhagic stroke, liver disease, or substance or alcohol use), indications for anticoagulation (AF, pulmonary embolism/infarction, deep venous thrombosis, arterial embolism/thrombosis, peripheral vascular disease, or hypercoagulable states), and presence and stage of kidney disease were identified according to the presence of the respective International Classification of Disease, ninth Revision (ICD-9) codes in a physician or facility claim within the year prior to the index date [21]. We categorized CKD stages 1 and 2 as non-CKD. CHA_2DS_2-VASC and HAS-BLED scores to assess the risk of stroke and bleeding outcomes, respectively, were calculated for patients with pre-existing AF [22, 23]. Comorbidities to calculate the CHA_2DS_2-VASC and HAS-BLED scores were also ascertained from ICD-9 codes; however, the labile international normalized ratio was not included, and renal disease was defined as having CKD 3–5 and ESKD in the HAS-BLED score. The use of antiplatelet medication was coded according to whether the patient had a prescription for the medication in the year prior to the index date.

Outcome Assessment

The main outcomes of interest were a composite cardiovascular disease (CVD) endpoint (combination of MI and ischemic stroke) and a composite bleeding endpoint (online suppl. Table 1). These outcomes were ascertained from validated ICD-9 codes in facility and physician claims from patients' index date until the end of the follow-up [22]. Patients were followed up from their respective index date until the date of the first event, end of continuous enrollment, end of prescription supply, or date of the final follow-up for all patients (September 30, 2017), whichever came first. Mortality information was not available for analysis.

Statistical Analysis

Patient demographic and clinical characteristics were ascertained for the total cohort and stratified by patients' anticoagulation treatment medication (DOAC vs. warfarin). Student's t and χ^2 tests for continuous and categorical variables, respectively, were used to test for statistically significant differences in patient characteristics between exposure groups.

We utilized a Cox model to perform a time-varying as-treated analysis (with time-updated information on anticoagulation medication type), where patients were considered at risk on the medication type until medication switch or end of the last prescription date (prescription date plus number of supplied days). Outcomes were attributed to the last anticoagulation prescription available, and patients were administratively censored at the end of the last prescription date, the end of continuous enrollment, or the end of the study period.

We performed three sequential levels of adjustment for hazard ratios: model 1: unadjusted (anticoagulation medication type only with DOAC as reference); model 2: adjusted for demographics (age, gender, and race), and year of the index anticoagulation prescription date; model 3: adjusted for model 2 plus comorbidities (diabetes, MI, CHF, ischemic stroke, and hemorrhagic stroke), antiplatelet medication use, and CKD stage. We defined model 3 as the primary model of interest to prevent over-adjustment. A fourth model (model 4) was used for sensitivity analyses and included adjustment for variables in model 3 plus other comorbidities including the anticoagulation indication (acute kidney disease, hypertension, AF, pulmonary embolism infarction, deep venous thrombosis, arterial embolism/thrombosis, peripheral vascular disease, or hypercoagulable states). There were no missing data on patient characteristics, anticoagulation medication prescription date, and comorbidities.

Association of anticoagulation treatments with the composite of CVD and the composite of bleeding outcomes was also examined across CKD stage strata (non-CKD, CKD stages 3–5, and ESKD on dialysis). We also performed a subgroup analysis examining a composite of CVD and composite of bleeding outcomes stratified by indication for anticoagulation (AF, deep venous thrombosis, pulmonary embolism, peripheral vascular disease, and arterial embolism).

To account for the treatment indication bias in the primary analysis, we performed a coarsened exact matching (CEM) as-treated analysis to improve the estimation of anticoagulation treatment effects on outcomes by stratifying patients by CKD stage and then matching them by anticoagulation treatment according to patients' demographics (age, gender, and race), year of the index date, comorbidities (diabetes, MI, CHF, ischemic stroke, and hemorrhagic stroke), and antiplatelet medication use. CEM models were also evaluated across covariate model adjustments as previously described. Patients were censored at the time of anticoagulation change or when there was a gap larger than 90 days from the end of the last prescription treatment date (prescription date plus day supply) to next subsequent prescription (suggesting medication discontinuation or nonadherence to treatment).

The proportionality assumption was checked for all statistical models. SAS (SAS Institute, Cary, NC, USA) was used for all statistical analysis. $p < 0.05$ was considered statistically significant.

Results

Baseline Demographic and Clinical Characteristics

The analytical cohort included 351,407 patients from the OLDW who met the inclusion criteria. 158,732 (45%) were treated with DOAC, and 192,675 (55%) were treated with warfarin as their index anticoagulant prescription. Patients were on average 67 ± 14 years old (mean ± SD), and our cohort consisted of 49% female, 79% non-Hispanic white, and 11% African-American (Table 1) patients. Thirty percent of patients had type 2 diabetes mellitus. Compared to warfarin-treated patients, patients initiating DOACs were slightly younger, less likely to be female or African-American, more likely to be Hispanic, less likely to have any comorbidities, and more likely to have AF as the indication for anticoagulation. After CKD stage stratification, there was no significant difference in age or gender between warfarin and DOAC treated patients; however, patients started on DOACs were more likely to be Hispanic, less likely to have any comorbidities, but more likely to have AF.

Among patients with AF as the indication for anticoagulation, warfarin-treated patients had a higher median CHA_2DS_2-VASC score in non-CKD and CKD stage 3 than DOAC-treated patients (online suppl. Table 2); however, there was no difference among CKD stages 4 and 5 and ESKD patients. There was also no difference in median HAS-BLED scores between DOAC- and warfarin-treated patients across all CKD strata.

Time-Varying As-Treated Analysis

In the time-varying as-treated analysis, 50,272 patients had at least one combined CVD outcome during a median follow-up time of 90 days (interquartile range, IQR: 30–279 days). Of the 17,836 patients taking DOACs, 4,269 developed an MI and 13,567 developed a stroke. Of the 32,436 patients taking warfarin, 8,388 developed an MI and 24,048 developed a stroke. The crude rate of combined CVD outcomes in DOAC-treated patients was 17.9 events per 100 person-years (95% CI: 17.6–18.1), while the crude rate of combined CVD outcomes in warfarin-treated patients was 25.4 events per 100 person-years (95% CI: 25.2–25.7) (online suppl. Table 3A). A lower combined CVD outcome risk was observed across all models of adjustment in DOAC-treated patients than warfarin-treated patients. Compared to warfarin-treated patients, those treated with DOAC had a 33% lower risk of combined CVD outcomes (HR: 0.67, 95% CI: 1.47–1.52) in the unadjusted model and a 22% lower risk of combined CVD outcomes (HR: 0.78, 95% CI: 0.77–0.80) after model 3 adjustment (online suppl. Table 3A). In our sensitivity analysis with adjustment for additional variables (model 4), there was no significant change in our findings.

We further assessed the association of anticoagulation treatments with CVD combined outcomes across CKD

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Table 1. Baseline characteristics of individuals in OLDW

Variable	Total cohort		Non-CKD		CKD 3		CKD 4 and 5		ESKD	
	DOAC	warfarin	DOAC	warfarin	DOAC	warfarin	DOAC	warfarin	DOAC	warfarin
Total number of patients	158,732 (45)	192,675 (55)	140,823 (46)	162,682 (54)	10,938 (43)	14,565 (57)	2,064 (32)	4,350 (68)	1,038 (20)	4,254 (80)
Age, years	66±13	67±13	65±13	66±14	75±10	74±10	76±9	75±10	68±12	67±12
Female	76,557 (48)	96,357 (50)	67,911 (48)	82,201 (51)	5,349 (49)	6,997 (48)	1,113 (54)	2,193 (50)	449 (43)	1,867 (44)
Race										
White	125,026 (79)	152,697 (79)	111,906 (79)	130,645 (80)	8,151 (75)	11,222 (77)	1,424 (69)	3,188 (73)	603 (58)	2,572 (60)
Black	15,965 (10)	21,259 (11)	13,210 (9.38)	16,318 (10.03)	1,564 (14)	2,058 (14)	366 (18)	713 (16)	274 (26)	1,069 (25)
Hispanic	9,595 (6)	9,990 (5)	8,497 (6)	8,325 (5)	621 (6)	683 (5)	171 (8)	257 (6)	105 (10)	370 (9)
Asian	2,862 (1.8)	2,864 (1.5)	2,526 (1.8)	2,387 (1.5)	216 (2)	199 (1.4)	42 (2)	72 (1.7)	26 (2.5)	124 (2.9)
Unknown	5,284 (3)	5,865 (3)	4,684 (3)	5,007 (3)	386 (4)	386 (3)	61 (3)	120 (3)	30 (3)	119 (3)
Comorbidity										
Acute kidney disease	13,442 (8)	22,899 (12)	7,201 (5)	10,918 (7)	3,527 (32)	5,060 (35)	1,016 (49)	2,225 (51)	506 (49)	2,294 (54)
CHF	53,181 (34)	77,315 (40)	42,160 (30)	57,366 (35)	6,452 (60)	8,976 (62)	1,520 (74)	3,216 (74)	782 (75)	3,431 (81)
Diabetes	45,692 (29)	60,559 (31)	36,351 (26)	44,227 (27)	5,570 (51)	7,446 (51)	1,272 (62)	2,617 (60)	713 (69)	3,008 (71)
Hypertension	62,554 (39)	80,514 (42)	49,676 (35)	58,712 (36)	7,778 (71)	10,199 (70)	1,693 (82)	3,454 (79)	851 (82)	3,567 (84)
MI	7,628 (5)	13,312 (7)	5,720 (4)	9,218 (6)	1,064 (10)	1,701 (12)	277 (13)	684 (16)	175 (17)	830 (20)
Hemostroke	294 (0.2)	742 (0.4)	241 (0.2)	615 (0.4)	30 (0.3)	65 (0.5)	*	*	*	*
Ischemic stroke	19,485 (12)	31,993 (17)	15,748 (11)	24,243 (15)	2,213 (20)	3,626 (25)	502 (24)	1,109 (25)	244 (24)	1,235 (29)
Indications										
AF	83,178 (52)	73,594 (38)	71,334 (51)	57,286 (35)	7,255 (66)	7,900 (54)	1,479 (72)	2,543 (58)	636 (61)	2,424 (57)
Pulmonary embolism	15,684 (10)	29,860 (16)	13,752 (10)	25,317 (16)	1,165 (11)	2,265 (16)	192 (9)	578 (13)	120 (12)	527 (12)
Deep venous thrombosis	28,215 (18)	52,031 (27)	24,466 (17)	42,589 (26)	2,118 (19)	4,152 (29)	448 (22)	1,448 (33)	355 (34)	1,641 (39)
Arterial embolism	2,354 (1)	5,873 (3)	1,876 (1)	4,470 (3)	267 (2)	587 (4)	53 (3)	189 (4)	56 (5)	332 (8)
Peripheral vasc. Dis	12,386 (8)	19,397 (10)	9,209 (7)	13,152 (8)	1,844 (17)	2,763 (19)	423 (20)	1,011 (23)	270 (26)	1,172 (28)
Hypercoagulable states	2,562 (2)	4,986 (3)	2,298 (2)	4,383 (3)	155 (1)	260 (2)	30 (1)	85 (2)	20 (2)	140 (3)
Medications										
Antiplatelets	16,799 (11)	20,707 (11)	13,293 (9)	15,035 (9)	2,094 (19)	2,511 (17)	483 (23)	955 (22)	251 (24)	1,021 (24)

Dis, disease; ESKD, end-stage kidney disease; OLDW, OptumLabs Data Warehouse; Vasc, vascular; DOAC, direct oral anticoagulant; AF, atrial fibrillation; CHF, congestive heart failure; MI, myocardial infarction. Data presented as mean ± standard deviation or proportion, where appropriate. NB: 2% of DOAC-treated and 4% of warfarin-treated patients from the total cohort were missing CKD information. * Values for cells with <20 patients are suppressed.

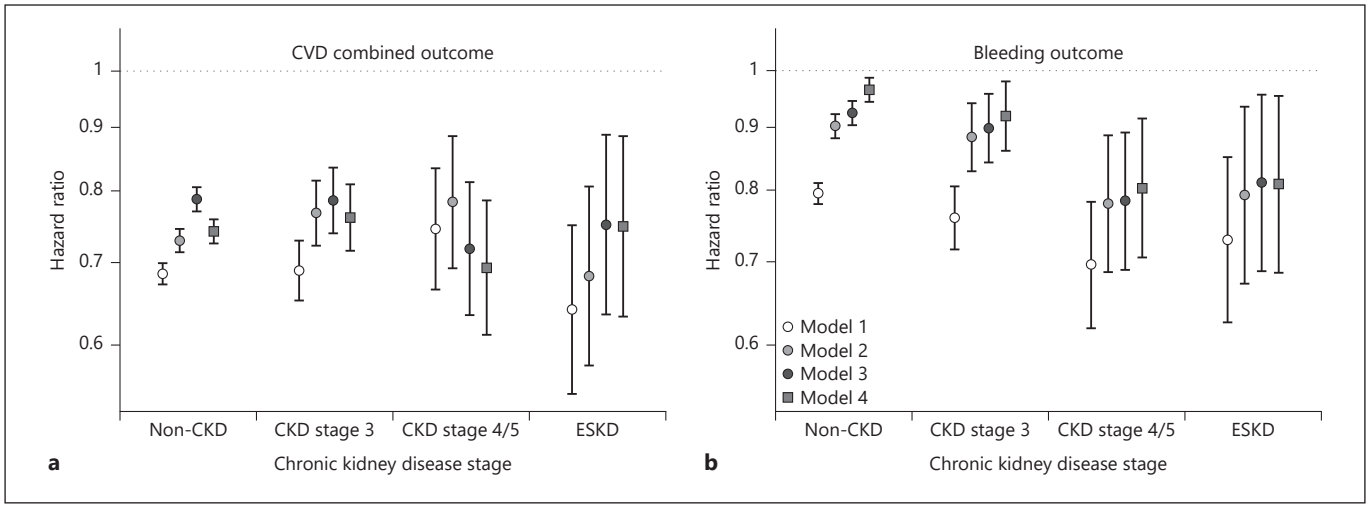

Fig. 1. Risk of time-varying cardiovascular and bleeding outcomes stratified by CKD stage (as-treated analysis). Hazard ratios are shown for the association between warfarin versus DOACs therapy with combined CVD (**a**) and bleeding outcomes (**b**) in a cohort of 351,407 individuals from the OptumLabs® Data Warehouse (warfarin as reference group). Note: model 1: unadjusted; model 2: adjusted for demographics (age, gender, and race) and year of the index anticoagulation prescription date; model 3: adjusted for model 2 plus comorbidities and medications (diabetes, MI, CHF, ischemic stroke, hemorrhagic stroke, and antiplatelet medication use), and CKD stage; model 4 (sensitivity analysis): adjusted for model 3 plus other comorbidities (acute kidney disease, hypertension, AF, pulmonary embolism infarction, deep venous thrombosis, arterial embolism/thrombosis, peripheral vascular disease, hypercoagulable state). CVD, cardiovascular disease; ESKD, end-stage kidney disease; DOAC, direct oral anticoagulant; AF, atrial fibrillation; CHF, congestive heart failure; MI, myocardial infarction.

stage. After model 3 adjustment, DOAC compared to warfarin use was associated a 21% lower risk of combined CVD outcomes in the non-CKD strata (HR: 0.79, 95% CI: 0.77–0.81). CKD stage 3 patients also had a 21% lower risk of CVD outcomes (HR: 0.79, 95% CI: 0.74–0.84), CKD stage 4 and 5 patients had a 28% lower risk of CVD outcomes (HR: 0.72, 95% CI: 0.63–0.81), and ESKD patients had a 25% lower risk of CVD outcomes (HR: 0.75, 95% CI: 0.64–0.89) (Fig. 1a; online suppl. Table 3B). These results remained consistent after model 4 adjustment.

Furthermore, in our analysis, 48,684 patients (18,311 on DOACs and 30,373 on warfarin) had at least one bleeding outcome with a crude rate of 20.6 events per 100 person-years (95% CI: 20.4–20.8) (online suppl. Table 4A). The median follow-up time for the bleeding outcome in the total cohort was 105 (IQR: 30–299) days. We also found that DOAC-treated patients had a 23% lower risk of bleeding in our unadjusted model (HR: 0.77, 95% CI: 0.76–0.78) than patients treated with warfarin and a 10% and 6% lower bleeding risk (HR: 0.90, 95% CI: 0.88–0.92; HR: 0.94, 95% CI: 0.92–0.96) after model 3 adjustment and in sensitivity analysis (model 4), respectively (online suppl. Table 4A).

In our CKD subgroup analysis, DOAC compared to warfarin was associated with a 8% lower risk of bleeding in non-CKD patients (HR: 0.92, 95% CI: 0.90–0.94), 10% lower risk of bleeding in CKD stage 3 patients (HR: 0.90, 95% CI: 0.84–0.96), 22% lower risk of bleeding in CKD stage 4 and 5 patients (HR: 0.78, 95% CI: 0.69–0.89), and 19% lower risk of bleeding in ESKD patients (HR: 0.81, 95% CI: 0.69–0.96) (Fig. 1b; online suppl. Table 4B). Adjustment with additional variables (model 4) did not significantly change our findings. All models met the proportionality assumption.

Subgroup Analysis by Anticoagulation Indication

In subgroup analysis by anticoagulation indication of all patients in our total cohort, DOAC-treated patients had a lower risk of composite CVD outcomes than warfarin-treated patients in all indication subgroups (Fig. 2a). For AF indication, DOAC-treated patients had a lower composite CVD risk than warfarin-treated patients across all stages of CKD. For the deep venous thrombosis and peripheral vascular disease indications, DOAC-treated patients also had a lower composite CVD risk in non-CKD and CKD stages 3–5. Among ESKD patients, DOAC-treated patients trended toward a lower risk of composite CVD outcomes. For patients with pulmonary

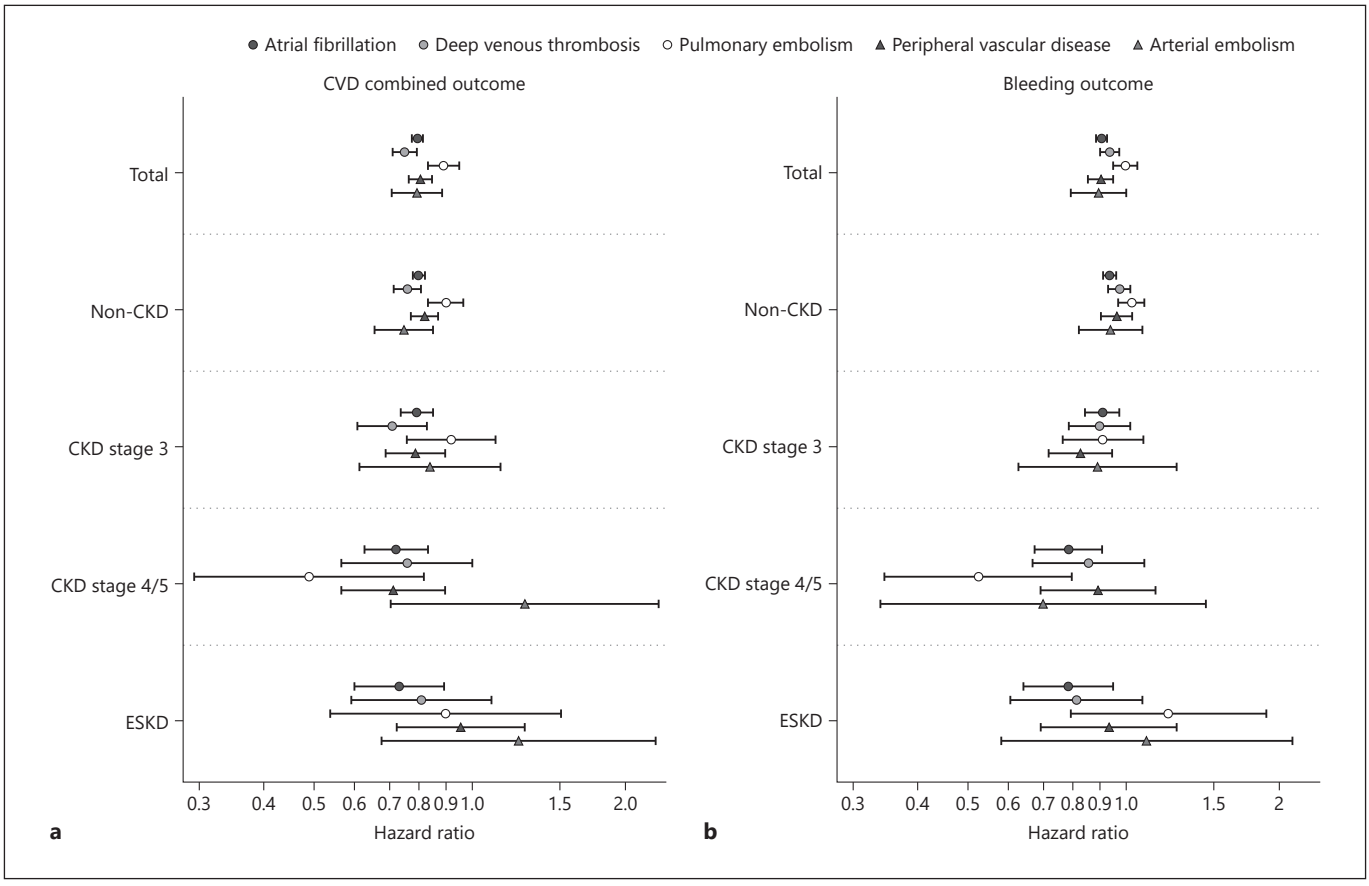

Fig. 2. Risk of time-varying cardiovascular and bleeding outcomes stratified by CKD stage and anticoagulation indication after model 3 adjustment. Hazard ratios are shown for subgroup analyses stratified by indication for anticoagulation, examining the association of warfarin versus DOACs therapy with combined (**a**) CVD and bleeding outcomes (**b**) in a cohort of 351,407 individuals from the OptumLabs® Data Warehouse (warfarin as the reference group, model 3 adjustment). CVD, cardiovascular disease; ESKD, end-stage kidney disease on dialysis; DOAC, direct oral anticoagulant.

embolism, DOAC use was associated with lower composite CVD risk in both non-CKD and CKD stage 4/5, but not in CKD stage 3 and ESKD. Patients with arterial embolism only had a significantly lower composite CVD risk among DOAC-treated patients in the non-CKD group.

With respect to our bleeding outcomes, DOAC use was associated with a lower risk of bleeding than warfarin for patients with AF. Patients with deep venous thrombosis and peripheral vascular disease on DOACs trended toward lower bleeding risk than warfarin for patients in our total cohort (Fig. 2b). For arterial embolism and pulmonary embolism, there did not appear to be a significant difference in bleeding risk among those treated with DOAC versus warfarin. No interaction was found between CKD stage and indication for anticoagulation. All models met the proportionality assumption.

CEM Analysis

In our CEM analysis, we found both bleeding and CVD risk decreased as CKD stage worsened in patients with DOAC treatment compared to warfarin-treated patients. Furthermore, across all CKD strata, both risk of bleeding and CVD outcomes were lower among DOAC users than warfarin users, similar to our previous analyses (online suppl. Table 5; Fig. 3).

Discussion

In a large and nationally representative US de-identified administrative claims database, we observed equal or reduced risk of composite CVD and composite bleeding outcomes with DOAC therapy compared to warfarin

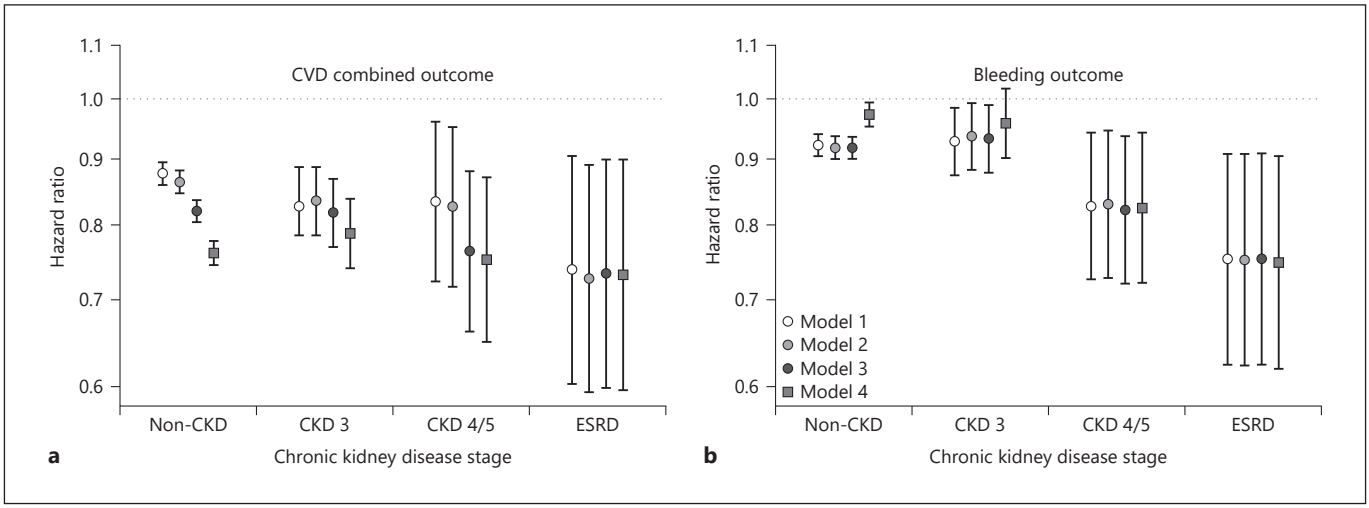

Fig. 3. Hazard ratios for the association of anticoagulation treatments with cardiovascular combined (**a**) and bleeding outcome (**b**) after matching DOAC-treated patients with warfarin-treated patients using CEM in 299,171 non-CKD, 23,012 CKD stage 3, 4,696 CKD stages 4–5, and 2,884 ESRD patients (reference: warfarin-treated patients). Note: patients were matched on variables in model 3. Model 3: demographics (age, gender, and race), year of the index anticoagulation prescription date, comorbidities and medications (diabetes, MI, CHF, ischemic stroke, hemorrhagic stroke, and antiplatelet medication use), and CKD stage. DOAC, direct oral anticoagulant; CHF, congestive heart failure; MI, myocardial infarction; CEM, coarsened exact matching.

across CKD stages. When assessing individual anticoagulation indications, AF was the only indication showing consistently lower risk of combined bleeding and CVD outcomes among DOAC users than warfarin users across non-CKD, CKD, and ESKD strata.

In non-CKD patients, our study is consistent with prior reports showing superior safety profiles of DOACs and is in line with guidelines recommending DOACs as first-line therapy for most anticoagulation indications [11, 12]. Our study adds to the prior report by Graham et al. [24], who observed a lower risk of thromboembolic stroke and intracranial bleeding with DOACs in a cohort of approximately 450,000 Medicare beneficiaries (of which 8.5–13.5% were nondialysis CKD patients). Our study also adds to the recent COMPASS trial showing a decrease risk of cardiovascular outcomes (cardiovascular death, stroke, or MI) among patients receiving rivaroxaban and aspirin versus aspirin alone or rivaroxaban alone [10]. While the COMPASS trial did not enroll patients with a GFR <15 mL/min, our data suggest that the cardioprotective effect of DOACs may extend to other DOACs and potentially to more severe stages of CKD.

In contrast to non-CKD patients, findings regarding safety and efficacy of DOACs from large retrospective nondialysis CKD and dialysis cohorts of patients have been conflicting. Data from a study investigating CKD stage 3–5 patients with AF reported similar ischemic stroke event rates with warfarin versus DOACs (apixaban, rivaroxaban, and dabigatran); however, there was a slightly higher risk of bleeding with DOACs [16]. Data from the Geisinger Health System also showed higher bleeding risks associated with DOACs than warfarin. This study utilized a smaller cohort of 6,412 AF patients of whom 4% had eGFR values less than 30 mL/min/1.73 m^2, and 0.4–0.5% were dialysis patients, potentially limiting generalizability to advanced CKD and ESKD populations [16]. In contrast, a recent meta-analysis comprising a subset of 78,053 patients among 15 studies showed that DOAC (vs. warfarin) use for any indication was associated with reduced risk of intracerebral hemorrhage, stroke, systemic embolism, mortality, and major bleeding among CKD patients [18].

In the dialysis population specifically, Siontis et al. [25] assessed 25,523 AF patients on dialysis and showed equivalent risks of stroke but lower risk of major bleeding with apixaban. In contrast, Chan et al. [26] analyzed the Fresenius Medical Care North America (FMCNA) ESKD database and noted that dabigatran and rivaroxaban were associated with a higher risk of adverse outcomes, especially bleeding risk. In this study published in 2015, only 525 patients on DOACs were assessed and newer DOACs such as apixaban were not

included, potentially limiting generalizability. A recent meta-analysis suggests that DOACs are associated with a reduced risk of thromboembolism in patients with AF on long-term dialysis, though findings were dominated by Siontis' large-single study comparing apixaban with warfarin [27].

Given these disparate findings, the relative safety profile of DOACs as an alternative to warfarin in the CKD and ESKD populations remains unclear. Nor is it clear if these studies done on AF patients are generalizable to patients who are on anticoagulation for other indications. Nonetheless, the results of our study provide further evidence that DOACs may be safer than warfarin in CKD and ESKD patients, though it remains unclear if DOACs are safer for other anticoagulation indications aside from AF.

The strengths of our study include a large cohort with a relatively long follow-up period of up to seven years, with comprehensive claims data. However, our large dataset containing commercial insurance coverage and MA enrollees, while representing a large swath of the American population, may underrepresent those among lower socioeconomic status (especially those who are unable to obtain or decline to obtain insurance coverage). There are other inherent limitations of retrospective database analysis with the potential for confounding by indication and selection bias. In addition, we utilized time-varying models in an attempt to overcome the limitation that some patients may have been switched from one anticoagulant to another, which may have introduced bias to our results. There may still be residual confounding by indication as the guidelines for using anticoagulation in ESKD patients remain controversial, despite expert opinion and a recent comprehensive systematic review on this topic [28–30]. In an attempt to assess residual confounding, we performed a CEM analysis which did not show any major differences to our analysis. We also acknowledge the lack of mortality data is a limitation to our study. The sources of mortality data available in the OLDW are incomplete; this is a known and inherent limitation to administrative claims databases in general [31]. However, as previous studies have shown a higher mortality with warfarin than DOACs, we do not believe that fewer events in the DOAC groups are due to a higher competing risk of death [32, 33].

While our cohort was constructed from 2010 onward, treatment guidelines for both VTE and AF have changed dramatically with the approval of new DOACs between 2010 and 2015. It is unlikely that we will be able to fully account for temporal changes in treatment strategies, despite sensitivity analysis our models. We also acknowledge potential inaccuracy by determining the stage of CKD as well as CVD and bleeding outcomes as we relied on ICD-9 codes [34]. Furthermore, some medications such as nonsteroidal anti-inflammatory medications, serotonin reuptake inhibitors, proton pump inhibitors, H2-blockers, and other anticoagulants such as heparin products can potentially alter bleeding risks that we were unable to account for in our analysis.

Our study was not able to address anticoagulation treatment efficacy, especially since there is heterogeneity across various anticoagulation indications in terms of treatment duration and stroke risk. We were also not able to construct a referent no-treatment group, which is particularly relevant in the setting of AF in ESKD where clinical equipoise exists and the risk of bleeding with any anticoagulant may outweigh potential benefits [35, 36]. We note the recent meta-analysis by Kuno and colleagues which suggests that there may not be a reduction in stroke risk in the addition of anticoagulation among dialysis patients with AF [27]. Further, a recent retrospective cohort study using 2012–2015 US Renal Data System data reported that apixaban did not impact stroke risk but was associated with a higher incidence of intracranial bleeding than maintenance dialysis patients not on any anticoagulation matched via a propensity score [37]. Randomized, placebo-controlled trials are needed to better define safe and effective treatment strategies for advanced CKD patients with VTE and AF.

While there are limitations in this investigation, we believe that our robust analysis provides insights into the safety profile of DOACs, especially in advanced CKD, a population that has traditionally been excluded from or has been difficult to study in clinical trials. The RENAL-AF trial, which compared apixaban to warfarin in US ESKD patients, was stopped early due to lack of funding after 155 of a planned 760 patients were enrolled and produced inconclusive results [38]. Outcomes data from large cohorts such as ours provide real-world evidence to guide clinical decision-making while prescribers await results from an ongoing German randomized trial in ESKD patients that directly compare apixaban and warfarin (the AXADIA trial) [39]. Overall, our data suggest an equivalent or superior safety profile with DOACs as compared to warfarin, across anticoagulation indications, which may factor in decision-making when providers are prescribing anticoagulation in the advanced CKD population.

Statement of Ethics

The study was based on de-identified OptumLabs© Data Warehouse (OLDW) data which contain information from an EMR database. Because data were de-identified, this study was classified as exempt by the University of California, Irvine Medical Center, and Tibor Rubin Veterans Affairs Medical Center Institutional Review Boards.

Conflict of Interest Statement

The authors report no disclosures relevant to the manuscript.

Author Contributions

J.S., J.-T.H., E.S., K.K.-Z., and W.L.L. contributed to writing the manuscript. J.-T.H., D.E., and E.S. contributed to data acquisition and processing. J.S., J.-T.H., E.S., and W.L.L. contributed to data analysis. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. This work was made possible by a research credit from OptumLabs granted to W.L.L. as part of a call for proposals within the University of California system. Preliminary findings were presented as a poster abstract at the American Society of Nephrology 2018 Kidney Week (San Diego, CA). W.L.L. acknowledges funding from the American Heart Association and the National Institutes of Health (Grants AHA 17IRG33410803 and NIH/NINDS R01 NS113337).

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