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Cardiorenal Outcomes Among Patients With Atrial Fibrillation Treated With Oral Anticoagulants

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Rationale & Objective: Direct oral anticoagulants (DOACs) have progressively replaced vitamin K antagonists (VKAs) for stroke prevention in patients with nonvalvular atrial fibrillation (AF). DOACs cause fewer bleeding complications, but their other advantages, particularly related to kidney outcomes, remain inconclusive. We studied the risks of chronic kidney disease (CKD) progression and acute kidney injury (AKI) after DOAC and VKA administration for nonvalvular AF.

Study Design: Retrospective cohort study.

Setting & Participants: Cohort study of Swedish patients enrolled in the Stockholm Creatinine Measurements (SCREAM) project with a diagnosis of nonvalvular AF during 2011-2018.

Exposure: Initiation of DOAC or VKA treatment.

Outcome: Primary outcomes were CKD progression (composite of >30% estimated glomerular filtration rate [eGFR] decline and kidney failure) and AKI (by diagnosis or KDIGO-defined transient creatinine elevations). Secondary outcomes were death, major bleeding, and the composite of stroke and systemic embolism.

Analytical Approach: Propensity score weighted Cox regression was used to balance 50 baseline confounders. Sensitivity analyses included

falsification end points, subgroups, and estimation of per-protocol effects.

Results: We included 32,699 patients (56% initiated DOAC) who were observed for a median of 3.8 years. Their median age was 75 years, 45% were women, and 27% had an eGFR <60 mL/min/1.73 m². The adjusted HRs for DOAC versus VKA were 0.87 (95% CI, 0.78-0.98) for the risk of CKD progression and 0.88 (95% CI, 0.80-0.97) for AKI. HRs were 0.77 (95% CI, 0.67-0.89) for major bleeding, 0.93 (95% CI, 0.78-1.11) for the composite of stroke and systemic embolism, and 1.04 (95% CI, 0.95-1.14) for death. The results were similar across subgroups of age, sex, and baseline eGFR when restricting to patients at high risk for thromboembolic events and when censoring follow up at treatment discontinuation or change in type of anticoagulation.

Limitations: Missing information on time in therapeutic range and treatment dosages.

Conclusions: Among patients with nonvalvular AF treated in routine clinical practice compared with VKA use, DOAC use was associated with a lower risk of CKD progression, AKI, and major bleeding but a similar risk of the composite of stroke, systemic embolism, or death.

Visual Abstract online

Complete author and article information provided before references.

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Atrial fibrillation (AF) is common, is present in >15% of individuals aged ≥75 years, and is one of the leading causes of ischemic stroke worldwide.¹ Oral anticoagulant treatment is recommended for most patients with nonvalvular AF to reduce the risk of stroke and systemic embolism.^{2,3} Randomized trials of warfarin against placebo reported risk reductions of 64% for stroke and systemic embolism.⁴ Subsequently, pivotal trials demonstrated similar or greater efficacy of direct oral anticoagulants (DOACs) compared with vitamin K antagonists (VKAs) in preventing those outcomes,⁵⁻⁸ with lower risks of major bleeding, including hemorrhagic strokes, more stable anticoagulant effects, and reduced need for monitoring.^{3,9} Consequently, their use has become more prevalent. Anticoagulation with either VKAs or DOACs may be associated with adverse kidney outcomes. Case reports and uncontrolled cohort studies have implicated VKAs as possibly causal in acute kidney injury (AKI)¹⁰⁻¹² and increased risk of decline in glomerular filtration rate (GFR), termed VKA-related nephropathy.^{10,13,14} The suggested mechanisms include glomerular hemorrhage,¹⁵ oxidative stress causing renal

tubular damage, and direct effects on renal vascular calcification by vitamin K-dependent alterations of matrix Gla protein.¹⁵⁻¹⁷ Reports have suggested there may be similar risks with DOAC treatment,¹⁸⁻²¹ but this is much less studied. VKAs inhibit the recycling of the anticalcification protein matrix Gla protein 1 and may be procalcific: this too has been suggested as a possible mechanism for worsening kidney function, distinct from their action as anticoagulants.²²⁻²⁵

However, post hoc analyses of 3 trials comparing DOACs with warfarin were not congruent; the rate of loss of GFR was reported as higher with warfarin,²⁶ higher with DOACs,²⁷ and similar in both groups.²⁸ A meta-analysis limited to randomized clinical trials (RCTs) evaluating “kidney failure” (reported either as serious adverse events or serum creatinine-based events) found no difference between DOACs and VKAs.²⁹ Other meta-analyses that included—and were dominated by—observational studies identified differences in variously defined AKI outcomes.^{30,31} However, observational studies in those meta-analyses used insensitive administrative codes to identify AKI, lacked information on baseline estimated

PLAIN-LANGUAGE SUMMARY

The relative safety of anticoagulation with direct oral anticoagulants (DOACs) or vitamin K antagonists like warfarin remains inconclusive, particularly with regard to outcomes related to kidney disease on injury. In a cohort of patients with nonvalvular atrial fibrillation from Sweden, we observed that initiation of a DOAC compared with warfarin was associated with a lower risk of the composite of kidney failure and sustained 30% decline in kidney function, as well as a lower risk of occurrence of acute kidney injury. In agreement with trial evidence, DOAC versus warfarin treatment was associated with a lower risk of major bleeding but a similar risk of the composite of stroke, systemic embolism, or death. Collectively, these findings add to the emerging evidence on the safety and effectiveness of DOAC administered for atrial fibrillation.

glomerular filtration rate (eGFR), were unable to evaluate long-term consequences to progressive eGFR loss, and were limited in follow-up time.

In this study we compare the risks of chronic kidney disease (CKD) progression and AKI among patients with nonvalvular AF initiating DOAC or VKA treatment. We used both administrative health care data and all creatinine measurements performed in our health care system.

Methods

The study derives from the Stockholm Creatinine Measurements (SCREAM) project, a health care utilization cohort from the region of Stockholm, Sweden.^{32,33} SCREAM is a repository of laboratory test results from 2006-2018 for any resident of the Stockholm region. These laboratory tests are linked using unique personal identification numbers to regional and national administrative databases with complete information on demographics, health care utilization, dispensed drugs, validated kidney replacement therapy outcomes, diagnoses, and vital status until the end of 2019, without loss to follow-up. The regional ethical review board in Stockholm approved the study; informed patient consent was deemed unnecessary because all data were deidentified at the Swedish Board of Health and Welfare.

Study Population and Study Design

We identified all adults (age ≥ 18 years) who had a diagnosis of AF in 2011-2018 and initiated DOAC or VKA treatment in Stockholm. New users of DOACs or VKA were defined as those with no previous dispensation of either treatment since at least 2006. Patients who had a history of valvular heart disease (mechanical prosthetic heart valve or moderate-to-severe mitral stenosis), were undergoing validated kidney replacement therapy, or had an eGFR

of <15 mL/min/1.73 m² or missing at baseline were excluded. The date of treatment initiation was defined as the index date and start of follow-up (T_0).

Exposure and Covariates

The study exposure was treatment with a DOAC (apixaban, dabigatran, rivaroxaban, or edoxaban) or warfarin (the VKA used in our region) at the index date. Baseline covariates were selected at the index date and included demographics (age, sex, attained education), prescription year, alcohol abuse, comorbidities (Table S1), ongoing medications (Table S2), stroke risk scores (CHA₂DS₂-VASc, and the modified-CHADS₂ score³⁴); a bleeding risk score (HAS-BLED; Table S3), and baseline eGFR. The same set of covariates was also defined as time-varying confounders in a sensitivity analysis, with the exception of sex and education, which were kept as time-fixed. The eGFR was calculated using routine ambulatory isotope-dilution mass spectrometry-traceable plasma creatinine measurements and applying the 2009 CKD-EPI equation without correction for race.³⁵ The eGFR at baseline was defined as the average of all creatinine measurements performed in the preceding 12 months and was categorized as ≥ 60 , 59-30, or <30 mL/min/1.73 m². Finally, to capture health care utilization and disease severity, we also considered the number of primary health care visits, outpatient specialist visits, International Classification of Diseases (ICD) diagnoses issued, and procedure codes issued in the 12 months before.

Outcomes

The primary study outcomes were (1) CKD progression and (2) AKI. CKD progression was specified as the composite of kidney failure or sustained 30% eGFR decline. Kidney failure was defined as the presence of sustained eGFR <15 mL/min/1.73 m², initiation of maintenance dialysis, or kidney transplantation (Table S4). To reduce outcome misclassification bias owing to intrinsic eGFR variability and to confirm whether eGFR declines were sustained over time, we used a linear interpolation method.³⁶ In brief, and for each individual, a linear regression line was fitted through all outpatient eGFR values. To be considered a sustained eGFR <15 mL/min/1.73 m², the linear regression slope needed to be negative, and the 15 mL/min/1.73 m² threshold needed to be crossed before the last assessment. The time to event was then defined as the interpolated moment in which the linear regression line crossed the 15 mL/min/1.73 m² threshold. A sustained 30% eGFR decline was defined in a similar manner. AKI was identified by a combination of diagnoses (ICD-10 code N17) in outpatient or hospital care and transient creatinine elevations during hospitalization according to KDIGO criteria³⁷ (increase in creatinine ≥ 26 μ mol/L over 48 hours or >1.5 times within 7 days; Table S4). For these outcomes, follow-up ended on the date an end point was reached, date of last laboratory measurement, or December 31, 2018, whichever came first.

In addition, we evaluated cardiovascular risk-benefit as secondary study outcomes to compare with the results from pivotal trials. These end points included (1) a composite of ischemic or undefined stroke and systemic embolism; (2) major bleeding (including intracranial bleeding/hemorrhagic stroke, gastrointestinal and other types of bleeding); and (3) all-cause and cardiovascular mortality. These outcomes were ascertained through ICD-10 codes issued at first and second diagnostic positions during a hospital admission, or as first diagnostic position as cause of death. For these outcomes, follow-up ended on the date of end points, death, or December 31, 2019, whichever came first.

Statistical Analyses

Continuous variables are presented as medians with IQR and categorical variables as numbers and percentages. We used inverse probability of treatment weighting to control for baseline confounding.^{38,39} We estimated the probability of receiving DOAC versus VKA treatment as a function of the baseline covariates listed above in a logistic regression model where treatment assignment was the dependent variable. Weighting was considered appropriate if the standardized mean difference (SMD) between treatment groups was <0.1. Weights were stabilized to increase precision by adding the marginal probability of treatment to the numerator of the weights. Weighted cause-specific hazard models were used to estimate hazard ratios (HR) and 95% CI between DOAC or VKA initiation and outcomes. Robust variance estimation was used to calculate confidence intervals after weighting. In the primary analysis, individuals were considered according to their initially assigned treatment group irrespective of discontinuation or treatment switch (intention-to-treat approach). Weighted cumulative incidence curves were estimated to graphically represent the effect of each treatment. Assuming no unmeasured confounding, the weighted cumulative incidence curves for a given treatment provide the hypothetical cumulative incidence that would have been observed had all patients followed that particular strategy.⁴⁰

Associations between DOAC and VKA with the study outcomes were investigated by strata of age (≥ 75 vs < 75 years), sex, and baseline eGFR (≥ 60 vs < 60 mL/min/ 1.73 m²). To calculate the stratum-specific HRs while preserving balance within subgroups, we re-estimated the probability of receiving DOAC versus VKA and refitted the weighted proportional hazards models in each stratum. Differences in the HRs between strata (ie, effect modification) were tested using the Wald test for interaction.

We performed several sensitivity analyses. First, to explore potential residual confounding due to unmeasured confounders, we assessed the association between DOAC versus VKA initiation and the falsification outcomes pneumonia or cataract surgery.⁴¹ Because we did not expect DOACs to be associated with either of the falsification outcomes, an association may point to residual confounding or information bias.⁴² Second, we restricted

our study population to (1) patients with CHA₂DS₂-VASc score of ≥ 2 because those with a score of 0 or 1 may have an indication for short-term DOAC treatment when they undergo cardioversion; (2) patients free from a history of venous thromboembolism, to evaluate whether dual indication for oral anticoagulant treatment would modify our observations; (3) patients initiating oral anticoagulant therapy within 90 days from an incident AF diagnosis, to increase confidence that this was the indication for oral anticoagulant use.

Third, we censored patients at treatment discontinuation or treatment switch (from VKA to DOAC or vice versa), thus emulating a per-protocol analysis. Because we expected the rate of discontinuation or switch to depend on the initial treatment assigned (ie, discontinuation would be more frequent among users of VKA), we used inverse probability of censoring weighting to account for the differential loss to follow-up (ie, informative censoring) between treatment groups. This method also takes into account differences in mortality risk as death was considered in the censoring event together with discontinuation and switch. To this end, we split the follow-up into monthly intervals, and at each interval we calculated the probability of remaining uncensored. These probabilities were used to calculate stabilized weights where the numerator of the stabilized weights was the probability of remaining uncensored conditional on time-fixed confounders at each month, and the denominator the probability of remaining uncensored conditional on time-fixed and time-varying confounders. Stabilized weights were truncated at the 99.99th percentile to avoid undue influence of large weights. We then estimated the discrete-time HR using a weighted pooled logistic regression model including the time-varying censoring and baseline treatment weights. Finally, to investigate potential differential outcome ascertainment due to differences in the frequency of serum creatinine testing between the DOAC and VKA groups, we calculated the proportion of individuals with a serum creatinine test during follow-up in each group. All analyses were performed using R version 4.0.5 (CRAN R Project).

Results

Demographics and Clinical Characteristics

In the region of Stockholm, 71,167 adults filled DOAC or VKA prescriptions during 2011-2018. After applying inclusion and exclusion criteria, we identified 32,699 individuals with AF who initiated either therapy and were considered for the analysis (Fig S1). Of those, 18,323 (56%) started DOAC and 14,376 (44%) started VKA treatment. The vast majority of patients (>95%) initiated oral anticoagulant treatment within 90 days after an incident AF diagnosis (Fig S2). Their median age was 75 (IQR, 68-83) years, and 45% were women (Table 1). The median eGFR was 73 (IQR, 59-85) mL/min/ 1.73 m², and 27% had an eGFR < 60 mL/min/ 1.73 m². Hypertension was the most common comorbidity (72%), followed by

Table 1. Baseline Characteristics of Patients Initiating Oral Anticoagulants in Stockholm in 2011-2018, Overall and Stratified by Initial Treatment Group

	Overall (N = 32,699)	Oral Anticoagulant Started	
		DOAC (n = 18,323)	VKA (n = 14,376)
Age, y	75 [68-83]	75 [68-83]	76 [68-83]
Age category			
<75 y	15,336 (47%)	8,742 (48%)	6,594 (46%)
≥75 y	17,363 (53%)	9,581 (52%)	7,782 (54%)
Women	14,816 (45%)	8,399 (45%)	6,417 (45%)
Access to health care in the previous year			
Primary care visits	5 [2-8]	4 [2-8]	5 [2-8]
Outpatient visits	3 [1-6]	3 [1-7]	2 [1-5]
Issued ICD-10 codes	15 [8-27]	16 [8-29]	15 [8-26]
Procedures	4 [1-10]	4 [1-11]	3 [1-8]
Education			
Compulsory	8,730 (27%)	4,530 (25%)	4,200 (29%)
Secondary	12,951 (40%)	7,213 (39%)	5,738 (40%)
University	10,385 (32%)	6,256 (34%)	4,129 (29%)
Missing	633 (2%)	324 (2%)	309 (2%)
eGFR, mL/min/1.73 m ²	73 [59-85]	74 [60-85]	72 [57-85]
eGFR category			
15-29 mL/min/1.73 m ²	670 (2%)	189 (1%)	481 (3%)
30-59 mL/min/1.73 m ²	8,078 (25%)	4,300 (24%)	3,778 (26%)
≥60 mL/min/1.73 m ²	23,951 (73%)	13,834 (75%)	10,117 (71%)
Medical history			
Hypertension	23,621 (72%)	13,156 (72%)	10,465 (73%)
Vascular disease	9,714 (30%)	4,896 (27%)	4,818 (33%)
Cancer	8,519 (26%)	4,994 (27%)	3,525 (24%)
CHF/LV dysfunction	8,089 (25%)	4,071 (22%)	4,018 (28%)
Heart failure	7,975 (24%)	3,999 (22%)	3,976 (28%)
Diabetes	6,906 (21%)	3,723 (20%)	3,183 (22%)
Stroke, TIA, or embolism	6,709 (20%)	3,649 (20%)	3,060 (21%)
Anemia	5,693 (17%)	3,203 (17%)	2,490 (17%)
Stroke	4,845 (15%)	2,632 (14%)	2,213 (15%)
Myocardial infarction	4,887 (15%)	2,366 (13%)	2,521 (17%)
Diabetic complications	4,473 (14%)	2,293 (12%)	2,180 (15%)
Prior bleeding	3,576 (11%)	2,133 (12%)	1,443 (10%)
COPD	3,566 (11%)	2,058 (11%)	1,508 (10%)
VTE	3,140 (10%)	1,648 (9%)	1,492 (10%)
PCI	2,641 (8%)	1,322 (7%)	1,319 (9%)
Rheumatoid arthritis	2,323 (7%)	1,307 (7%)	1,016 (7%)
Kidney disease	2,329 (7%)	1,225 (7%)	1,104 (8%)
Fracture	1,964 (6%)	1,180 (6%)	784 (5%)
DVT or knee/hip replacement	1,761 (5%)	904 (5%)	857 (6%)
Alcohol abuse	1,768 (5%)	1,129 (6%)	639 (4%)
AKI	890 (3%)	499 (3%)	391 (3%)
Liver disease	726 (2%)	428 (2%)	298 (2%)
Risk score			
CHA ₂ DS ₂ -VASc	3 [2-5]	3 [2-4]	3 [2-5]
Modified-CHADS ₂	5 [3-7]	5 [3-7]	5 [3-7]
HAS-BLED	2 [2-3]	2 [2-3]	3 [2-3]
Concomitant medications			
β-blocker	26,174 (80%)	14,485 (79%)	11,689 (81%)
RAAS inhibitor	18,248 (56%)	10,005 (55%)	8,243 (57%)
Aspirin	14,538 (44%)	7,106 (39%)	7,432 (52%)
Statin	11,911 (36%)	6,339 (35%)	5,572 (39%)
Diuretic	11,240 (34%)	5,607 (31%)	5,633 (39%)

(Continued)

Table 1 (Cont'd). Baseline Characteristics of Patients Initiating Oral Anticoagulants in Stockholm in 2011-2018, Overall and Stratified by Initial Treatment Group

	Overall (N = 32,699)	Oral Anticoagulant Started	
		DOAC (n = 18,323)	VKA (n = 14,376)
Calcium channel blocker	10,018 (31%)	5,539 (30%)	4,479 (31%)
PPI	7,946 (24%)	4,396 (24%)	3,550 (25%)
NSAID	4,152 (13%)	2,263 (12%)	1,889 (13%)
Antidepressant	3,925 (12%)	2,348 (13%)	1,577 (11%)
Nitrate	4,078 (12%)	1,810 (10%)	2,268 (16%)
Oral antidiabetic drug	3,468 (11%)	1,897 (10%)	1,571 (11%)
Corticosteroids	3,020 (9%)	1,712 (9%)	1,308 (9%)
Digoxin	2,687 (8%)	1,280 (7%)	1,407 (10%)
Clopidogrel	2,143 (7%)	1,032 (6%)	1,111 (8%)
Insulin	2,095 (6%)	1,008 (5%)	1,087 (8%)
Other antiplatelet	849 (3%)	403 (2%)	446 (3%)
Calendar year of initiation			
2011-2014	15,130 (46%)	3,472 (19%)	11,658 (81%)
2015-2018	17,569 (54%)	14,851 (81%)	2,718 (19%)

Abbreviations: AKI, acute kidney injury; CHA₂DS₂-VAsC [score], score for atrial fibrillation stroke risk based on congestive heart failure, hypertension, age, diabetes, stroke/transient ischemic attack/thromboembolism, sex, and vascular disease; CHADS₂ [score], score for atrial fibrillation stroke risk based on CHF, hypertension, age, diabetes, stroke (doubled); CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; HAS-BLED score, bleeding risk score based on hypertension, abnormal renal and liver function, stroke, bleeding tendency or predisposition, labile international normalized ratio, elderly, and drugs; ICD-10, *International Classification of Diseases, Tenth Revision*; LV, left ventricular; NSAID, nonsteroidal anti-inflammatory drug; PCI, percutaneous coronary intervention; PPI, proton pump inhibitors; RAAS, renin-angiotensin-aldosterone system; TIA, transient ischemic attack; VKA, vitamin K antagonist; VTE, venous thromboembolism.

vascular disease (30%), history of cancer (26%), and congestive heart failure or left ventricular dysfunction (25%). The median CHA₂DS₂-VAsC score was 3 (IQR, 2-5), the median modified-CHADS₂ score was 5 (IQR, 3-7),

and the median HAS-BLED score was 2 (IQR, 2-3). Patients also commonly used β -blockers (80%), renin-angiotensin-aldosterone system (RAAS) inhibitors (56%), aspirin (44%), and statins (36%). Apixaban was the most

Table 2. Number of Events, Incidence Rates, and AHRs for the Association Between DOAC Versus VKA Initiation and Outcomes

	No. of Events (IR/1,000 Person-Years) ^a		AHR (95% CI) for DOAC vs VKA ^b
	VKA	DOAC	
Kidney Outcomes			
CKD progression	2,244 (36.3)	1,208 (30.4)	0.87 (0.78-0.98)
Sustained 30% eGFR decline	2,205 (35.7)	1,202 (30.3)	0.88 (0.78-0.98)
Kidney failure	196 (3.0)	42 (1.0)	0.43 (0.25-0.73)
AKI	3,277 (54.5)	1,825 (46.7)	0.88 (0.80-0.97)
Cardiovascular Outcomes			
Composite of stroke or systemic embolism	1,118 (15.3)	734 (13.3)	0.93 (0.78-1.11)
Ischemic stroke	991 (13.2)	658 (11.9)	0.88 (0.73-1.06)
Bleeding Outcomes			
Major bleeding	1,414 (19.5)	808 (14.7)	0.77 (0.67-0.89)
Intracranial bleeding	635 (8.5)	316 (5.6)	0.59 (0.47-0.75)
Gastrointestinal bleeding	615 (8.3)	398 (7.1)	0.96 (0.79-1.17)
Other bleeding	311 (4.2)	170 (3.0)	0.88 (0.66-1.18)
Mortality			
All-cause mortality	4,842 (64.1)	3,222 (57.1)	1.04 (0.95-1.14)
CV death	2,351 (31.1)	1,467 (26.0)	0.99 (0.84-1.17)

Median follow-up: kidney outcome 3.0 (IQR, 1.4-5.0) years, all others 3.8 (IQR, 2.1-5.8) years. Abbreviations: AHR, adjusted hazard ratio; AKI, acute kidney injury; CKD, chronic kidney disease; CV, cardiovascular; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; IR, incidence rate; VKA, vitamin K antagonist.

^aNumber of events and incidence rates were calculated in the original, unweighted population.

^bAnalyses were adjusted for the following 50 variables: age; sex; calendar year; number of primary health care visits; number of outpatient specialist visits; number of diagnoses issued; number of procedure codes; education; eGFR; hypertension; anemia; liver disease; kidney disease; alcohol abuse; prior bleeding; stroke/transient ischemic stroke/embolism; stroke; myocardial infarction; heart failure; congestive heart failure; vascular disease; chronic obstructive pulmonary disease; rheumatoid arthritis; diabetes; diabetic complications; cancer; deep vein thrombosis; knee/hip surgery; percutaneous coronary intervention; venous thromboembolism; fracture; risk scores (Table 1); and concomitant use of aspirin, clopidogrel, nonsteroidal anti-inflammatory drugs, other antiplatelet, corticosteroids, diuretics, β -blockers, calcium channel blockers, renin-angiotensin-aldosterone-system inhibitors, statin, insulin, other antidiabetic medications, antidepressants, digoxin, nitrate, and proton-pump inhibitors using inverse probability of treatment weighting.

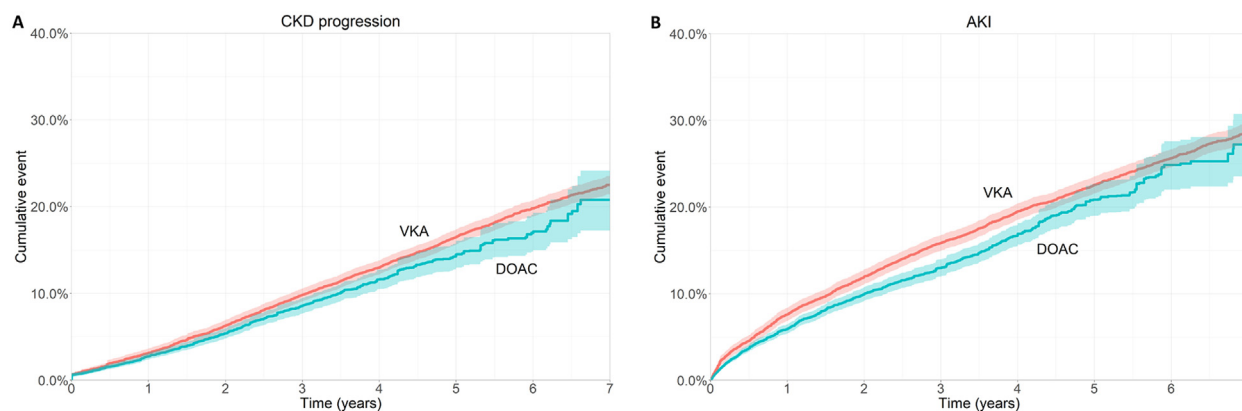


Figure 1. Weighted cumulative incidence curves for (A) CKD progression and (B) AKI by DOAC or VKA initiation. Shaded areas represent 95% CI. Abbreviations: AKI, acute kidney injury; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

prescribed DOAC at therapy initiation (71%), followed by dabigatran (17%) and rivaroxaban (12%). Edoxaban was rarely prescribed (0.2%). The proportion of patients prescribed DOAC instead of VKA treatment increased steadily over time (Fig S3A). By 2018, prescriptions for a DOAC rather than warfarin were given to 98% of users with $eGFR \geq 60$ mL/min/1.73 m², 95% of those with $eGFR$ 30–59 mL/min/1.73 m², and 69% of participants with $eGFR$ 15–29 mL/min/1.73 m² (Fig S3B). Figure S4 shows good balance in all measured covariates after inverse probability of treatment weighting with all SMDs <0.1 (Fig S4).

Comparative Effectiveness of DOAC Versus VKA Treatment on Kidney Outcomes

The median follow-up time before censoring or end of follow-up was 3.0 (IQR, 1.4–5.0) years. CKD progression occurred in 1,208 individuals in the DOAC group and 2,244 individuals in the VKA group, corresponding to incidence rates of 30.4 and 36.3 per 1,000 person-years, respectively (Table 2). Compared with VKA users, the adjusted HR for CKD progression for DOAC users was 0.87 (95% CI, 0.78–0.98). The weighted cumulative incidence curves are depicted in Figure 1A. The lower adjusted HR for CKD progression reflected lower risks of both components of the composite: sustained 30% $eGFR$ decline (HR, 0.88 [95% CI, 0.78–0.98]) and kidney failure (HR, 0.43 [95% CI, 0.25–0.73]). During the same period, 1,825 patients in the DOAC group and 3,277 patients in the VKA group experienced an AKI event, corresponding to incidence rates of 46.7 and 54.5 per 1,000 person-years, respectively. Compared with VKA use, DOAC use was associated with a lower AKI risk, with an adjusted HR of 0.88 (95% CI, 0.80–0.97). The weighted cumulative incidence curves showed good separation between the groups in the first years of follow-up (Fig 1B).

Comparative Effectiveness of DOAC Versus VKA on Cardiovascular Outcomes, Bleeding, and Death

The median follow-up time for all-cause mortality was 3.8 (IQR, 2.1–5.8) years. No differences were observed

between DOAC versus VKA treatment for the composite outcome of ischemic stroke or systemic embolism (HR, 0.93 [95% CI, 0.78–1.11]). There was a significantly lower risk for major bleeding (HR, 0.77 [95% CI, 0.67–0.89]) (Table 2; Fig S5). For the single components, a significantly lower risk was observed for intracranial bleeding (HR, 0.59 [95% CI, 0.47–0.75]) but there was no significant difference between treatment groups for the risk of ischemic stroke (HR, 0.88 [95% CI, 0.73–1.06]), gastrointestinal bleeding (HR, 0.96 [95% CI, 0.79–1.17]), or other types of bleeding (HR, 0.88 [95% CI, 0.66–1.18]).

A total of 3,222 individuals died in the DOAC group and 4,842 in the VKA group, corresponding to incidence rates of 57.1 and 64.1 per 1,000 person-years, respectively. After adjustment, this resulted in a HR of 1.04 (95% CI, 0.95–1.14) for all-cause death and 0.99 (95% CI, 0.84–1.17) for cardiovascular death with DOAC compared with VKA (Fig S6; Table 2).

Subgroup and Sensitivity Analyses

We generally observed consistent results with no signs of heterogeneity for the risk of CKD progression or AKI across prespecified subgroups of age (Fig S7) and baseline $eGFR$ strata (Fig S8). There was a suggestion of heterogeneity with lower risk of the composite of ischemic/systemic embolism and ischemic stroke associated with DOAC compared with VKA treatment among women (HR, 0.78 [95% CI, 0.60–1.01]) compared with men (HR, 1.16 [95% CI, 0.91–1.49]; P for interaction, <0.001) (Fig S9).

We obtained findings similar to our primary analysis when restricting the population to patients with CHA_2DS_2-VASc score of ≥ 2 (Table S5), to patients free from venous thromboembolism history (Table S6), and to patients starting treatment within 90 days from an incident AF diagnosis (Table S7). During follow-up, 15,339 individuals discontinued treatment or switched to the other therapy. The proportion of patients who discontinued/switched was higher in the VKA group (77%) than in the DOAC group (21%), and mostly attributed to switching.

After accounting for the propensity of discontinuing/switching, DOAC use was still associated with a lower risk of CKD progression (HR, 0.77 [95% CI, 0.64-0.92]) and of AKI (HR, 0.79 [95% CI, 0.71-0.89]) compared with VKA. We also observed similar results regarding our secondary cardiovascular outcomes, with the only exception of a significantly lower risk of ischemic stroke (HR, 0.59 [95% CI, 0.36-0.98]) associated with DOAC versus VKA treatment (Table S8). Use of DOAC versus VKA was not associated with the falsification outcomes of pneumonia or cataract surgery (Table S9). Both DOAC initiators and VKA initiators had a similar rate of outpatient creatinine tests per person-years of follow-up (Table S10).

Discussion

In this cohort study of 32,699 nonvalvular AF patients from routine clinical practice, initiation of DOAC versus VKA was associated with more favorable kidney outcomes: a lower risk of the composite of kidney failure and sustained 30% eGFR decline, as well as a lower risk of AKI occurrence. In agreement with trial evidence, we showed that DOAC versus VKA treatment was associated with a lower risk of major bleeding but a similar risk of the composite of stroke, systemic embolism, or death. The observed associations were consistent across levels of baseline eGFR and across sensitivity analyses, including per-protocol analyses and restricting to patients at high risk for thromboembolic events. The results from the stratified analyses should be interpreted with caution and considered as hypothesis-generating only because they are not corrected for multiple testing and may be subject to false positives.

The possibility of better kidney outcomes in patients receiving DOAC compared with VKA treatment was initially suggested by a post hoc analysis of the RE-LY trial, in which open-label warfarin was compared with dabigatran treatment in patients with AF who were at high risk of stroke. The results showed that the dabigatran group had a slower decline in eGFR compared with warfarin, as well as a lower risk for 25% eGFR decline.²⁶ However, subsequent analyses in pivotal trials comparing rivaroxaban (ROCKET-AF) or apixaban (ARISTOTLE) with warfarin treatment did not confirm these findings.^{27,28} A meta-analysis of these RCTs did not show a difference,²⁹ but some of the original RCTs were limited to “kidney failure” reported as a serious adverse event and the others used variously defined changes in creatinine, which could have resulted in lack of sensitivity of outcome detection and misclassification.

Several observational studies have attempted to compare DOAC and VKA treatment with regard to CKD progression.⁴³⁻⁴⁸ The majority of these studies defined CKD progression using diagnostic codes of CKD, which are sensitive to detection bias given the poor awareness and underutilization of ICD diagnoses for this condition.^{49,50} Other identified limitations are restriction to

certain population segments,^{44,48} low sample size,⁴⁶ short follow-up period, or inclusion of prevalent users of the medication.⁴³ A 2021 meta-analysis³¹ pooled data from 7 of these studies with data from 11 RCTs. For the outcomes AKI and “worsening renal function,” the pooled hazard ratios for DOAC versus VKA were 0.70 (95% CI, 0.64-0.77) and 0.83 (95% CI, 0.73-0.95), respectively. This meta-analysis was dominated by cohort studies because of their comparatively large event numbers and were highly heterogeneous (I^2 of 84% and 76%, respectively).

The study of Yao et al⁴⁷ is, to the best of our knowledge, the sole observational study investigating the risk of CKD progression of these therapies using laboratory measurements. They studied administrative and laboratory data in a private health care system from the United States, including 9,769 patients with nonvalvular AF starting DOAC or VKA treatment in 2010-2016. With a median follow-up of 10.7 months, the number of kidney events detected was low. Despite this, they found that DOAC compared with VKA treatment was associated with lower risks of a $\geq 30\%$ decline in eGFR (HR, 0.77 [95% CI, 0.66-0.89]) and a doubling of creatinine (HR, 0.62 [95% CI, 0.40-0.95]). Our study agrees with and expands this evidence to a larger, more contemporary population with substantially longer follow up.

Further, our study setting is in the context of universal health care access and uses patients' data from an entire region, which make it less susceptible to biases arising from differential access to health care. An additional strength is the use of a linear interpolation method³⁶ to ascertain chronic declines in eGFR. Given the many factors influencing eGFR, this method is less susceptible to transient variation that may misclassify the outcome when requiring only one assessment to pass the threshold.

Several large observational studies have also investigated differences in the risk of AKI between DOAC and VKA users.^{43-45,47,51,52} Again, their limitation has been the reliance on insensitive diagnostic codes for AKI. Recently, Harel et al⁵³ evaluated the risk of AKI associated with initiation of DOAC or warfarin among 20,683 older adults (aged ≥ 66 years) from Ontario, Canada, during a median follow-up period of 308 days. Compared with users of warfarin, they observed a relative lower risk among users of apixaban (HR, 0.81 [95% CI, 0.72-0.93]), rivaroxaban (HR, 0.85 [95% CI, 0.73-0.98]), and dabigatran (HR, 0.65 [95% CI, 0.53-0.80]). Although our results agree and serve to increase the generalizability of the finding, we note several differences: we had a larger sample size, a broader population of all ages, and considerably longer follow-up period. Our lack of selection by age likely explains our approximately 60% lower incidence rates of AKI compared with Harel et al. However, because of the predominant use of apixaban in our setting, we were unable to conduct drug-stratified analyses. Our evaluation of cardiovascular effectiveness and safety outcomes gives indirect validity to our kidney end points. Consistent with

trials and existing observational reports,⁵⁴⁻⁵⁷ patients on DOACs in our study had lower risks of major bleeding and intracranial bleeding, but similar risks of stroke and systemic embolism, ischemic stroke, and death. These findings agree with a previous study from our region⁵⁸ with the exception of a higher risk of gastrointestinal bleeds with DOACs versus VKA in that study. This difference may be related to control for eGFR as a confounder in our study and that we have a more contemporary population, which is characterized by the increased use of apixaban during recent years. As shown in trials, apixaban is associated with a lower bleeding risk compared with other DOACs.²⁹⁻³¹

Our study also has limitations. We lacked information on the time in therapeutic range (TTR) for VKA. Though it is a possibility that outcome differences are explained by inadequate TTR control, external data show that Sweden has generally excellent international normalized ratio (INR) control, with a mean TTR over 75% in RCTs^{59,60} and observational studies.⁶¹ We had few patients initiating therapy with eGFR <30 mL/min/1.73 m² and also lacked information on DOAC dosages, but when accounting for changes in the treatment strategy during follow-up, our results were consistent.

Our study is observational, and residual confounding cannot be excluded. However, given our design and extensive adjustment for confounders, the agreement with trial evidence, as well as the negative control outcome analysis, we find it unlikely that residual confounding fully explains the observed reduction in kidney outcomes. Unlike in trials, creatinine levels in our study were not tested at predefined intervals but in connection with routine health care, with variable rates of monitoring. Nonetheless, we believe that our findings are not explained by differential outcome ascertainment because the frequency of creatinine testing was similar in the 2 treatment groups and because the outcome of kidney failure (which is not affected by outcome ascertainment bias) showed findings consistent with eGFR decline. Finally, the reduction in kidney outcomes is an “unintended” effect of anticoagulation treatment, as this is not an indication for treatment, and unintended effects generally suffer less from confounding by indication.^{62,63} To conclude, in this observational study from the routine care of an entire region, initiation of DOAC compared with VKA treatment was associated with lower risks of CKD progression, AKI, and major bleeding but a similar risk of the composite of stroke and systemic embolism.

Supplementary Material

Supplementary File (PDF)

Figure S1: Selection of the study population.

Figure S2: Cumulative proportion of time between AF diagnosis and treatment initiation.

Figure S3: Pattern of oral anticoagulant prescription over time (A) overall and (B) by eGFR categories.

Figure S4: Standardized mean difference before and after inverse probability of treatment weighting.

Figure S5: Weighted cumulative incidence curves for (A) composite of stroke and systemic embolism and (B) major bleeding by DOAC or VKA initiation.

Figure S6: Weighted cumulative incidence curves for (A) all-cause death and (B) cardiovascular death by DOAC or VKA initiation.

Figure S7: Association between DOAC versus VKA use and outcomes by age strata.

Figure S8: Association between DOAC versus VKA use and outcomes by eGFR strata.

Figure S9: Association between DOAC versus VKA use and outcomes by sex.

Table S1: Definition of comorbidities.

Table S2: Definition of medications.

Table S3: Risk scores.

Table S4: Definition of outcomes.

Table S5: Number of events, incidence rates, and adjusted HRs for the association between DOAC vs VKA initiation and outcomes in patients with CHA₂DS₂-VASc ≥ 2.

Table S6: Number of events, incidence rates, and adjusted HRs for the association between DOAC vs VKA initiation and outcomes among patients without history of venous thromboembolism and <3 months between AF diagnosis and treatment initiation.

Table S7: Number of events, incidence rates, and adjusted HRs for the association between DOAC versus VKA initiation and outcomes among patients with <3 months between AF diagnosis and treatment initiation.

Table S8: Number of events, incidence rates, and adjusted HRs for the association between DOAC versus VKA initiation and outcomes accounting for treatment switch and discontinuation.

Table S9: Number of events, incidence rates, and adjusted HRs for the association between DOAC versus VKA initiation and falsification outcomes.

Table S10: Frequency of creatinine measurement during follow-up in the observed and weighted population.

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Cardiorenal Outcomes Among Patients With Atrial Fibrillation Treated With Oral Anticoagulants

Setting, Participants, and Methods	Findings	
 Retrospective cohort study Stockholm, Sweden (<i>SCREAM Project</i>)	DOAC vs VKA: Adjusted Hazard Ratio (95% CI)	
 N = 32,699 non-valvular atrial fibrillation patients	 CKD progression	0.87 (0.78-0.98)
 New users of direct oral anticoagulants (DOAC) vs vitamin K antagonists (VKA)	 AKI	0.88 (0.80-0.97)
 Propensity-score weighted Cox regression	 Stroke/systemic embolism	0.93 (0.78-1.11)
 2011-2018 • Median follow-up for kidney outcomes: 3.0 years • Median follow-up for CV outcomes: 3.8 years	 Major bleeding	0.77 (0.67-0.89)

CONCLUSION: In routine clinical practice, compared with VKA, DOAC use was associated with a lower risk of CKD progression, AKI, and major bleeding, but similar risk of stroke/systemic embolism.

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