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Original Article

ORIGINAL ARTICLE

Oral anticoagulant treatment and risk of kidney disease—a nationwide, population-based cohort study

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ABSTRACT

Background. Direct oral anticoagulants (DOACs) are recommended as first-line treatment of atrial fibrillation. Whether DOAC use is associated with lower risks of kidney complications compared with vitamin K antagonists (VKAs) remains unclear. We examined this association in a nationwide, population-based cohort study.

Methods. We conducted a cohort study including patients initiating oral anticoagulant treatment within 3 months after an atrial fibrillation diagnosis in Denmark during 2012–18. Using routinely collected creatinine measurements from laboratory databases, we followed patients in an intention-to-treat approach for acute kidney injury (AKI) and chronic kidney disease (CKD) progression. We used propensity-score weighting to balance baseline confounders, computed weighted risks and weighted hazard ratios (HRs) with 95% confidence intervals (CIs) comparing DOACs with VKAs. We performed several subgroup analyses and a per-protocol analysis.

Results. We included 32 781 persons with atrial fibrillation initiating oral anticoagulation (77% initiating DOACs). The median age was 75 years, 25% had a baseline estimated glomerular filtration rate <60 mL/min/1.73 m^2, and median follow-up was 2.3 (interquartile range 1.1–3.9) years. The weighted 1-year risks of AKI were 13.6% in DOAC users and 15.0% in VKA users (HR 0.86, 95% CI 0.82; 0.91). The weighted 5-year risks of CKD progression were 13.9% in DOAC users and 15.4% in VKA users (HR 0.85, 95% CI 0.79; 0.92). Results were similar across subgroups and in the per-protocol analysis.

Conclusions. Initiation of DOACs was associated with a decreased risk of AKI and CKD progression compared with VKAs. Despite the potential limitations of observational studies, our findings support the need for increased clinical awareness to prevent kidney complications among patients who initiate oral anticoagulants.

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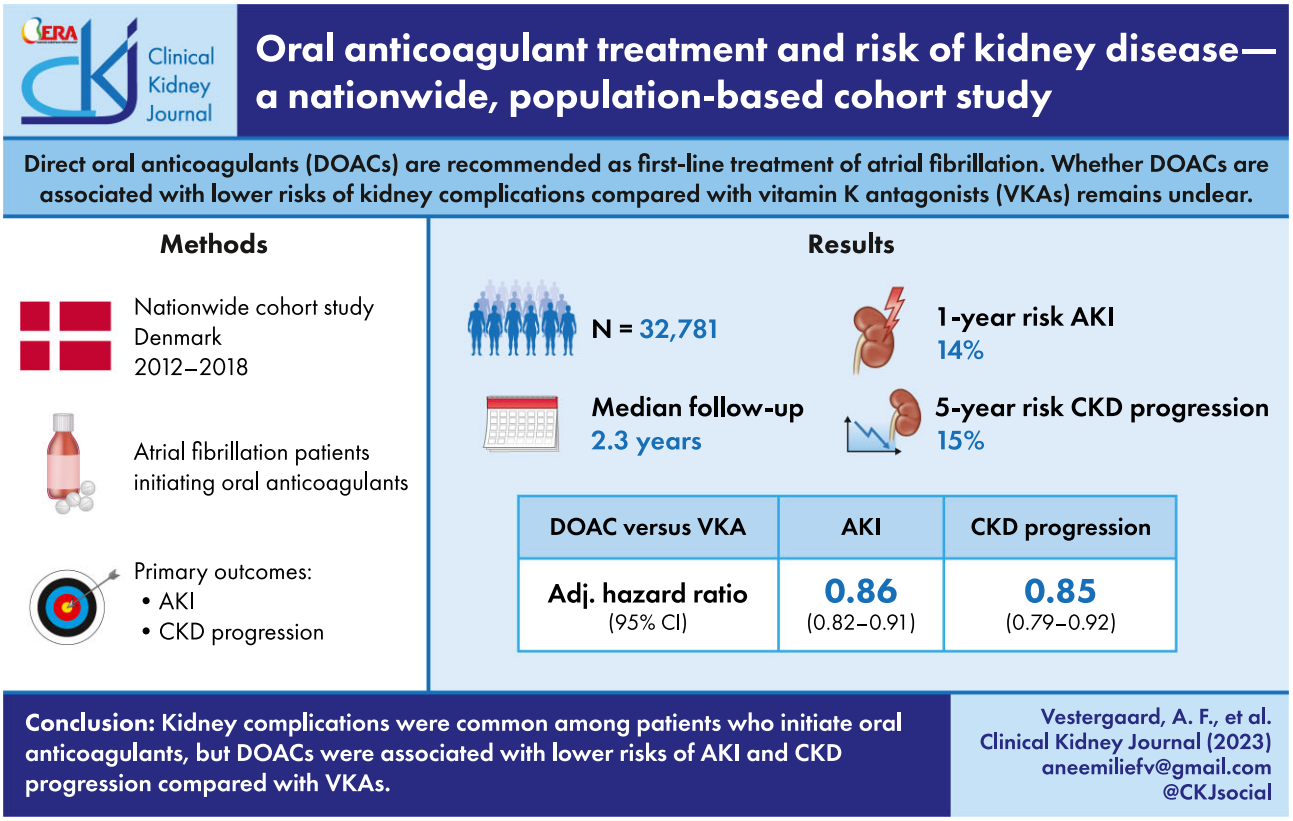
GRAPHICAL ABSTRACT



Keywords: acute kidney injury, anticoagulant drugs, atrial fibrillation, pharmacoepidemiology, renal insufficiency

KEY LEARNING POINTS

What was known:

- Oral anticoagulant treatment has been associated with kidney injury.
- Whether anticoagulation with direct oral anticoagulants (DOACs) is associated with lower risks of kidney injury than vitamin K antagonists (VKAs) remain unclear.

This study adds:

- Acute kidney injury (AKI) and chronic kidney disease (CKD) progression were common among patients with atrial fibrillation treated with oral anticoagulant drugs.
- Initiation of DOACs was associated with a decreased risk of AKI and CKD progression compared with VKAs.

Potential impact:

- Our findings underscore the need for routinely monitoring of creatinine and efforts to prevent and treat kidney injury among patients with atrial fibrillation treated with oral anticoagulant drugs.

INTRODUCTION

Oral anticoagulants (OACs) are widely used to prevent blood clots in patients with atrial fibrillation (AF). For more than half a century, vitamin K antagonists (VKAs) were the only option for long-term oral anticoagulation, but in the last decade direct oral anticoagulants (DOACs) have been introduced [1] (Supplementary data, Fig. S1). DOACs have advantages such as fixed dosing with no monitoring requirements, fewer pharmacological interactions and a substantially lower risk of intracranial bleeding [2]. Accordingly, there has been a shift from VKA to DOAC in clinical practice, and DOACs are now preferred over VKAs for newly diagnosed AF patients [3].

OAC treatment has been described as a potential cause of kidney complications [4–6]. Unexplained acute kidney injury (AKI) in an OAC-treated patient has been labeled "anticoagulant-related nephropathy" [7–9], and linked to specific histopathologic findings including glomerular hemorrhage and tubular injury [4–6]. The phenomenon has most often been

described in patients with VKA-induced coagulopathy—a population with observed AKI prevalences between 19% and 63% at the time of overanticoagulation [10]. Comparisons of kidney outcomes in DOAC- versus VKA-treated patients have been made in secondary analyses of randomized controlled trials designed to evaluate cardiovascular outcomes and in observational studies [11–24]. A secondary analysis of the The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial found that patients treated with dabigatran had less decline in estimated glomerular filtration rate (eGFR) compared with patients randomized to VKA treatment [11], but subsequent analyses of Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) (rivaroxaban) and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) (apixaban) did not confirm this finding [12, 13]. Previous observational studies have suggested lower risks of kidney outcomes such as AKI and kidney failure with DOACs than VKAs [14–24]. However, these studies have been limited by having no control for baseline eGFR [16–18, 21, 23], identification of AKI by diagnostic codes with low sensitivity [14–18] or only by laboratory data during hospitalization [19, 24], and limited follow-up to evaluate long-term kidney outcomes such as chronic kidney disease (CKD) progression. To address these limitations, we conducted a large nationwide, population-based cohort study using creatinine measurements to compare the risk of AKI and CKD progression in patients initiating DOACs or VKAs.

MATERIALS AND METHODS

Setting and data sources

We conducted this nationwide, new-user, active comparator cohort study using routinely collected healthcare data from the Danish registries. The Danish healthcare system is tax-funded and provides equal access to general practitioners and hospitals as well as partial reimbursement for most prescribed medications [25]. All Danish inhabitants have a unique identification number, allowing individual-level linkage of data across registries [26].

This study is based on prescription data from the Danish National Prescription Registry (Prescription Registry) [27]; data on outpatient and in-hospital plasma creatinine (pCr) measurements from the regional Clinical Laboratory Information System Research Database and the national Register of Laboratory Results for Research [28–30]; data on diagnoses and hospital treatments from the Danish National Patient Registry (Patient Registry) [31]; and data on demographics and vital status from the Danish Civil Registration System [26].

Ethical approval

The study was reported to the Danish Data Protection Agency through registration at Aarhus University (record number: 2016-051-000001/812). According to Danish legislation, approval from an ethics committee or informed consent from patients is not required for registry-based studies.

Study population

Using the Prescription Registry, we identified all adults (age ≥18 years) who initiated OAC treatment between 1 January 2012 and 31 December 2018. We included only new users, defined as those with no history of either VKA or DOAC treatment since 1995. The date of treatment initiation was defined as the index date and start of follow-up. Patients were required to have an AF diagnosis registered in the Patient Registry within 90 days prior to the index date (Supplementary data, Fig. S2). To ensure data on baseline kidney function, we excluded patients without an outpatient pCr measurement within 365 days before index. We also excluded patients with kidney failure [CKD category G5 (eGFR <15 mL/min/1.73 m^2) or kidney replacement therapy] at index, AKI within 7 days before index, or conditions only treated with either DOACs or VKAs (Supplementary data, Fig. S3).

Outcomes

The primary outcomes were AKI and CKD progression. AKI was identified using pCr measurements according to the KDIGO guidelines [32]. We implemented the AKI definition by evaluating each pCr result in three steps: (i) an absolute increase of at least 26.5 mmol/L within 48 h; and/or (ii) a 1.5-fold increase in creatinine compared with the lowest pCr measurement within 7 days; and/or (iii) a 1.5-fold increase in creatinine compared with the baseline, which was defined as the median value of all outpatient tests taken within 8–365 days before the current sample. CKD progression was defined as sustained 30% decline in eGFR or incident kidney failure. We used a linear interpolation method to identify sustained 30% decline in eGFR, i.e. for each patient, we fitted a linear regression to all outpatient eGFR measurements during follow-up [33]. The time to CKD progression was defined as the moment the value of the regression represented a 30% decline in eGFR and only if this occurred before the last pCr measurement. Kidney failure was defined according to the KDIGO criteria as two outpatient eGFR measurements <15 mL/min per 1.73 m^2 at least 90 days apart [34] or the recording of codes representing kidney replacement therapy in the Patient Registry (either chronic dialysis or kidney transplantation).

As secondary outcomes, we assessed effectiveness and safety of OACs using outcomes from landmark trials [35–38]: a composite of ischemic stroke and systemic embolism; major bleeding (intracranial hemorrhage, gastrointestinal bleeding and other types of bleeding); and all-cause mortality (Supplementary data, Table S1).

Covariates

Baseline covariates included age, sex, year of treatment initiation, baseline eGFR, comorbidities, proxies for lifestyle factors (smoking, obesity, alcoholism) and use of medications increasing the risk of kidney injury and bleeding (non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, aspirin, clopidogrel). We calculated eGFR by applying the CKD Epidemiology Collaboration equation assuming non-Black race [39]. eGFR at baseline was based on the median of all outpatient pCr measurements performed in the preceding 12 months. We identified comorbidities within 10 years prior to index from the Patient Registry. For hypertension, diabetes and dementia, which are often handled in primary care, we supplemented hospital-based diagnosis codes with medication use (codes are provided in Supplementary data, Table S1). Medication use was defined as a redeemed prescription recorded in the Prescription Registry within 90 days before index. Finally, as a proxy for general health in the year before index, the number of outpatient specialist visits, distinct dispensed drugs and distinct hospital diagnoses were assessed.

Statistical methods

We tabulated patient characteristics according to exposure group (DOAC or VKA) before and after propensity score

Table 1: Characteristics of patients with atrial fibrillation initiating OACs before and after IPTW.

	Unweighted cohort				IPTW cohort			
	Overall (n = 32 781)	DOAC (n = 25 241)	VKA (n = 7540)	SMD	Overall (n = 32 788)	DOAC (n = 25 234)	VKA (n = 7554)	SMD
Sex (female), *n* (%)	15 919 (49)	12 484 (50)	3435 (46)	0.078	15 939 (49)	12 262 (49)	3677 (49)	0.002
Age, median (IQR)	75 (68–83)	75 (68–83)	75 (67–82)	0.116	75 (68–83)	75 (68–83)	75 (68–83)	0.006
Age categories, *n* (%)								
<65 years	5783 (18)	4290 (17)	1493 (20)		5772 (18)	4448 (18)	1325 (18)	
65–74 years	10 547 (32)	8143 (32)	2404 (32)		10 525 (32)	8107 (32)	2418 (32)	
75–84 years	10 589 (32)	8087 (32)	2502 (33)		10 602 (32)	8161 (32)	2441 (32)	
85+ years	5862 (18)	4721 (19)	1141 (15)		5888 (18)	4519 (18)	1370 (18)	
Baseline eGFR, median (IQR)	75 (60–87)	75 (61–87)	74 (57–86)	0.128	75 (60–87)	75 (60–87)	75 (60–87)	0.002
eGFR categories, *n* (%)								
15–29 mL/min/1.73 m^2	735 (2)	374 (2)	361 (5)		721 (2)	552 (2)	169 (2)	
30–59 mL/min/1.73 m^2	7525 (23)	5701 (23)	1824 (24)		7524 (23)	5786 (23)	1738 (23)	
>60 mL/min/1.73 m^2	24 521 (75)	19 166 (76)	5355 (71)		24 543 (75)	18 896 (75)	5648 (75)	
Comorbidities (within prior 10 years), *n* (%)								
Hypertension	21 221 (65)	16 275 (65)	4946 (66)	0.023	21 208 (65)	16 333 (65)	4875 (65)	0.004
Diabetes	5935 (18)	4428 (18)	1507 (20)	0.063	5951 (18)	4571 (18)	1380 (18)	0.004
Ischemic heart disease	7305 (22)	5250 (21)	2055 (27)	0.152	7288 (22)	5620 (22)	1668 (22)	0.005
Heart failure	4182 (13)	2980 (12)	1202 (16)	0.120	4188 (13)	3224 (13)	964 (13)	0.000
Stroke	4095 (13)	3305 (13)	790 (11)	0.081	4093 (13)	3153 (13)	940 (12)	0.001
Cancer	3894 (12)	3043 (12)	851 (11)	0.024	3903 (12)	2999 (12)	905 (12)	0.003
Liver disease	400 (1)	281 (1)	119 (2)	0.040	404 (1)	309 (1)	95 (1)	0.003
Dementia	789 (2)	691 (3)	98 (1)	0.102	795 (2)	608 (2)	187 (3)	0.004
Urologic diseases	2410 (7)	1809 (7)	601 (8)	0.030	2414 (7)	1856 (7)	558 (7)	0.001
Connective tissue disease	2107 (6)	1561 (6)	546 (7)	0.042	2110 (6)	1622 (6)	488 (7)	0.001
Peripheral vascular disease	2596 (8)	1883 (8)	713 (10)	0.072	2595 (8)	1998 (8)	597 (8)	0.000
Prior major bleeding	2870 (9)	2211 (9)	659 (9)	0.001	2890 (9)	2213 (9)	677 (9)	0.007
Lifestyle factors, *n* (%)								
Obesity diagnoses or medications	2471 (8)	1848 (7)	623 (8)	0.035	2462 (8)	1899 (8)	563 (8)	0.003
Markers of smoking	11 381 (35)	8718 (35)	2663 (35)	0.016	11 398 (35)	8768 (35)	2631 (35)	0.002
Alcoholism-related diagnoses or medications	1406 (4)	1102 (4)	304 (4)	0.017	1409 (4)	1082 (4)	327 (4)	0.002
Comedications (within prior 90 days), *n* (%)								
NSAIDs	3248 (10)	2480 (10)	768 (10)	0.012	3252 (10)	2502 (10)	750 (10)	0.000
ACEi/ARBs	11 913 (36)	9090 (36)	2823 (37)	0.030	11 930 (36)	9172 (36)	2758 (37)	0.003
Aspirin	8583 (26)	6232 (25)	2351 (31)	0.145	8606 (26)	6618 (26)	1989 (26)	0.002
Clopidogrel	2977 (9)	2361 (9)	616 (8)	0.042	2964 (9)	2288 (9)	676 (9)	0.004
Antibiotics (within prior 7 days)	1009 (3)	782 (3)	227 (3)	0.005	1006 (3)	773 (3)	233 (3)	0.001
General health in the previous year, median (IQR)								
Dispensed drugs	7 (4–11)	7 (4–11)	8 (5–11)	0.088	7 (4–11)	7 (4–11)	7 (4–11)	0.006
ICD-10 codes	4 (2–6)	4 (2–6)	4 (2–7)	0.134	4 (2–6)	4 (2–6)	4 (2–6)	0.003
Outpatient visits	2 (1–3)	2 (1–3)	2 (1–3)	0.043	2 (1–3)	2 (1–3)	2 (1–3)	0.001

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ICD-10, International Classification of Diseases, Tenth Revision; NSAIDs, non-steroidal anti-inflammatory drugs.

weighting. Propensity scores, i.e. the probability of receiving DOAC versus VKA treatment, were estimated for all individuals by applying a logistic regression model including all covariates in Table 1. Age and eGFR were included using restricted cubic splines with eight knots [40]. We applied stabilized inverse probability of treatment weighing (IPTW) [41], and assessed the ability of the IPTW to form comparable treatment groups by graphical inspection of their propensity score distributions (Supplementary data, Fig. S4). The balance of each covariate was evaluated by absolute standardized mean differences (SMDs), using a threshold >0.1 to indicate imbalance (Supplementary data, Fig. S5). In the primary analysis we used an intention-to-treat approach and followed patients from the day of their first OAC prescription and—irrespective of discontinuation or switch—until outcome of interest, death, emigration or end of follow-up on 31 December 2018. We plotted cumulative incidence curves before and after IPTW and estimated raw and weighted 1- and 5-year risks of AKI and CKD progression, taking into account the competing risk of death. Cox regression with adjustment for year of treatment initiation was applied in the weighted population to estimate hazard ratios (HR) of the outcomes comparing DOAC and VKA initiation. The proportional hazard assumption was examined using Schoenfeld residual plots and found appropriate. Confidence intervals (CI) were obtained by bootstrapping (details are given in the Supplementary data) [42]. Subgroup analyses were conducted to evaluate the presence of effect modification by age group (≥75 years, <75 years), sex, baseline eGFR (≥60 mL/min/1.73 m^2, <60 mL/min/1.73 m^2), diabetes, CHA_2DS_2-VASc score (score ≥2 or <2) (definition of CHA_2DS_2-VASc score is provided in Supplementary data, Table S2) and DOAC type (dabigatran, rivaroxaban, apixaban). We re-estimated propensity scores in each stratum separately to preserve balance within each group. Lastly, to investigate potential surveillance

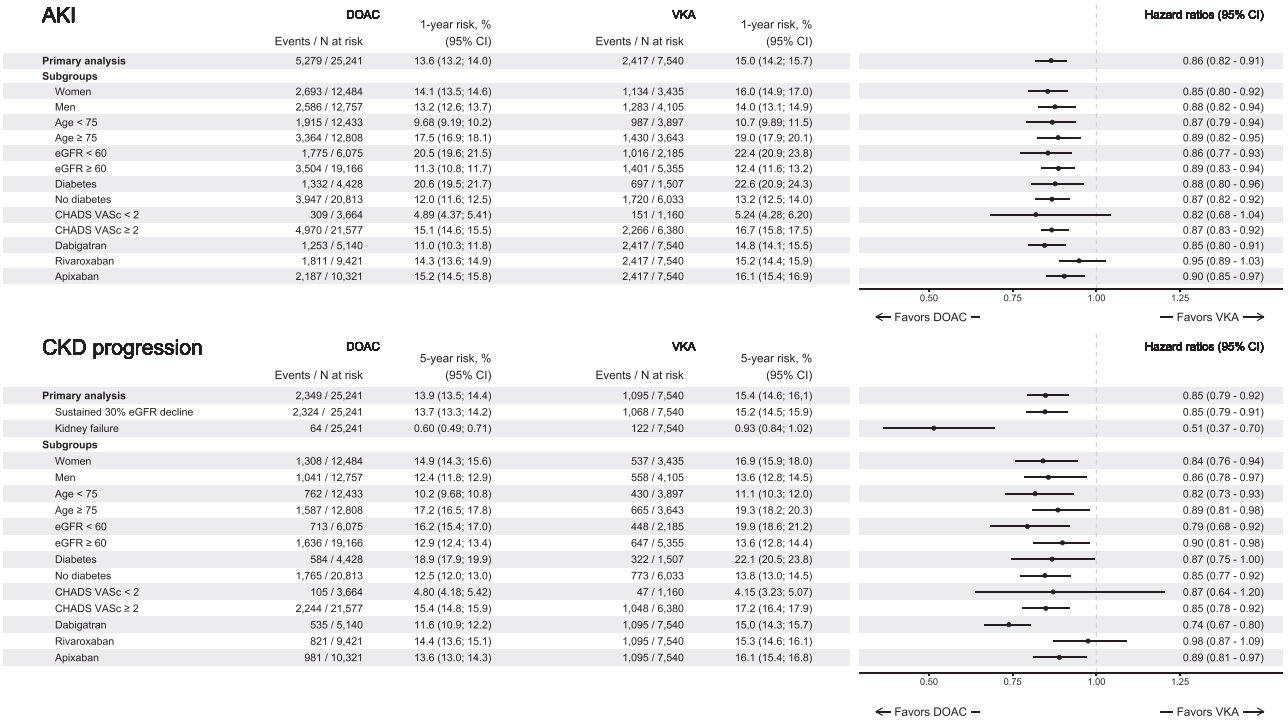


Figure 1: Kidney outcomes in DOAC users compared with VKA users, adjusted by IPTW and year of treatment initiation.

bias due to differences in pCr testing between treatment groups, we also calculated the frequency of pCr testing in DOAC and VKA users.

To examine the robustness of our findings, we also emulated a per-protocol analysis in which patients were censored at discontinuation of anticoagulant treatment (defined as not filling a new prescription 180 days after the last prescription) or switch of OAC type. However, as there could be a risk of informative censoring, since we expected a higher rate of discontinuation or switch in the VKA-treated group, we applied a weighted Cox regression including both IPTW and inverse probability of censoring weights (details are given in the Supplementary data) [43, 44].

All analyses were performed using R version 4.1.3.

RESULTS

From the source population of 179 624 oral anticoagulant initiators, 32 781 AF patients were included in the analysis. Most prominently, patients were excluded due to missing information in baseline pCr (Supplementary data, Fig. S3). Baseline characteristics on these patients are shown in Supplementary data, Table S3. Among included individuals, 25 241 (77%) initiated DOACs and 7540 (23%) initiated VKAs (99.9% warfarin) (Table 1). Most DOAC users initiated apixaban (41%) and rivaroxaban (37%), followed by dabigatran (20%) and edoxaban (1%). The proportion of DOAC initiators increased steadily over time (Supplementary data, Fig. S6). In 2012, 47% of the study population were prescribed DOACs, while the proportion was 97% in 2018.

The median age at treatment initiation was 75 [interquartile range (IQR) 68–83] years and 25% had a baseline eGFR <60 mL/min/1.73 m^2. Among VKA users, there were fewer women, and a higher proportion of patients with a baseline eGFR <60 mL/min/1.73 m^2, ischemic heart disease and heart failure, but no other major differences between the treatment groups.

The median follow-up was 2.3 (IQR 1.1–3.9) years, during which patients had a median of 12 (IQR 5–24) pCr tests, with similar frequency of testing between treatment groups (Supplementary data, Table S4).

Kidney outcomes

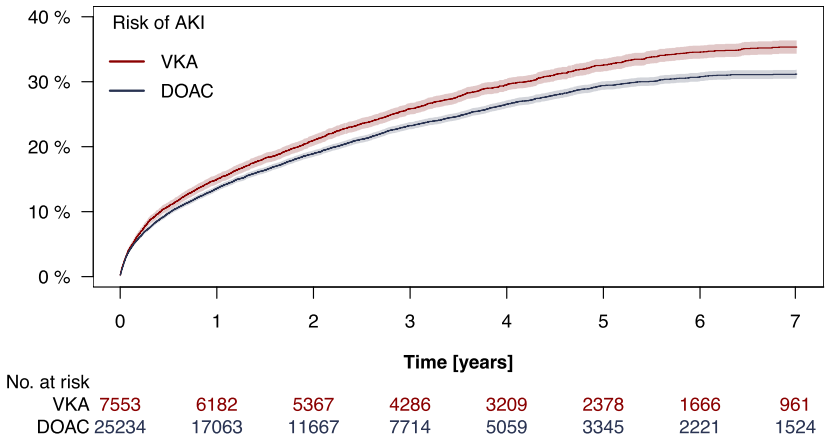
AKI occurred in 7696 individuals during follow-up. The 1-year cumulative risk of AKI was 14.0% (95% CI 13.6; 14.4). There were lower weighted risks of AKI in DOAC- versus VKA-treated patients, which was also reflected in lower rates of AKI with an adjusted HR of 0.86 (95% CI 0.82; 0.91) (Figs 1 and 2).

CKD progression occurred in 3444 individuals, of which 31% were preceded by an AKI (30% in DOAC users and 32% in VKA users). The overall 5-year risk of CKD progression was 15.1% (95% CI 14.5; 15.6). Compared with VKA, there were slightly lower weighted risks of CKD progression in DOAC users, and the adjusted HR was 0.85 (95% CI 0.79; 0.92).

Similar HRs were found across age, sex, eGFR, diabetes and CHA_2DS_2-VASc score subgroups (Fig. 1). Among DOAC subgroups, dabigatran was associated with the lowest risk of AKI and CKD progression.

Secondary outcomes

No difference was observed between DOAC and VKA treatment for the composite of ischemic stroke or systemic embolism (HR 1.02, 95% CI 0.87; 1.18) (Supplementary data, Table S5). Compared with VKAs, DOACs were associated with lower rates of major bleeding (HR 0.77, 95% CI 0.71; 0.86), including intracranial hemorrhage (HR 0.64, 95% CI 0.55; 0.78) and gastrointestinal bleeding



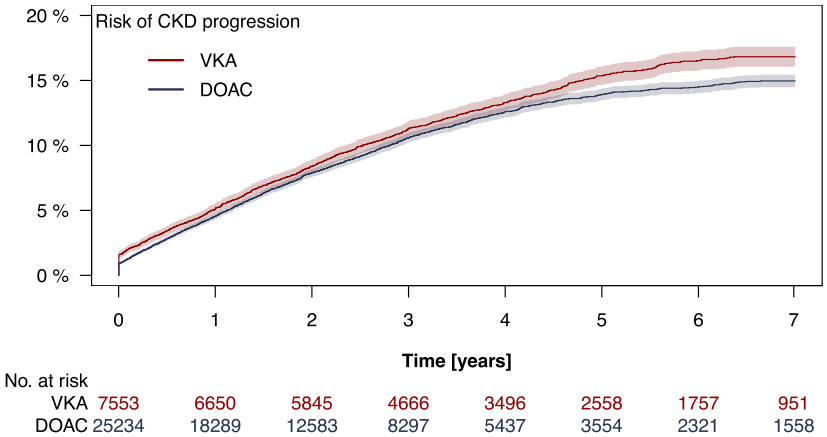


Figure 2: Weighted cumulative incidence curves for AKI (top) and CKD progression (bottom) by DOAC or VKA initiation. The unweighted cumulative incidence curves are presented in Supplementary data, Fig. S7. Please note that the steep fall in numbers at risk are the combined effect of censoring due to outcome, death, emigration and end-of-follow-up.

(HR 0.84, 95% CI 0.73; 0.95). The all-cause mortality HR was 0.94 (95% CI 0.90; 0.98).

Sensitivity analysis

In the per-protocol analysis, 12 487 patients were artificially censored: 31% due to a switch of OAC type and 69% due to discontinuation of treatment. Switching was most common among VKA users (62% of switchers). Before censoring, 6293 had AKI (4616 DOAC users, 1677 VKA users) and 2703 had CKD progression (1978 DOAC users, 725 VKA users). Compared with VKA, DOAC treatment remained associated with lower rates of AKI (HR 0.93, 95% CI 0.78; 1.12) and CKD progression (HR 0.87, 95% CI 0.75; 1.02) after applying inverse probability weighting of both treatment and censoring.

DISCUSSION

In this cohort study, we found that kidney complications were common among AF patients treated with OACs. Around one in seven had an episode of AKI within the first year of treatment initiation and a similar proportion had CKD progression within 5 years. In comparison with VKAs, DOACs were associated with a ∼14% reduction in the rate of AKI and a ∼15% reduction in the rate of CKD progression. The observed associations were consistent among subgroups of baseline eGFR.

Strengths and limitations

A major strength of our study is its large size, comprising a nationwide cohort treated in a setting with universal healthcare coverage. In addition, we were able to control for baseline eGFR and accurately ascertain kidney outcomes through creatinine tests. AKI was identified using consensus definitions, and the linear interpolation method to ascertain sustained decline in kidney function minimized the effect of short-term creatinine fluctuations compared with other methods for identifying CKD progression [45]. However, some limitations can be identified. First, our inclusion criteria of an available outpatient pCr at baseline introduce selection. Although all patients should have a blood sample taken before starting OAC treatment [3], baseline creatinine level was only available for 62% of OAC initiators with AF. Some tests may be missing completely at random, as laboratory data is only complete from October 2015 [29]. However, we did identify some differences in baseline characteristics between patients with and without a pCr at baseline,

suggesting that patients with a pCr at baseline had more comorbidities than those without (Supplementary data, Table S3). Second, we restricted the study population to patients with an AF diagnosis within 3 months before OAC initiation to obtain a more homogenous study population, to minimize misclassification of treatment indication and to prevent immortal time bias. Some excluded patients were recorded with an AF diagnosis shortly after OAC initiation (Supplementary data, Fig. S2). These patients most likely represent individuals initiating OAC treatment in primary care, unlike the study population of patients initiating treatment following a hospital-diagnosis of AF. The requirement for a pCr and AF diagnosis at baseline could affect the extrapolation of our absolute risks of kidney complications to AF populations, as included patients are probably more comorbid and thus have a higher risk of adverse outcomes. Third, pCr was not measured at pre-defined intervals, but as part of clinical controls and depending on patients' health, potentially leading to surveillance bias. However, the frequency of testing between treatment groups were largely similar, and our linear interpolation method used the collective information to draw eGFR decline slopes. Furthermore, the association between OAC type and eGFR decline was supported by a similar association with the more robust outcome of kidney failure. Another limitation that should be mentioned is that the CKD progression event in part depends on later creatinine measurements, however problems associated with this conditioning on the future is expected to be balanced between exposure groups. Finally, as is the case for all pharmacoepidemiologic studies, there is a risk of confounding by indication despite the active comparator design. The choice of OAC type depends on guideline recommendations, which have changed during the study period [3]. In addition, patients prescribed DOACs and VKAs are selected based on factors such as their preferences and ability to comply with the treatment, expected side effects and consideration of drug-specific interactions [46]. We implemented weighting methods that included a large number of potential confounders to minimize the risk of bias, however residual confounding cannot entirely be ruled out. Nevertheless, it provides indirect validity to the kidney outcomes that our results in the evaluation of cardiovascular effectiveness and risk of major bleeding were consistent with trial evidence [35–38].

Interpretation

Our findings are in line with results from other observational studies [14–23]. A 2021 meta-analysis dominated by findings from six of these studies reported pooled HRs of 0.70 (95% CI 0.64; 0.77) for AKI and 0.83 (95% CI 0.73; 0.95) for "worsening renal function" when comparing DOACs versus VKAs [47]. However, the included studies were highly heterogeneous, which may be due to different definitions of the kidney outcomes, control for baseline eGFR level and utilization pattern of the individual DOAC drugs. Several studies did not adjust for baseline kidney function [16–18, 21, 23], which could amplify the association between kidney complications and VKA treatment, as VKAs are more often used for patients with reduced kidney function (i.e. patients with a higher *a priori* risk of kidney complications). Similarly, dabigatran is often avoided in patients at greater risk of kidney complications, as this OAC exhibits the highest degree of renal clearance. A recently published Swedish study with a setting, study population, analytical approach and outcome identification comparable to our study, evaluated kidney outcomes in 32 600 AF patients initiating OACs during 2011–18 [24]. Findings were consistent with ours in both direction and magnitude. The replication of these results in two distinct health systems supports the generalizability of our findings.

Mechanisms behind the lower risks of AKI and progressive CKD associated with DOACs compared with VKAs are not clear. Suggested mechanisms behind VKA-related kidney complications are a tendency towards overanticoagulation, glomerular hemorrhage and subsequent oxidative stress to renal tubules [48], and renovascular calcification leading to CKD progression [49]. In contrast, DOACs have been attributed anti-inflammatory and antioxidative effects [8].

Implications

Our study has important implications for clinical practice. Kidney complications are common among AF patients treated with OACs. This can be attributed to both comorbidities and OAC treatment, but irrespective of this, it underscores the need for routine monitoring of pCr as well as efforts to prevent and treat kidney injury in this population. Prevention of declining kidney function is especially important among AF patients, as studies have shown that worsening kidney function increases the risk of stroke and bleeding further [13, 50]. Moreover, kidney complications should be considered when clinicians and patients weigh the benefits and risks of DOACs versus VKAs. Finally, our data showed that there has been some caution in prescribing DOACs to patients with eGFR <60 mL/min/1.73 m^2 (Table 1). Our results were robust across baseline kidney function, suggesting that the potential benefit of DOAC compared with VKA with respect to kidney outcomes are independent of eGFR.

CONCLUSIONS

Kidney complications were common among patients with AF initiating OACs. This underscores the need for routinely monitoring and efforts to prevent AKI and progressive CKD. The current observational study supported the notion that DOACs are associated with lower risks of kidney complications than VKAs.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

FUNDING

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AUTHORS' CONTRIBUTIONS

A.E.F.V., S.K.J., U.H.-J., K.A., H.B., J.-J.C. and C.F.C. planned and designed the study. All authors participated in the interpretation of the data. A.E.F.V. reviewed the literature, conducted the statistical analyses and wrote the initial manuscript, supervised by S.K.J. and C.F.C. All authors critically reviewed the manuscript and approved the final version for submission. The

corresponding author attests that all listed authors meet authorship criteria.

DATA AVAILABILITY STATEMENT

According to Danish guidelines, individual-level data from Danish registries cannot be extracted and shared.

CONFLICT OF INTEREST STATEMENT

The Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital, is involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of these studies is related to the current study. J.-J.C. acknowledges consultancy for AstraZeneca and Baxter, and grant support to Karolinska Institutet from AstraZeneca, Viforpharma and Astellas, all outside the submitted work. H.B. acknowledges research grant or contracts (paid to institution) from Vifor Pharma and GSK; consulting and/or advisory board fees from AstraZeneca, Vifor Pharma, Boehringer Ingelheim and GSK; payment or honoraria for manuscripts, lectures, presentations or chair at meetings from AstraZeneca, Alexion, NOVO, Netdoktor.dk; support for meetings and/or travel from AstraZeneca, expert testimony/working groups within the Danish Society of Nephrology and Danish Board of Health; and chair of the Danish Society of Nephrology. K.A. was employed at Aarhus University Hospital during the preparation of this work, but is now an employee of Novo Nordisk A/S.

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