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Cardiorenal Outcomes Among Patients With Atrial Fibrillation Treated With Oral Anticoagulants

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Cardiorenal Outcomes Among Patients With Atrial Fibrillation Treated With Oral Anticoagulants

Setting, Participants, and Methods

Retrospective cohort study
Stockholm, Sweden *(SCREAM Project)*

N = 32,699 non-valvular atrial fibrillation patients

New users of direct oral anticoagulants (DOAC) vs vitamin K antagonists (VKA)

Propensity-score weighted Cox regression

2011-2018

- **Median follow-up for kidney outcomes: 3.0 years**
- **Median follow-up for CV outcomes: 3.8 years**

Findings

DOAC vs VKA: Adjusted Hazard Ratio (95% CI)

CKD progression	**0.87 (0.78-0.98)**
AKI	**0.88 (0.80-0.97)**
Stroke/systemic embolism	**0.93 (0.78-1.11)**
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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ABSTRACT

Rationale & Objective

Direct oral anticoagulants (DOAC) have progressively replaced vitamin K antagonists (VKA) for stroke prevention in patients with non-valvular atrial fibrillation (AF). DOACs cause fewer bleeding complications but other advantages of DOACs, particularly related to kidney outcomes, remain inconclusive. We studied the risks of CKD progression and AKI following DOAC and VKA administration for non-valvular AF.

Study design

Retrospective cohort study.

Setting and participants

Cohort study of non-valvular AF patients resident in Stockholm, Sweden, during 2011-2018.

Exposure

Initiation of DOACs or VKA treatment.

Outcome(s)

Primary outcomes were CKD progression (composite of >30% 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 endpoints, subgroups, and estimation of per-protocol effects.

Results

32,699 patients were included (56% initiated DOAC) and followed for median 3.8 years. Their median age was 75 years, 45% were women and 27% had eGFR<60 ml/min/1.73 m^2. The adjusted hazard ratio for DOAC vs. VKA was 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. Hazard ratios 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/systemic embolism, and 1.04 (95% CI 0.95-1.14) for death. 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 switches in type of anticoagulation.

Limitations

Missing information on time in therapeutic range and treatment dosages.

Conclusions

Among patients with non-valvular AF treated in routine clinical practice, compared with VKA, 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 and death.

Key words: SCREAM, warfarin, acute kidney injury, creatinine, safety, effectiveness, apixaban

Plain-Language Summary

The relative safety of anticoagulation with direct oral anticoagulants (DOAC) or vitamin K antagonists (VKA) remains inconclusive, particularly with regards to kidney outcomes. In a cohort of patients with non-valvular atrial fibrillation from Sweden, we observed that compared with VKA, DOAC initiation was associated with 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, DOAC vs VKA 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 emerging evidence on the safety and effectiveness of DOAC administered for atrial fibrillation.

INTRODUCTION

Atrial fibrillation (AF) is common, being 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 non-valvular 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 (DOAC) compared with vitamin K antagonists (VKA) 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]: hence their use has become more prevalent.

Anticoagulation with either VKA or DOAC 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 GFR, termed VKA-related nephropathy.[10,13,14] 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 suggest that there may be similar risks with DOAC treatment[18-21], but this is much less studied. VKAs inhibit the recycling of anti-calcification protein matrix Gla protein 1 and may be pro-calcific: 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, with rate of loss of GFR 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 as serious adverse events or 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 glomerular filtration rate (eGFR), were unable to evaluate long-term consequences to kidney function (progressive eGFR loss) and were limited in follow-up time.

In this study, we compare the risks of CKD progression and AKI among patients with non-valvular AF initiating DOAC or VKA treatment, using both administrative healthcare data and all measurements of creatinine performed in our healthcare system.

METHODS

The study derives from the Stockholm Creatinine Measurements (SCREAM) project, a healthcare utilization cohort from the region of Stockholm, Sweden[32,33]. SCREAM is a repository of laboratory tests from any resident of the Stockholm region during 2006-2018. These laboratory tests are linked using unique personal identification numbers to regional and national administrative databases with complete information on demographics, healthcare 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 not necessary since all data were de-identified 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 between 2011 and 2018 and newly-started 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, had eGFR<15 ml/min/1.73m^2 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 (CHA_2DS_2-VASc, and the modified-$CHADS_2$[34]); 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. 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]. eGFR at baseline was defined as the average of all creatinine measurements performed in the

preceding 12 months and categorized as ≥60, 59-30 and <30 ml/min/1.73m^2. Finally, to capture healthcare utilization and disease severity, we also considered the number of primary healthcare visits, outpatient specialist visits, 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/1.73m^2, 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 measurements. To be considered a sustained eGFR<15 ml/min/1.73m^2, the linear regression slope needed to be negative, and the 15 ml/min/1.73m^2 threshold needed to be crossed before the last measurement. The time to event was then defined as the interpolated moment in which the linear regression line crossed the 15 ml/min/1.73m^2 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 criteria[37] (increase in creatinine-≥-26 μmol/L over 48 hours or >1.5 times within 7 days, **Table S4)**. For these outcomes, follow-up ended on the date of endpoints, last laboratory measurement or December 31, 2018, whichever came first.

In addition, we evaluated cardiovascular risk-benefit as secondary study outcomes to compare with results from pivotal trials. These endpoints 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 endpoints, death or December 31, 2019, whichever came first.

Statistical analyses

Continuous variables are presented as medians with interquartile ranges (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 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% confidence intervals (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 (eGFR≥ or <60 ml/min per 1.73m^2). To calculate the stratum-specific hazard ratios while preserving balance within subgroups, we re-estimated the probability of receiving DOAC versus VKA and re-fit the weighted proportional hazards models in each stratum. Differences in the hazard ratios between strata (i.e., 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 vs. VKA initiation and the falsification outcomes pneumonia or cataract surgery[41]. 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 a) patients with CHA_2DS_2-VASc ≥2, as those with a score of 0 or 1 may have an indication for short-term DOAC treatment when they undergo cardioversion; b) patients free from history of VTE, to evaluate whether dual indication for OAC treatment would modify our observations; c) patients initiating OAC therapy within 90 days from an incident AF diagnosis, to increase confidence that this was the indication for OAC use. Third, we censored patients at treatment discontinuation or treatment switch (from VKA to DOAC or vice versa), thus emulating a per-protocol analysis. Since we expected the rate of discontinuation or switch to be dependent on the initial treatment assigned (i.e., discontinuation would be more frequent among users VKA), we used inverse probability of censoring weighting

to account for the differential loss to follow-up (i.e., 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 99.99^{th} percentile to avoid undue influence of large weights. We then estimated the discrete-time hazard ratio using a weighted pooled logistic regression model including the time-varying censoring and baseline treatment weights. Lastly, 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.

RESULTS

Demographics and clinical characteristics

During 2011-2018, 71,167 adults filled DOAC or VKA prescriptions in the region of Stockholm. After applying inclusion and exclusion criteria, we identified 32,699 individuals with AF who initiated either therapy and were considered for the analysis (**Figure S1**). Of those, 18,323 (56%) started DOAC and 14,376 (44%) started VKA treatment. The vast majority of patients (>95%) initiated OAC treatment within 90 days after an incident AF diagnosis (**Figure S2**). Their median age was 75 years (IQR: 68-83) and 45% were women (**Table 1**). The median eGFR was 73 (IQR

59-85) ml/min/1.73m^2 and 27% had an eGFR<60 ml/min/1.73m^2. Hypertension was the most common comorbidity (72%), followed by vascular disease (30%), history of cancer (26%) and congestive heart failure or left ventricular dysfunction (25%). The median CHA_2DS_2-VASc score was 3 (IQR 2-5), the median modified-$CHADS_2$ score was 5 (IQR 3-7) and the median HAS-BLED score was 2 (IQR 2-3). Patients also commonly used β-blockers (80%), RAASi (56%), aspirin (44%) and statins (36%).

Apixaban was the most 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 increased steadily over time (**Figure S3, panel A**). When stratifying by baseline eGFR, by 2018 98% of users with KDIGO category G1-2 GFR, and 95% of those with G3 were prescribed DOAC rather than warfarin, while in that year 69% of participants with G4 CKD were prescribed DOACs (**Figure S3, panel B**). Figure S4 shows good balance in all measured covariates after IPTW with all SMDs <0.1 (**Figure S4**).

Comparative effectiveness of DOAC vs 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 1208 individuals in the DOAC group and 2244 individuals in the VKA group, corresponding to incidence rates of 30.4 and 36.3 per 1000 person-years, respectively (**Table 2**). Compared with VKA, 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 1, panel A**. Reduced CKD progression resulted from reductions in the 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, 1825 patients in the DOAC group and 3277 patients in the VKA group experienced an AKI event, corresponding to incidence rates of 46.7 and 54.5 per 1000 person-years, respectively. Compared to VKA, 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 (**Figure 1, panel B)**.

Comparative effectiveness of DOAC vs 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 vs 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, Figure S5**). For the single components, a significantly lower risk was observed for intracranial bleeding (HR 0.59, 95% CI 0.47-0.75) but no 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 3222 individuals died in the DOAC group and 4842 in the VKA group, corresponding to incidence rates of 57.1 and 64.1 per 1000 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 to VKA (**Table 2, Figure S6**).

Subgroup and sensitivity analyses

We generally observed consistent results with no signs of heterogeneity for the risk of CKD progression or AKI across pre-specified subgroups of age (Figure S7) and baseline eGFR strata (Figure 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, with a HR of 0.78 (95% CI 0.60-1.01) compared to men, with a HR of 1.16 (95% CI 0.91-1.49); p-value for interaction = <0.001) (Figure S9).

We obtained findings similar to our primary analysis when restricting the population to patients with CHA_2DS_2-VASc ≥2 (**Table S5**), to patients free from VTE 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 that 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 to 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 vs VKA treatment (**Table S8**). Use of DOAC vs 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 non-valvular AF patients from routine clinical practice, initiation of DOAC vs VKA was associated with more favorable kidney outcomes, i.e., 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 vs 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 kidney function 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 carefully interpreted and considered as hypothesis generating only, as they are not corrected for multiple testing and may be subject to false positives.

The possibility of better kidney outcomes in patients treated with DOAC compared with VKA was initially suggested by a *post hoc* analysis of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. In this trial, open-label warfarin was compared to dabigatran treatment in patients with AF and 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 (ARISTOTELE) to 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 vs 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 or inclusion of prevalent users of the medication[43]. A 2021 meta-analysis[31] 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 vs 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 84% and 76%, respectively).

The study of Yao *et al.*[47] is, to the best of our knowledge, the sole observational study investigating the risk of CKD progression between these therapies using laboratory measurements. They studied administrative and laboratory data in a private health care system from the US, including 9,769 patients with non-valvular AF starting DOAC or VKA during 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 to VKA treatment was associated with lower risks of a ≥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 healthcare 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 method[51] to ascertain chronic declines in kidney function. Given the many factors influencing eGFR, this method is less susceptible to transient variation that may misclassify the outcome when requiring only one measurement to pass the threshold.

Several large observational studies have also investigated differences in the risk of AKI between DOAC and VKA users[43-45,47,52,53]. Again, their limitation has been the reliance on insensitive diagnostic codes for AKI. Recently, Harel *et al.*[54] evaluated the risk of AKI associated with initiation of DOAC or warfarin among 20,683 older adults (≥66 years) from Ontario, Canada, during a median follow-up 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. 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 endpoints. Consistent with trials and existing observational reports[55-58], 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 region [59] with the exception of a higher risk of gastrointestinal bleeds with DOACs vs.

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 to 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 INR control, with a mean TTR over 75% in RCTs[60,61] and observational studies[62]. We had too few patients initiating therapy with eGFR<30 ml/min/1.73 m^2, 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 pre-defined intervals but in connection with routine healthcare, 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 two 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[63,64].

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

Article Information

Authors' Contributions: Research idea and study design: MT, PH, ELF, JJC; data acquisition: JJC ME; data analysis/interpretation: All authors; statistical analysis: MT; supervision or mentorship: JJC, PH. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Table 1. Baseline characteristics of the patients initiating oral anticoagulants in Stockholm between 2011 and 2018, overall and stratified by initial treatment group.

	Overall (N = 32,699)	**DOAC (N = 18,323)**	**VKA (N = 14,376)**
Age (years), median (IQR)	75 [68, 83]	75 [68, 83]	76 [68, 83]
Age category (years)			
<75	15,336 (47%)	8742 (48%)	6594 (46%)
≥75	17,363 (53%)	9581 (52%)	7782 (54%)
Women, N (%)	14,816 (45%)	8399 (45%)	6417 (45%)
Access to health care in the previous year, median (IQR)			
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, N (%)			
Compulsory	8730 (27%)	4530 (25%)	4200 (29%)
Secondary	12,951 (40%)	7213 (39%)	5738 (40%)
University	10,385 (32%)	6256 (34%)	4129 (29%)
Missing	633 (2%)	324 (2%)	309 (2%)
eGFR (ml/min/1.73m^2), median (IQR)	73 [59, 85]	74 [60, 85]	72 [57, 85]
eGFR category (ml/min/1.73m^2), N (%)			
15-29	670 (2%)	189 (1%)	481 (3%)
30-59	8078 (25%)	4300 (24%)	3778 (26%)
≥60	23,951 (73%)	13,834 (75%)	10,117 (71%)
Medical history, N (%)			
Hypertension	23,621 (72%)	13,156 (72%)	10,465 (73%)
Vascular disease	9714 (30%)	4896 (27%)	4818 (33%)
Cancer	8519 (26%)	4994 (27%)	3525 (24%)
Congestive heart failure/LV dysfunction	8089 (25%)	4071 (22%)	4018 (28%)
Heart failure	7975 (24%)	3999 (22%)	3976 (28%)
Diabetes	6906 (21%)	3723 (20%)	3183 (22%)
Stroke, TIA or embolism	6709 (20%)	3649 (20%)	3060 (21%)
Anemia	5693 (17%)	3203 (17%)	2490 (17%)

Stroke	4845 (15%)	2632 (14%)	2213 (15%)
Myocardial infarction	4887 (15%)	2366 (13%)	2521 (17%)
Diabetic complications	4473 (14%)	2293 (12%)	2180 (15%)
Prior bleeding	3576 (11%)	2133 (12%)	1443 (10%)
COPD	3566 (11%)	2058 (11%)	1508 (10%)
Venous thromboembolism	3140 (10%)	1648 (9%)	1492 (10%)
PCI	2641 (8%)	1322 (7%)	1319 (9%)
Rheumatoid arthritis	2323 (7%)	1307 (7%)	1016 (7%)
Renal disease	2329 (7%)	1225 (7%)	1104 (8%)
Fracture	1964 (6%)	1180 (6%)	784 (5%)
DVT or knee/hip replacement	1761 (5%)	904 (5%)	857 (6%)
Alcohol abuse	1768 (5%)	1129 (6%)	639 (4%)
AKI	890 (3%)	499 (3%)	391 (3%)
Liver disease	726 (2%)	428 (2%)	298 (2%)
Risk score, median (IQR)			
CHA_2DS_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, N (%)			
Beta blocker	26,174 (80%)	14,485 (79%)	11,689 (81%)
RAAS inhibitor	18,248 (56%)	10,005 (55%)	8243 (57%)
Aspirin	14,538 (44%)	7106 (39%)	7432 (52%)
Statin	11,911 (36%)	6339 (35%)	5572 (39%)
Diuretic	11,240 (34%)	5607 (31%)	5633 (39%)
Calcium channel blocker	10,018 (31%)	5539 (30%)	4479 (31%)
PPI	7946 (24%)	4396 (24%)	3550 (25%)
NSAID	4152 (13%)	2263 (12%)	1889 (13%)
Antidepressant	3925 (12%)	2348 (13%)	1577 (11%)
Nitrate	4078 (12%)	1810 (10%)	2268 (16%)
Oral antidiabetic drug	3468 (11%)	1897 (10%)	1571 (11%)
Corticosteroids	3020 (9%)	1712 (9%)	1308 (9%)
Digoxin	2687 (8%)	1280 (7%)	1407 (10%)
Clopidogrel	2143 (7%)	1032 (6%)	1111 (8%)
Insulin	2095 (6%)	1008 (5%)	1087 (8%)
Other antiplatelet	849 (3%)	403 (2%)	446 (3%)

Calendar year of initiation, N (%)			
2011-2014	15,130 (46%)	3472 (19%)	11,658 (81%)
2015-2018	17,569 (54%)	14,851 (81%)	2718 (19%)

Abbreviations: DOAC, direct oral anticoagulant; VKA, vitamin K antagonist; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack, LV, left ventricular; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; PCI, percutaneous coronary intervention; NSAID, non-steroidal anti-inflammatory drug; RAAS, renin-angiotensin-aldosterone system; PPI, proton pump inhibitors

Table 2. Number of events, incidence rates and adjusted hazard ratios for the association between DOAC vs. VKA initiation and outcomes.

	VKA: No of Events (IR/ 1000 person-years)*	DOAC: No of Events (IR/1000 person-years)*	Adjusted HR DOAC vs. VKA (95% CI)**
Kidney outcomes			
CKD progression	2244 (36.3)	1208 (30.4)	0.87 (0.78-0.98)
Sustained 30% eGFR decline	2205 (35.7)	1202 (30.3)	0.88 (0.78-0.98)
Kidney Failure	196 (3.0)	42 (1.0)	0.43 (0.25-0.73)
AKI	3277 (54.5)	1825 (46.7)	0.88 (0.80-0.97)
Cardiovascular outcomes			
Composite of stroke or systemic embolism	1118 (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	1414 (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	4842 (64.1)	3222 (57.1)	1.04 (0.95-1.14)
CV death	2351 (31.1)	1467 (26.0)	0.99 (0.84-1.17)

Abbreviations: VKA, vitamin K antagonist; DOAC, direct oral anticoagulants; IR, incidence rate; HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; CV, cardiovascular

Follow-up, median (interquartile range): kidney outcome 3.0 (1.4-5.0), all others 3.8 (2.1-5.8)

* Number of events, incidence rates were calculated in the original, unweighted population.

** Analyses were adjusted for the following 50 variables: age, sex, calendar year, numbers of primary healthcare visits, numbers of outpatient specialist visits, numbers of diagnoses issued, numbers of procedure codes, education, estimate glomerular filtration rate, hypertension, anemia, liver disease, renal 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 (CHA2DS2-VASc, modified $CHADS_2$, HAS-BLED), concomitant use of: aspirin, clopidogrel, non-steroidal anti-inflammatory drugs, other antiplatelet, corticosteroids, diuretics, beta blockers, calcium channel blockers, renin-angiotensin-aldosterone-system inhibitors, statin, insulin, other antidiabetic medications, antidepressants, digoxin, nitrate, 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% confidence intervals.