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ORIGINAL PAPER

Real-world use of direct oral anticoagulants in atrial fibrillation patients with moderate/severe chronic kidney disease: a propensity score matched analysis from the START registry

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Abstract

Background Chronic kidney disease (CKD) often coexists in patients with atrial fibrillation (AF), worsening patients' prognosis. Direct oral anticoagulants (DOACs) are increasingly used also in patients with AF and CKD, but limited evidence exists regarding outcomes in advanced CKD.

Methods Patients with AF and CKD from the Italian prospective nationwide START registry were included. Patients were divided into three groups based on the estimated glomerular filtration rate (eGFR): (1) eGFR 59–46, (2) 45–30, and (3) 29–15 ml/min/1.73 m^2. The association of DOACs or vitamin K antagonists (VKAs) use with all-cause mortality, cardiovascular events (CVEs), and bleedings was assessed using Cox regression and Fine-Gray competing risk models. Propensity score matching (PSM) was used to confirm the robustness of the analysis.

Results Among 4849 patients with AF and CKD, the mean age was 81.5 ± 6.7 years, 57.9% were women, and 55.8% were on DOACs. DOAC (vs. VKAs) was inversely associated with all-cause mortality in group 1 (HR 0.49, 95% CI 0.36–0.67, $p < 0.001$), group 2 (HR 0.42, 95% CI 0.31–0.58, $p < 0.001$), and group 3 (HR 0.20, 95% CI 0.10–0.39, $p < 0.001$). Similar results were obtained for CVEs (sHR 0.64, 95% CI 0.49–0.85, $p = 0.002$ for group 1, sHR 0.56, 95% CI 0.42–0.75, $p < 0.001$ for group 2, sHR 0.31, 95% CI 0.17–0.55, $p < 0.001$ for group 3), while no differences emerged for bleedings. No significant differences were observed among DOACs.

Conclusions In this real-world contemporary cohort of patients with AF receiving oral anticoagulants, DOAC use was associated with a lower risk of all-cause mortality and cardiovascular events across all stages of CKD.

Trial registration
NCT02219984

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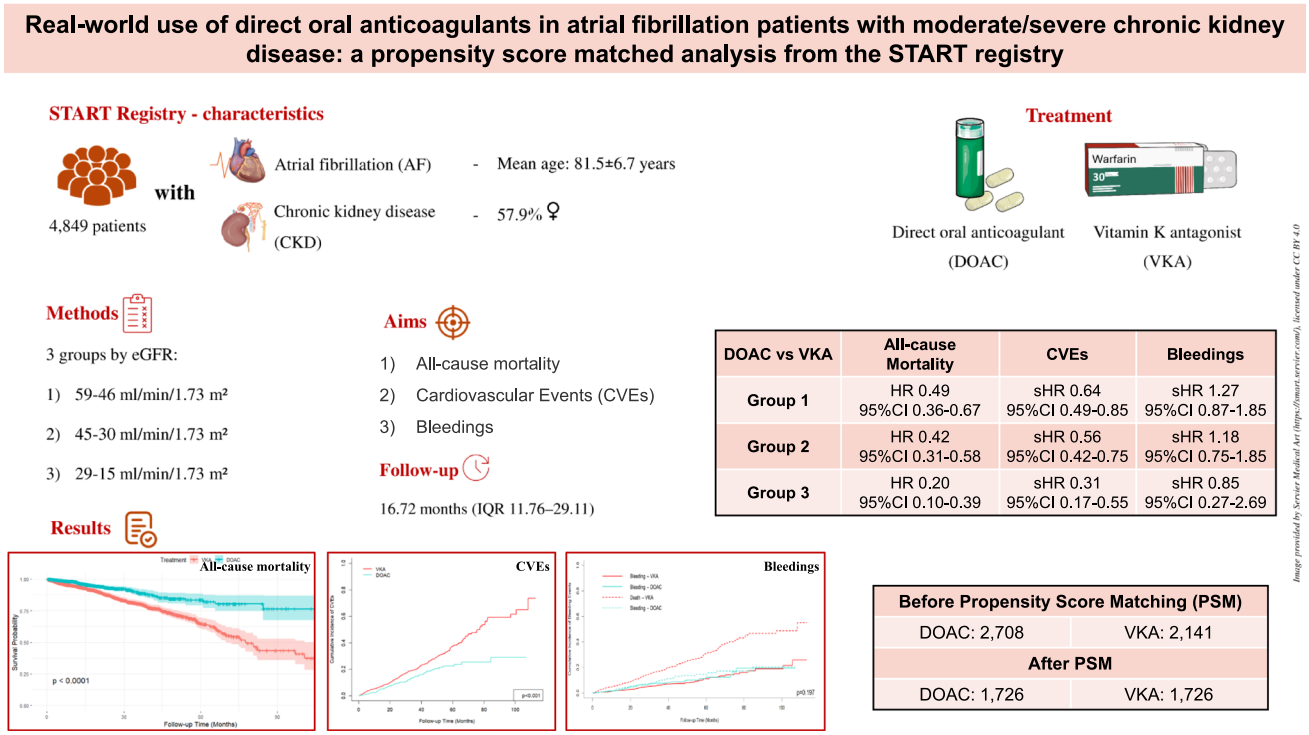
Graphical abstract



DOAC vs VKA	All-cause Mortality	CVEs	Bleedings
Group 1	HR 0.49 95%CI 0.36-0.67	sHR 0.64 95%CI 0.49-0.85	sHR 1.27 95%CI 0.87-1.85
Group 2	HR 0.42 95%CI 0.31-0.58	sHR 0.56 95%CI 0.42-0.75	sHR 1.18 95%CI 0.75-1.85
Group 3	HR 0.20 95%CI 0.10-0.39	sHR 0.31 95%CI 0.17-0.55	sHR 0.85 95%CI 0.27-2.69

Before Propensity Score Matching (PSM)	
DOAC: 2,708	VKA: 2,141
After PSM	
DOAC: 1,726	VKA: 1,726

Keywords Atrial fibrillation · Chronic kidney disease · Anticoagulants · All-cause mortality · Bleeding

Introduction

Chronic kidney disease (CKD) is a chronic progressive condition with a high prevalence and incidence worldwide [1]. A recent comprehensive systematic review and meta-analysis of 100 studies including 6,908,440 patients reported a global CKD prevalence of 13.4% for CKD stages 1–5 and 10.6% for CKD stages 3–5 [2]. Furthermore, the all-cause mortality related to CKD is also increasing, and the global all-age mortality rate increased by 41.5% between 1990 and 2017 [3], resulting in 1.2 million deaths and the 12th leading cause of death worldwide [4].

Commonly, CKD coexists with atrial fibrillation (AF), as shown by the US Renal Data System data, in which 24% of Medicare beneficiaries with CKD have a diagnosis of non-valvular AF, significantly higher than 10% of the non-CKD population [5]. In addition, a recent study performed on 48,518 participants with a median follow-up of 8 years showed a higher risk of new-onset AF in patients with CKD compared to those without [6].

On the other hand, CKD is highly prevalent in patients with AF; in a cohort of 2772 AF patients [7], the prevalence of CKD was 32.9%. In particular, a study performed on EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot Registry showed that 47.2% of AF patients with AF have mild and 17% moderate CKD [8]. In addition, CKD complicates the clinical course of AF patients as it is associated with both stroke and bleeding complications [9], with a high cerebrovascular disease prevalence, estimated at about 19% in the Medicare beneficiaries with CKD stage 4–5 [10, 11].

CKD and AF share a complex, bidirectional relationship, with each condition influencing the progression and prognosis of the other. CKD contributes to the development of AF through mechanisms such as atrial structural remodelling driven by electrolyte imbalances, activation of the renin–angiotensin–aldosterone system (particularly angiotensin II), and chronic low-grade systemic inflammation. These factors promote atrial fibrosis and electrophysiological alterations, increasing the susceptibility to AF. Conversely, AF is a common complication in CKD, as they share similar risk factors, and is associated with adverse outcomes, including accelerated progression to end-stage renal disease, likely due to its impact on renal perfusion [12, 13].

Patients with AF also disclose an accelerated worsening of kidney function [14–16], as a result of the distal

micro-embolization [17] and the use of some drugs, including amiodarone [18] and vitamin K antagonists (VKAs), which have been shown to facilitate glomerular sclerosis and bleeding [19–21].

This poses a clinical challenge to physicians in balancing bleeding and ischemic stroke when starting oral anticoagulation for thromboprophylaxis. While randomized clinical trials have shown the benefit of direct oral anticoagulants (DOACs) use in patients with AF and CKD [22], real-world data in complex elderly patients managed in clinical practice with advanced CKD are less robust.

For this reason, the aims of our study were to investigate the impact of CKD and the role of each oral anticoagulant on survival and cardiovascular events (CVEs) in patients with AF.

Methods

START registry

The START registry is an observational, multicentre, ongoing cohort study that includes patients (aged ≥ 18 years) who start anticoagulation therapy, either vitamin K antagonist (VKAs) (warfarin or acenocoumarol) or DOACs, throughout Italy until December 2023. Details of the START registry have been previously described [23]. The START registry has been previously registered on ClinicalTrials.gov (NCT02219984). The study protocol was accepted by the Institutional Review Board of each participating center, and informed consent was obtained from patients at enrolment. The study protocol complies with the ethical guidelines of the 1975 Helsinki Declaration, and informed consent was obtained from each patient.

Patients treated with low-molecular-weight heparin were excluded as well as patients already enrolled in phase 2 or 3 clinical studies. Patients enrolled in other observational or phase 4 studies were considered eligible for the study. Anticoagulation prescription, especially both clinical indication and dose choice, was performed according to local regulatory approval and international guidelines [24].

Baseline characteristics

Patient's clinical features are recorded by participants on web-based case report forms (CRF). Baseline data are demographic and clinical characteristics of patients, including cardiovascular risk factors, laboratory routine data, smoking habits, indication for anticoagulant treatment, type of oral anticoagulation, and concomitant drugs.

Previous cardiovascular disease was defined as a history of coronary artery disease (CAD), either ischemic heart disease or coronary revascularization with a stent or coronary artery bypass graft, while cerebrovascular disease is defined as a previous ischemic stroke or transient ischaemic attack (TIA).

Chronic kidney disease

For this analysis, we included only patients with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2. In particular, G3 to G4 stages of CKD (15 mL/min/1.73 m^2 ≤ eGFR ≤ 60 mL/min/1.73 m^2) according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines were recruited [25]. Patients with an eGFR < 15 mL/min/1.73 m^2 or in haemodialysis were excluded from this study. eGFR was calculated using the Cockcroft–Gault formula.

Study endpoints

The primary endpoints of the studies were (1) to evaluate the risk of all-cause mortality, CVEs, and bleedings according to CKD severity in AF patients, (2) to establish the all-cause mortality risk in patients with AF and CKD on treatment with DOACs or VKA, and (3) to evaluate the CVEs and bleeding risk in AF patients and CKD on treatment with DOACs or VKA. Secondary endpoints were to establish the risk of all-cause death, CVEs, and bleeding among DOACs.

CVEs were defined as fatal/non-fatal myocardial infarction, cardiac revascularization, fatal or non-fatal ischemic stroke, and transient ischemic attack. All events were collected prospectively during follow-up visits and reported in the electronic CRF by each investigator of the registry.

Statistical analysis

Categorical variables were reported as numbers and percentages and were compared using Pearson's $\chi 2$ test. Mean and standard deviation (SD) or median and interquartile range (IQR) were used for continuous variables and were compared by Student's *t*-test or Mann–Whitney *U* test, respectively. Normal distribution of variables was assessed with the Kolmogorov–Smirnov test. Baseline characteristics were reported according to the type of anticoagulant administered (DOAC or VKA).

To minimize confounding between patients receiving DOACs and those receiving VKAs, propensity score matching (PSM) was performed. Matching was based on the following covariates: age, sex, BMI, hypertension, diabetes, coronary artery disease, anaemia, eGFR, heart failure (HF), peripheral artery disease (PAD), chronic obstructive pulmonary disease or obstructive sleep apnoea (COPD/OSAS), antiplatelet use, class 1c anti-arrhythmic drugs, amiodarone, lipid-lowering therapy, renin–angiotensin–aldosterone system inhibitors, beta blockers, calcium channel blockers, diuretics, digoxin, and proton pump inhibitors. Using

nearest-neighbour matching at a 1:1 ratio with a caliper width of 0.1 and without replacement, we matched patients in the DOAC group with those in the VKA group. A summary of PSM balance was reported in Supplementary Table 1. Covariate balance post-matching was evaluated with standardized mean differences (SMDs), considering an SMD < 0.1 indicative of adequate balance (a love plot illustrating covariate balance is shown in Supplementary Fig. 1). Kaplan–Meier survival analysis was used to estimate the cumulative incidence of all-cause mortality for each anticoagulant group, with survival curves compared using the log-rank test.

To assess the relationship between renal function and mortality risk, we first fitted a Cox proportional hazards model treating eGFR as a linear predictor. We then constructed a more flexible model using restricted cubic splines to account for potential nonlinear associations. Model performance was compared using the Akaike information criterion (AIC), where a lower AIC indicated a better fit. Additionally, we performed a likelihood ratio test to formally evaluate whether the spline model provided a significantly improved fit over the linear model. Univariable and multivariable Cox proportional hazards regression analysis was used to calculate the adjusted relative hazard ratios (HRs) and 95% confidence interval (95% CI) of all-cause death by each clinical variable according to eGFR classes (eGFR 59–46 mL/min/1.73 m^2, eGFR 45–30 mL/min/1.73 m^2, eGFR ≤ 29 mL/min/1.73 m^2).

We performed similar time-to-event analyses for CVE and bleeding risks. However, to account for the competing risks of all-cause mortality, the Fine–Gray subdistribution hazard model was used instead of the Cox regression model, and the results were expressed as subdistribution HR (sHR) and 95% CI. Similarly, cumulative incidence functions (CIF) were plotted to visualize cumulative incidence instead of Kaplan–Meier curves, and Gray's test was applied for group comparisons.

Lastly, we performed an exploratory subgroup analysis to estimate the all-cause mortality, CVEs, and bleeding risk according to each type of DOAC.

Only p values < 0.05 were considered as statistically significant. All tests were two-tailed and analyses were performed using computer software packages (IBM SPSS-25, SPSS Inc. and R software version 4.2.3).

Results

Overall, 4849 out of 10,369 AF patients from the START registry had CKD (46.8%) and were included in the analysis. The mean age was 81.5 ± 6.7 years, 57.9% were women, and 55.8% of patients were taking DOACs. According to KDIGO Classification, 2578 patients (53.2%) were classified as class 3a (eGFR 59–46 mL/min/1.73 m^2), 1750 patients (36.1%) as class 3b (eGFR 45–30 mL/min/1.73 m^2), and 521 patients (10.7%) as class 4 (eGFR ≤ 29 mL/min/1.73 m^2). Mean CHA_2DS_2-VASc was 4.2 ± 1.2, and results were significantly higher in patients with worse kidney function (4.0 ± 1.3 in the CKD class 3a, 4.4 ± 1.3 in class 3b, and 4.6 ± 1.3 in class 4, $p < 0.001$). The mean HAS-BLED was 2.3 ± 0.8 and was higher in class 4 compared to class 3a and 3b stages ($p < 0.001$). In class 3a, the most frequently prescribed DOACs were apixaban (33.7%) and rivaroxaban (26.0%), followed by dabigatran (21.7%) and edoxaban (18.6%). In class 3b, apixaban (37.1%) and edoxaban (28.7%) were the most commonly used, with rivaroxaban (22.3%) and dabigatran (11.9%) prescribed less frequently. In class 4, apixaban (50.3%) and edoxaban (34.6%) predominated, while rivaroxaban accounted for 15.1% of prescriptions. Dabigatran was not used in this group due to the lack of institutional approval for patients with eGFR < 30 mL/min/1.73 m^2.

The clinical characteristics of AF patients according to DOAC and VKA treatment before and after PSM were reported in Table 1. Overall, patients on DOACs were older, with a higher proportion of women and were more commonly affected by arterial hypertension, CAD, PAD, while patients on VKA, before PSM, were more commonly affected by HF, as shown in Table 1. In our cohort, the median follow-up was 16.72 (11.76–29.11) months.

CKD severity and study endpoints

During follow-up, eGFR as a continuous variable was inversely associated with all-cause mortality at univariable Cox regression analysis (HR 0.96, 95% CI 0.95–0.97, $p < 0.001$), also after adjustment for potential confounding factors such as age, sex, and anticoagulant treatment. Figure 1 shows HRs for all-cause mortality according to eGFR, produced by the univariate model incorporating RCS. The model produced no indication of significant nonlinear associations and indicated no substantial improvement in the model fit with the nonlinear approach ($p = 0.579$).

Comparing CKD class 3a (eGFR 59–46 mL/min/1.73 m^2), 3b (eGFR 45–30 mL/min/1.73 m^2), and 4 (≤ 29 mL/min/1.73 m^2) at Kaplan Meier survival curves, a lower CKD class had a higher incidence of all-cause death (Supplementary Fig. 2, panel A, log-rank test $p < 0.001$). In multivariable analysis, Cox regression showed that CKD class 3b and 4 were both associated with a higher risk of all-cause mortality compared to CKD class 3a (Supplementary Table 2, panel A).

For CVE and bleeding risk, CIFs are shown in Supplementary Fig. 2, panel B (Gray's test $p < 0.001$) and panel C (Gray's test $p = 0.430$), respectively; the multivariable Fine–Gray model indicated a similarly elevated risk in

Table 1 Population characteristics according to anticoagulant treatment before and after propensity score matching

	Total Cohort *N* **= 4,849**	**All patients (unmatched)**			**Matched patients**		
		VKA, *N* = 2,141	**DOAC**, *N* = 2,708	p-value	**VKA**, *N* = 1,726	**DOAC**, *N* = 1,726	p-value
Age (years)	81.52 ± 6.74	79.85 ± 6.90	82.84 ± 6.30	<0.001	81.25 ± 5.68	81.55 ± 6.44	0.142
Women (%)	2,806 (58%)	1,197 (56%)	1,609 (59%)	0.014	1,016 (59%)	1,016 (59%)	>0.999
BMI	25.13 ± 4.24	25.23 ± 4.27	25.06 ± 4.22	0.180	25.05 ± 4.12	25.04 ± 4.25	0.943
Hypertension (%)	4,071 (84%)	1,769 (83%)	2,302 (85%)	0.025	1,436 (83%)	1,436 (83%)	>0.999
Diabetes (%)	960 (20%)	440 (21%)	520 (19%)	0.242	329 (19%)	338 (20%)	0.698
CAD (%)	940 (19%)	506 (24%)	434 (16%)	<0.001	359 (21%)	332 (19%)	0.251
Anaemia (%)	1,683 (35%)	775 (36%)	908 (34%)	0.053	575 (33%)	570 (33%)	0.857
eGFR (min/ml)	43.72 ± 10.76	42.01 ± 11.94	45.06 ± 9.51	<0.001	43.91 ± 10.49	43.99 ± 9.70	0.810
Heart failure (%)	1,328 (27%)	655 (31%)	673 (25%)	<0.001	480 (28%)	472 (27%)	0.761
PAD (%)	331 (6.8%)	171 (8.0%)	160 (5.9%)	0.004	122 (7.1%)	124 (7.2%)	0.895
COPD/OSAS (%)	613 (13%)	276 (13%)	337 (12%)	0.642	230 (13%)	213 (12%)	0.387
Antiplatelet (%)	663 (14%)	355 (17%)	308 (11%)	<0.001	252 (15%)	232 (13%)	0.327
Class 1c AAD (%)	309 (6.4%)	97 (4.5%)	212 (7.8%)	<0.001	94 (5.4%)	109 (6.3%)	0.278
Amiodarone (%)	674 (14%)	315 (15%)	359 (13%)	0.146	237 (14%)	239 (14%)	0.921
LLT (%)	1,726 (36%)	795 (37%)	931 (34%)	0.047	621 (36%)	600 (35%)	0.455
RAASi (%)	2,731 (56%)	1,176 (55%)	1,555 (57%)	0.082	976 (57%)	966 (56%)	0.732
Beta blockers (%)	2,323 (48%)	1,215 (57%)	1,108 (41%)	<0.001	890 (52%)	840 (49%)	0.089
CCB (%)	1,138 (23%)	534 (25%)	604 (22%)	0.031	409 (24%)	403 (23%)	0.810
Diuretics (%)	2,289 (47%)	1,045 (49%)	1,244 (46%)	0.047	805 (47%)	801 (46%)	0.891
Digoxin (%)	455 (9.4%)	216 (10%)	239 (8.8%)	0.134	185 (11%)	177 (10%)	0.657
PPI (%)	1,913 (39%)	930 (43%)	983 (36%)	<0.001	699 (40%)	678 (39%)	0.465

AAD: Antiarrhythmic drugs, BMI: body mass index, CAD: coronary artery disease, CCB: Calcium channel blockers, COPD/OSAS: chronic obstructive pulmonary disease/obstructive sleep apnoea syndrome; DOAC: direct oral anticoagulants, eGFR: estimated glomerular filtration rate; LLT: Lipid lowering therapy, PAD: peripheral artery disease, PPI: proton pump inhibitors, RAASi: renin-angiotensin-aldosterone inhibitors, VKA: vitamin K antagonist.

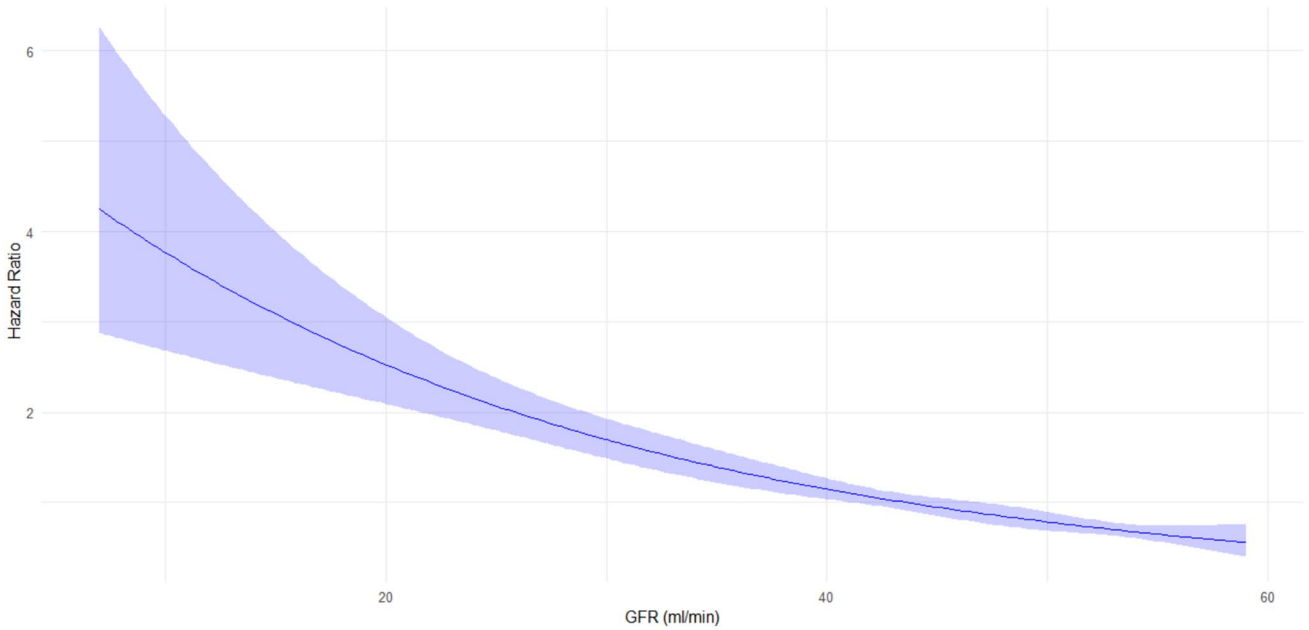


Fig. 1 Association of estimated glomerular filtration rate (GFR) as a continuous variable with all-cause mortality as modelled by restricted cubic splines regression analysis

CKD class 3b and CKD class 4 compared to CKD class 3a for CVEs, while no differences emerged for bleeding risk (Supplementary Table 2, panel B for CVEs and panel C for bleedings, respectively).

All-cause mortality

During follow-up, 512 deaths occurred. We performed a multivariable Cox analysis for each CKD class. DOACs were associated with a lower risk of all-cause mortality in all three groups of CKD classes (HR 0.49, 95% CI 0.36–0.67, $p < 0.001$ for class 3a, HR 0.42, 95% CI 0.31–0.58, $p < 0.001$ for class 3b, HR 0.20, 95% CI 0.10–0.39, $p < 0.001$ for class 4, respectively), as shown in Table 2. Age, PAD, and COPD/OSAS were associated with an increased risk of all-cause death in all CKD classes, while female sex was inversely associated. Of note, digoxin was associated with an increased risk of all-cause mortality only in CKD class 4 (full Cox model shown in Table 2.).

We then compared all-cause mortality between patients receiving DOACs and those on VKAs in the propensity score-matched cohort (cohorts' details available in Table 1). Kaplan–Meier survival curves (Fig. 2A) show that the DOAC group consistently exhibited a significantly higher survival probability than the VKA group throughout the follow-up period, with a statistically significant difference between the two groups (log-rank $p < 0.001$). In univariable Cox regression analysis of the propensity score-matched cohort, treatment with DOACs was associated with a significantly lower risk of all-cause mortality compared to VKAs (HR 0.47, 95% CI 0.37–0.59, $p < 0.001$).

Among DOACs, no difference was observed in all-cause mortality incidence at Kaplan–Meier curves (Supplementary Fig. 3, panel A, log-rank test $p = 0.370$). Furthermore, no association was observed in univariable and multivariable Cox regression analysis (shown in Supplementary Table 3, panel A) comparing each DOAC to apixaban.

Cardiovascular events

During follow-up, 582 CVEs occurred. A multivariable Fine–Gray model was applied to assess CVE risk for each

Table 2. Multivariable Cox analysis of clinical factors associated with all-cause mortality according to estimated glomerular filtration rate (eGFR)

	eGFR 59-46 ml/min/1.73 m^2 N=2,578 (53.2%)			eGFR 45-30 ml/min/1.73 m^2 *N=1,750 (36.1%)*			eGFR <30 ml/min/1.73 m^2 **N=521 (10.7%)**		
	HR	**95% CI**	**p**-value	**HR**	**95% CI**	p-value	**HR**	95% CI	p-value
DOAC vs VKA)	0.49	0.36–0.67.36.67	<0.001	0.42	0.31–0.58.31.58	<0.001	0.20	0.10–0.39.10.39	<0.001
Age (years)	1.10	1.07–1.13.07.13	<0.001	1.09	1.06–1.13.06.13	<0.001	1.09	1.05–1.13.05.13	<0.001
Women	0.65	0.48–0.88.48.88	0.005	0.71	0.53–0.94.53.94	0.018	0.48	0.30–0.77.30.77	0.003
BMI	0.99	0.95–1.03.95.03	0.572	1.02	0.98–1.05.98.05	0.420	1.01	0.96–1.06.96.06	0.734
Hypertension	1.09	0.71–1.67.71.67	0.698	0.96	0.64–1.45.64.45	0.863	0.99	0.46–2.13.46.13	0.986
Diabetes	1.35	0.94–1.93.94.93	0.101	1.38	0.97–1.97.97.97	0.074	1.11	0.68–1.82.68.82	0.669
CAD	1.46	1.01–2.11.01.11	0.045	1.12	0.79–1.59.79.59	0.534	1.25	0.73–2.14.73.14	0.422
Anaemia	1.57	1.15–2.13.15.13	0.004	1.10	0.82–1.47.82.47	0.515	1.01	0.66–1.57.66.57	0.949
Heart failure	0.93	0.64–1.35.64.35	0.716	1.32	0.96–1.80.96.80	0.086	1.08	0.72–1.62.72.62	0.719
PAD	2.39	1.49–3.84.49.84	<0.001	1.66	1.04–2.66.04.66	0.035	1.42	0.70–2.88.70.88	0.325
COPD/OSAS	1.81	1.23–2.66.23.66	0.003	1.52	1.07–2.17.07.17	0.020	1.67	1.00–2.78.00.78	0.050
Antiplatelet	1.06	0.71–1.59.71.59	0.781	0.90	0.58–1.39.58.39	0.634	0.92	0.47–1.79.47.79	0.809
Class 1c AAD	0.57	0.23–1.40.23.40	0.219	0.77	0.33–1.77.33.77	0.536	NA	NA	NA
Amiodarone	1.11	0.70–1.75.70.75	0.654	1.01	0.67–1.53.67.53	0.950	0.90	0.51–1.57.51.57	0.702
Lipid lowering therapy	0.56	0.40–0.80.40.80	0.001	0.57	0.40–0.80.40.80	0.002	0.81	0.50–1.33.50.33	0.407
RAASi	0.77	0.57–1.05.57.05	0.096	0.69	0.51–0.92.51.92	0.012	0.70	0.46–1.08.46.08	0.105
Beta blockers	1.32	0.97–1.80.97.80	0.076	0.78	0.59–1.03.59.03	0.077	1.30	0.82–2.05.82.05	0.263
Calcium channel blockers	1.28	0.92–1.78.92.78	0.138	1.06	0.75–1.48.75.48	0.751	0.60	0.36–1.02.36.02	0.058
Diuretics	0.86	0.62–1.19.62.19	0.370	1.14	0.83–1.57.83.57	0.425	1.06	0.66–1.71.66.71	0.812
Digoxin	0.90	0.54–1.47.54.47	0.662	1.26	0.85–1.86.85.86	0.251	2.64	1.47–4.73.47.73	0.001
PPI	1.32	0.97–1.80.97.80	0.074	1.06	0.79–1.43.79.43	0.704	1.20	0.79–1.83.79.83	0.382

AAD: anti-arrhythmic drugs; BMI: body mass index; CAD: coronary artery disease; CI: Confidence Interval; COPD/OSAS: chronic obstructive pulmonary disease/obstructive sleep apnoea syndrome; DOAC: direct oral anticoagulants; HR: Hazard Ratio; NA: Not Applicable; PAD: peripheral artery disease; PPI: proton pump inhibitors; RAASi: renin-angiotensin-aldosterone inhibitors; VKA: vitamin K antagonist.

CKD class. Treatment with DOACs was associated with a reduction of CVEs risk across all three CKD classes, as shown in Table 3.. Age was associated with an increased risk of CVEs in all CKD classes, while female sex was inversely associated. Of note, digoxin was associated with an increased risk of CVEs only in CKD class 4.

We then compared CVEs' risk in patients treated with DOACs or VKAs in the propensity score-matched cohort. CIFs' curves are shown in Fig. 2B. The probability of remaining event-free was consistently higher in the DOAC group throughout the follow-up period. A statistically significant difference between the two groups was observed (Gray's $p < 0.0001$), with a lower risk of CVEs among patients receiving DOACs. Univariable Fine–Gray analysis of the propensity score–matched cohorts revealed that DOAC use was associated with a significantly lower risk of CVEs in AF patients with CKD, compared to VKA use (sHR 0.60, 95% CI 0.49–0.74; $p < 0.001$).

In the exploratory analysis on patients receiving DOACs, no significant difference in CVE incidence was observed across the different agents in Kaplan–Meier curves (Supplementary Fig. 3, panel B, Gray's test $p = 0.443$). Furthermore, no association was observed in univariable and multivariable Fine–Gray analysis (shown in Supplementary Table 3, panel B) comparing each DOAC to apixaban.

Bleedings

During follow-up, a total of 240 bleeding events occurred: 120 in CKD class 3a, 94 in class 3b, and 26 in class 4. In the multivariable Fine–Gray model evaluating bleeding risk separately within each CKD class, the use of DOACs was not significantly associated with an increased risk of bleeding in any of the three CKD stages (Table 4).

CIFs curves for bleeding events in the propensity score–matched cohort are presented in Fig. 2C. No significant differences in bleeding risk were observed between anticoagulant types (Gray's test $p = 0.197$). Similarly, in the Fine–Gray analysis within the matched cohort, no significant difference was found for DOAC versus VKA use (sHR 1.18, 95% CI 0.87–1.60, $p = 0.280$).

Finally, in the exploratory analysis restricted to patients receiving DOACs, no significant differences in bleeding risk emerged across different DOAC molecules, as illustrated in the CIF plots (Supplementary Fig. 3, panel C) and confirmed by the multivariable Fine–Gray model (Supplementary Table 3, panel C).

Discussion

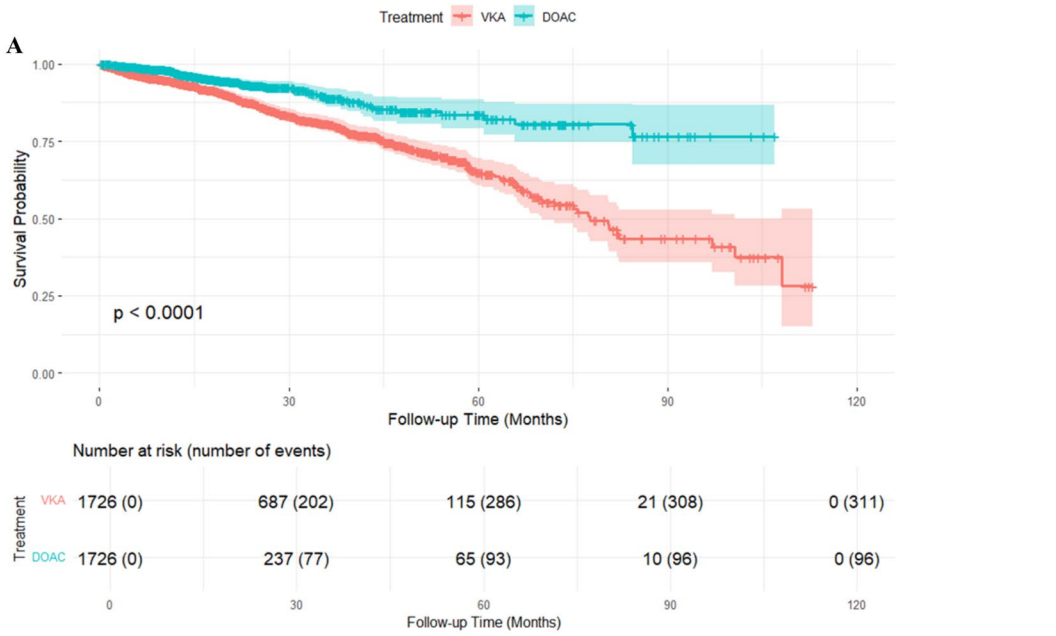
Our multicentre observational cohort study provides important insights into the outcomes of elderly patients with AF and CKD. We found that, also in real-world complex patients, DOACs are inversely associated with the risk of mortality and CVEs across CKD stages with this association being more evident in patients with more advanced CKD. Notably, we did not find any difference among different DOACs.

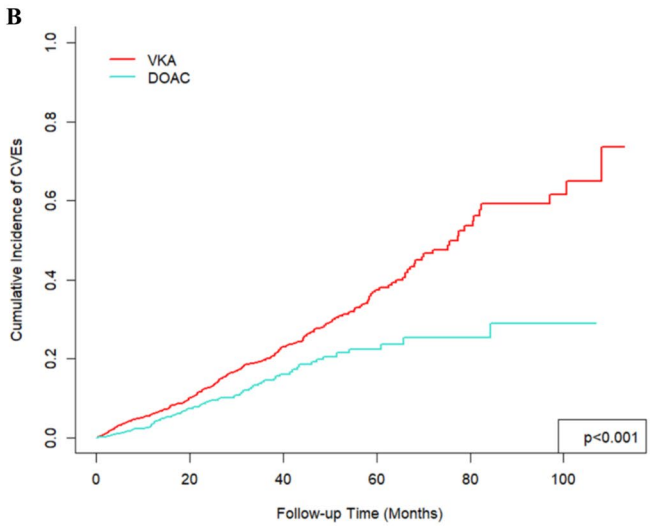
A first finding of our study was the confirmation of an increased mortality risk in patients with AF when CKD coexists. A study on 7412 AF patients found that CKD was significantly associated with the composite outcome of cardiovascular death and HF hospitalization after multivariable adjustment (adjusted HR 1.87, 95% CI 1.55–2.25) [26]. Furthermore, a recent prospective study highlighted that the risk of stroke in AF patients was higher in those with advanced CKD stages (stage 4 and 5 non-dialysis CKD), with adjusted hazard ratios of 3.31 (95% CI, 2.46–4.45) and 2.73 (95% CI, 1.88–3.96), respectively [27]. Our findings align with this evidence, further reinforcing the concept that CKD exacerbates every aspect of major adverse cardiovascular events (MACE) and mortality in AF patients, with the impact becoming more pronounced as GFR declines.

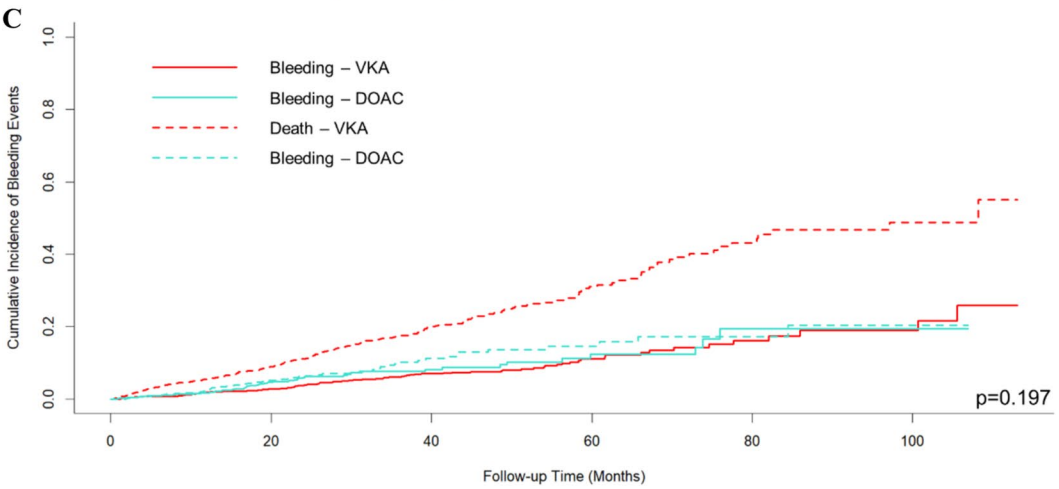
Beyond CKD, this study also found an association among age, male sex, PAD, and pulmonary diseases and an increased risk of overall mortality. Notably, in our cohort, digoxin use was associated with a higher mortality risk only in severe CKD. This may be explained by a higher risk of electrolyte imbalance and a higher serum concentration of digoxin in advanced CKD [28, 29].

As for the anticoagulant choice, we found that, across all analyses and strata, DOAC use was associated with a lower risk of overall mortality and CVEs, without an associated increase in bleeding risk. The association between DOAC use and lower CV risk has been well established [30]. The limited efficacy of warfarin in CKD has also been previously highlighted: a meta-analysis of AF patients with end-stage renal disease (ESRD) suggested that warfarin use was not associated with a significant reduction in stroke risk (HR 0.96; 95% CI 0.82–1.13) and had no impact on overall mortality (HR 0.95; 95% CI 0.83–1.09) [31]. However, a meta-analysis on this topic demonstrated a modest yet significant reduction in major adverse cardiovascular events (MACE) for DOACs compared to VKAs in CKD patients with AF [32]. In this context, our findings align with previous studies indicating that DOACs may be the preferred choice in patients with CKD and AF [33].

Several factors may explain why DOACs may carry an advantage in patients with AF and CKD over VKAs.


A
Treatment VKA DOAC
Survival Probability
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
30
60
90
120
Follow-up Time (Months)
Number at risk (number of events)
Treatment
VKA 1726 (0) 687 (202) 115 (286) 21 (308) 0 (311)
DOAC 1726 (0) 237 (77) 65 (93) 10 (96) 0 (96)
0
30
60
90
120
Follow-up Time (Months)


B
VKA
DOAC
Cumulative Incidence of CVEs
0.0
0.2
0.4
0.6
0.8
1.0
p<0.001
0
20
40
60
80
100
Follow-up Time (Months)


C
Bleeding – VKA
Bleeding – DOAC
Death – VKA
Bleeding – DOAC
Cumulative Incidence of Bleeding Events
0.0
0.2
0.4
0.6
0.8
1.0
p=0.197
0
20
40
60
80
100
Follow-up Time (Months)

◂**Fig. 2** Kaplan–Meier curve evaluating all-cause mortality (**A**) and cumulative incidence function plots of cardiovascular events (**B**) and bleedings (**C**) in patients with atrial fibrillation and chronic kidney disease treated with direct oral anticoagulants or vitamin K antagonists on propensity score–matched cohorts. *There were no competing events for CVEs. DOAC, direct oral anticoagulants; VKA, vitamin K antago*nists*

Warfarin has a high risk for drug–drug interactions and is highly sensitive to variations in absorption and pharmacogenetic factors, which may affect its efficacy. Additionally, poor adherence and compliance with warfarin therapy have been documented [34], and even minor dosing errors or missed doses have been associated with altered haemostasis and worse clinical outcomes [35]. These factors contribute to time spent outside the therapeutic international normalized ratio (INR) range, increasing the risk of adverse events and mortality.

Furthermore, VKAs has been associated with a progressive renal function worsening compared to DOACs [14]. This may be explained by the anticoagulation nephropathy typically associated with episodic above therapeutic range INR in patients taking VKAs. in these patients, microbleeds lead to red blood cells casts formation and to a consequent obstructive ischemia that permanently decreases the nephron mass of the kidney, favouring nephron sclerosis [20]. On the other hand, the tubules that survive the ischemic injury developed a hyperfiltration damage that leads to CKD rapid progression [20]. An additional mechanism related to the worsening of kidney function is related to the warfarin-related calciphylaxis. Clinical data has shown that warfarin is related to the calcification of small and medium-sized arteries leading to a deterioration of renal function [36–38].

Conversely, DOACs have a more predictable pharmacokinetic and pharmacodynamic profile, with a lower risk of drug interactions and a higher probability of target attainment. These reasons may also explain why, in our cohort, patients prescribed with DOACs tended to be older and had a higher prevalence of cardiovascular comorbidities such as hypertension, CAD, and PAD. This prescribing pattern could reflect a physician's preference for protecting more vulnerable patients—both due to disease burden and the increased risk of age-related non-compliance associated with warfarin.

Importantly, most evidence comparing DOACs with VKAs in AF CKD patients relies on subgroup analyses of major phase 3 randomized clinical trials.

In a sub-analysis of the ARISTOTLE trial [39] performed on 10,604 AF patients with eGFR < 80 ml/min and evaluating the effectiveness and safety of apixaban compared to warfarin across different kidney function stages, the authors found a reduction in major bleeding and ischemic stroke/systemic embolism, but not all-cause mortality, in patients with AF and CKD. Conversely, in our study, we found an inverse association between all-cause mortality and DOAC use. This difference may be explained by characteristics of our cohort, which was older, more frequently women, and had a higher proportion of patients with severe CKD. Indeed, only 269 patients [40] had an eGFR < 30 ml/min in the ARISTOTLE study, and although a reduction in major bleeding seems to be observed in this cohort, the effectiveness and safety of DOACs in these patients were still controversial.

In the sub-analysis of the ENGAGE-AF TIMI trial [41], edoxaban, compared to warfarin, showed a reduction in major bleeding and all-cause mortality risk, but not ischemic stroke/systemic embolism risk in patients with CKD and AF. However, only 2740 AF patients with eGFR 30–50 ml/min were included, and AF patients with eGFR < 30 ml/min were excluded from the analysis. These criteria limited the generalizability of the findings of this sub-analysis.

In the RE-LY trial [42] sub-analysis, no difference was observed between dabigatran 150 mg bid, 110 mg bid, and warfarin on ischemic stroke/systemic embolism, all-cause of death, and major bleeding. However, similarly to the ENGAGE-AF TIMI, only 19.8% of the 17,951 AF patients enrolled had an eGFR < 50 ml/min, and patients with eGFR < 30 ml/min were excluded from the trial. In addition, the RE-LY cohort was younger, with a higher proportion of men and a low proportion of patients with advanced CKD compared to our observational real-world cohort.

Overall, subgroup analysis from clinical trials should be interpreted with caution as it is not always powered for the secondary/not pre-specified endpoints.

A previous large retrospective analysis [43] performed on 74,542 AF patients from Australia and Canada explored the composite risk of all-cause death and thromboembolic stroke and bleeding risk at 1 year of follow-up according to kidney function. The authors found that DOACs were associated with a reduction of composite risk compared to warfarin across kidney function classes [43]. However, compared to our cohort, this study included younger patients (average of 5 years younger) with a lower proportion of patients with advanced CKD [43].

Regarding DOAC selection, our analysis did not reveal significant differences in outcomes based on the specific DOAC used, suggesting that DOACs as a class are generally superior to VKAs without a clear preference for one over another. Therefore, the choice of DOAC should be individualized, considering factors such as patient personal preferences (e.g. dosing frequency for once versus twice daily), drug interaction risk, level of renal impairment (Xa inhibitors preferred over dabigatran in patients with GFR < 30 ml/min/1.73 m^2), and other comorbidities (e.g. hepatic impairment, previous gastrointestinal bleeding).

Table 3. Multivariable Fine-Gray models of clinical factors associated with cardiovascular events (CVEs) according to estimated glomerular filtration rate (eGFR) classes

Variable	eGFR 59-46 ml/min/1.73 m2N=2,578 (53.2%)			eGFR 45-30 ml/min/1.73 m2N=1,750 (36.1%)			eGFR ≤29 ml/min/1.73 m2N=521 (10.7%)		
	sHR	95% CI	p-value	sHR	95% CI	p-value	sHR	95% CI	p-value
DOAC (vs VKA)	0.64	0.49–0.85.49.85	0.002	0.56	0.42–0.75.42.75	<0.001	0.31	0.17–0.55.17.55	<0.001
Age (years)	1.08	1.06–1.11.06.11	<0.001	1.08	1.06–1.11.06.11	<0.001	1.07	1.03–1.12.03.12	<0.001
Female	0.66	0.50–0.87.50.87	0.003	0.70	0.53–0.92.53.92	0.011	0.54	0.34–0.85.34.85	0.008
BMI	0.99	0.95–1.02.95.02	0.449	1.02	0.98–1.05.98.05	0.369	1.00	0.96–1.05.96.05	0.900
Hypertension	0.97	0.66–1.43.66.43	0.897	1.03	0.70–1.52.70.52	0.880	0.89	0.45–1.79.45.79	0.751
Diabetes	1.29	0.92–1.80.92.80	0.134	1.25	0.89–1.76.89.76	0.192	1.20	0.75–1.92.75.92	0.441
CAD	1.48	1.05–2.08.05.08	0.024	1.12	0.81–1.56.81.56	0.493	1.34	0.80–2.24.80.24	0.270
Anaemia	1.48	1.12–1.96.12.96	0.007	1.09	0.83–1.43.83.43	0.548	1.01	0.66–1.54.66.54	0.957
Heart failure	1.07	0.77–1.50.77.50	0.679	1.27	0.94–1.71.94.71	0.117	1.11	0.74–1.65.74.65	0.614
PAD	2.53	1.66–3.85.66.85	<0.001	1.59	1.02–2.47.02.47	0.040	1.44	0.73–2.84.73.84	0.287
COPD/OSAS	1.74	1.22–2.49.22.49	0.002	1.46	1.04–2.05.04.05	0.028	1.61	0.97–2.67.97.67	0.063
Antiplatelet	1.03	0.71–1.50.71.50	0.890	1.19	0.81–1.74.81.74	0.371	0.98	0.52–1.83.52.83	0.942
Class 1c AAD	0.69	0.33–1.42.33.42	0.309	0.85	0.41–1.76.41.76	0.669	NA	NA	NA
Amiodarone	1.04	0.68–1.59.68.59	0.849	0.92	0.61–1.37.61.37	0.666	0.89	0.52–1.53.52.53	0.674
Lipid lowering therapy	0.60	0.44–0.82.44.82	0.001	0.68	0.49–0.93.49.93	0.016	0.77	0.48–1.23.48.23	0.272
RAASi	0.88	0.66–1.17.66.17	0.386	0.64	0.49–0.85.49.85	0.002	0.72	0.48–1.09.48.09	0.118
Beta blockers	1.09	0.82–1.44.82.44	0.555	0.80	0.61–1.04.61.04	0.100	1.19	0.77–1.84.77.84	0.439
Calcium channel blockers	1.16	0.86–1.57.86.57	0.340	0.94	0.68–1.31.68.31	0.720	0.60	0.36–1.00.36.00	0.049
Diuretics	0.85	0.63–1.15.63.15	0.296	1.10	0.81–1.48.81.48	0.552	1.06	0.67–1.67.67.67	0.805
Digoxin	0.88	0.56–1.40.56.40	0.595	1.24	0.85–1.80.85.80	0.267	2.27	1.28–4.02.28.02	0.005
PPI	1.25	0.94–1.66.94.66	0.120	1.03	0.77–1.36.77.36	0.856	1.20	0.80–1.79.80.79	0.383

AAD: anti-arrhythmic drugs; BMI: body mass index; CAD: coronary artery disease; CI: Confidence Interval; COPD/OSAS: chronic obstructive pulmonary disease/obstructive sleep apnoea syndrome; DOAC: direct oral anticoagulants; NA: Not Applicable PAD: peripheral artery disease; PPI: proton pump inhibitors; RAASi: renin-angiotensin-aldosterone inhibitors; sHR: subdistribution Hazard Ratio; VKA: vitamin K antagonist.

Limitations

Several limitations should be acknowledged. First, we lack longitudinal data to assess how CKD and renal function progressed over time in this cohort. As a result, we cannot determine whether continuous DOAC use instead of warfarin may slow the decline of GFR, though this has been suggested in prior research [14]. Additionally, our study does not include albuminuria data, which could have further refined the characterization of renal impairment. Second, patients with eGFR < 15 mL/min/1.73 m^2 or those on haemodialysis were excluded from this analysis. In addition, due to the low number of patients in CKD stage 4 and the low number of events in each DOAC group in the lower stage of CKD, this analysis should be considered merely exploratory and not conclusive. While the observed trend of increasing mortality with declining eGFR may extend to this population, direct conclusions cannot be drawn. Third, the study cohort predominantly consisted of Caucasian patients due to the demographic characteristics of the participating centres, limiting the generalizability of our findings to other ethnic groups. Finally, as an observational study, we cannot exclude the presence of unintended biases or infer causality in the associations observed.

Despite these limitations, our findings contribute to the growing body of evidence supporting the use of DOACs over VKAs in patients with CKD and AF, emphasizing the need for individualized treatment decisions based on patient-specific factors.

In conclusion, patients with AF and CKD had a worse prognosis than those without CKD. DOACs seem to be associated with a lower risk of all-cause mortality and CVEs compared to VKAs, especially in more severe CKD.

AAD anti-arrhythmic drugs, *BMI* body mass index, *CAD* coronary artery disease, *CCB* calcium channel blockers, *COPD/OSAS* chronic obstructive pulmonary disease/obstructive sleep apnoea syndrome; *DOAC* direct oral anticoagulants, *eGFR* estimated glomerular filtration rate; *LLT* lipid lowering therapy, *PAD* peripheral artery disease, *PPI* proton pump inhibitors, *RAASi* renin–angiotensin–aldosterone inhibitors, *VKA* vitamin K antagonist

Table 4 Multivariable Fine–Gray models of clinical factors associated with bleedings according to estimated glomerular filtration rate (eGFR) classes

Variable	eGFR 59–46 ml/min/1.73 m^2 $N=2578$ (53.2%)			eGFR 45–30 ml/min/1.73 m^2 $N=1750$ (36.1%)			eGFR ≤ 29 ml/min/1.73 m^2 $N=521$ (10.7%)		
	sHR	**95% CI**	***p*-value**	**sHR**	**95% CI**	***p*-value**	**sHR**	**95% CI**	***p*-value**
DOAC (vs. VKA)	1.27	0.87, 1.85	0.220	1.18	0.75, 1.85	0.470	0.85	0.27, 2.69	0.780
Age (years)	1.00	0.97, 1.03	0.960	1.03	0.99, 1.06	0.130	1.06	0.96, 1.17	0.230
Female	0.80	0.55, 1.16	0.240	0.72	0.48, 1.09	0.120	0.43	0.16, 1.16	0.096
BMI	0.93	0.88, 0.98	0.009	1.00	0.95, 1.06	0.970	0.92	0.80, 1.05	0.220
Hypertension	1.50	0.84, 2.67	0.170	0.75	0.40, 1.42	0.380	1.39	0.36, 5.38	0.630
Diabetes	1.00	0.62, 1.63	>0.999	1.31	0.79, 2.19	0.300	0.72	0.30, 1.74	0.470
CAD	0.98	0.60, 1.59	0.920	1.12	0.68, 1.86	0.660	1.21	0.34, 4.29	0.770
Anaemia	1.58	1.08, 2.32	0.019	1.29	0.84, 1.99	0.250	0.51	0.20, 1.31	0.160
Heart failure	2.10	1.35, 3.27	<0.001	0.76	0.44, 1.31	0.320	1.13	0.50, 2.58	0.760
PAD	0.91	0.44, 1.89	0.800	1.50	0.78, 2.91	0.220	1.80	0.50, 6.42	0.370
COPD/OSAS	1.38	0.83, 2.29	0.220	1.50	0.88, 2.58	0.140	0.94	0.24, 3.68	0.920
Antiplatelet	1.25	0.76, 2.05	0.390	1.33	0.76, 2.34	0.320	2.83	0.87, 9.24	0.085
Class 1c AAD	0.67	0.26, 1.69	0.400	1.19	0.53, 2.70	0.670	NA	NA	NA
Amiodarone	0.73	0.40, 1.32	0.300	1.62	0.95, 2.78	0.078	0.79	0.19, 3.24	0.740
Lipid lowering therapy	0.81	0.55, 1.20	0.290	1.21	0.77, 1.91	0.420	1.72	0.59, 5.04	0.320
RAASi	0.81	0.55, 1.20	0.290	1.24	0.76, 2.02	0.390	0.84	0.34, 2.04	0.700
Beta blockers	0.67	0.45, 1.00	0.050	0.90	0.60, 1.34	0.610	1.11	0.41, 2.99	0.840
Calcium channel blockers	0.61	0.38, 0.99	0.045	0.93	0.56, 1.56	0.790	1.27	0.47, 3.47	0.630
Diuretics	1.24	0.80, 1.93	0.330	0.87	0.54, 1.41	0.580	0.95	0.39, 2.30	0.900
Digoxin	0.67	0.33, 1.36	0.260	1.06	0.54, 2.09	0.870	1.10	0.27, 4.53	0.890
PPI	0.85	0.57, 1.28	0.440	0.72	0.47, 1.10	0.130	0.36	0.13, 0.99	0.048

AAD: anti-arrhythmic drugs; BMI: body mass index; CAD: coronary artery disease; CI: Confidence Interval; COPD/OSAS: chronic obstructive pulmonary disease/obstructive sleep apnoea syndrome; DOAC: direct oral anticoagulants; NA: Not Applicable PAD: peripheral artery disease; PPI: proton pump inhibitors; RAASi: renin-angiotensin-aldosterone inhibitors; sHR: subdistribution Hazard Ratio; VKA: vitamin K antagonist.

AAD anti-arrhythmic drugs, *BMI* body mass index, *CAD* coronary artery disease, *CI* confidence interval, *COPD/OSAS* chronic obstructive pulmonary disease/obstructive sleep apnoea syndrome, *DOAC* direct oral anticoagulants, *HR* hazard ratio, *NA* not applicable, *PAD* peripheral artery disease, *PPI* proton pump inhibitors, *RAASi* renin–angiotensin–aldosterone inhibitors, *VKA* vitamin K antagonist

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Supplementary information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00392-025-02765-7.

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