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ARTICLE

Consequences of oral antithrombotic use in patients with chronic kidney disease

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Abstract

We assessed the risks of bleeding, acute kidney injury (AKI), and kidney failure associated with the prescription of antithrombotic agents (oral anticoagulants and/or antiplatelet agents) in patients with moderate-to-advanced chronic kidney disease (CKD). CKD-REIN is a prospective cohort of 3022 nephrology outpatients with CKD stages 2–5 at baseline. We used cause-specific Cox proportional hazard models to estimate hazard ratios (HRs) for bleeding (identified through hospitalizations), AKI, and kidney failure. Prescriptions of oral antithrombotics were treated as time-dependent variables. At baseline, 339 (11%) patients (65% men; 69 [60–76] years) were prescribed oral anticoagulants only, 1095 (36%) antiplatelets only, and 101 (3%) both type of oral antithrombotics. Over a median (interquartile range [IQR]) follow-up period of 3.0 (IQR, 2.8–3.1) years, 152 patients experienced a bleeding event, 414 patients experienced an episode of AKI, and 270 experienced kidney failure. The adjusted

*CKD-REIN Study Collaborators are present in the Acknowledgements section.

2012 to 2017, Sanofi-Genzyme from 2012 to 2015, and Vifor Fresenius and AstraZeneca since 2018. INSERM Transfert set up and has managed this partnership since 2011. A specific project on drug optimization in patients with CKD was funded by the French National Agency for Medicines and Health Products Safety (ANSM).

HRs (95% confidence interval [95% CI]) for bleeding associated with prescriptions of antiplatelets only, oral anticoagulants only, and antiplatelet + oral anticoagulant were, respectively, 0.74 (95% CI, 0.46–1.19), 2.38 (95% CI, 1.45–3.89), and 3.96 (95% CI, 2.20–7.12). An increased risk of AKI risk was associated with the prescription of oral anticoagulants (adjusted HR, 1.90, 95% CI, 1.47–2.45) but not the prescription of antiplatelets (HR, 1.24, 95% CI, 0.98–1.56). Kidney failure was not associated with the prescription of oral antithrombotics of any type. This study confirms the high risk of AKI associated with oral anticoagulants prescription in patients with CKD and also highlights the potential aggravating effect of combining vitamin K antagonist (VKA) and antiplatelets on the risk of bleeding.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Patients with chronic kidney disease (CKD) are prone to develop serious adverse drug reactions due to antithrombotic agents. Randomized clinical trial rarely include patients with moderate to severe CKD.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study assesses the impact of (i) oral antithrombotics and (ii) the interactions between oral anticoagulants and antiplatelet agents on the occurrence of serious adverse events, such as bleeding episodes requiring an emergency department visit or hospital admission, acute kidney injury (AKI), and CKD progression.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The risk of bleeding associated to oral anticoagulant was high in patients with CKD with estimated glomerular filtration rate (eGFR) less than 30 ml/min/1.73 m^2 and was even higher when patients take concomitantly oral anticoagulant and antiplatelet therapy. Oral anticoagulant is also associated with an increased risk of developing AKI. In contrast, taking an oral anticoagulant was not associated with progression to kidney failure.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The risks associated to the use of oral anticoagulant agents might be greater than the benefits. The concomitant use of two antithrombotic agents is not recommended in patients with CKD especially in the later stages.

INTRODUCTION

Patients with chronic kidney disease (CKD) have an elevated risk of cardiovascular morbidity and mortality.[1–6] CKD is associated with a high prevalence of both atheromatous cardiovascular vascular disease (CVD; such as coronary artery disease and stroke) and nonatheromatous CVD (such as heart failure and atrial fibrillation).[7] These comorbidities result in the frequent prescription of cardiovascular drugs.[8] In fact, CKD is an important risk factor for thrombosis independently of comorbidities, like diabetes, hypertension, and high blood cholesterol.[9] Specific risk factors for thrombosis have been identified in patients with CKD, such as uremic toxins (notably indoxyl sulfate and indole-3-acetic acid).[10–12] The pathogenesis of bleeding in CKD is considered to be multifactorial. The main abnormalities concern primary hemostasis and platelet-platelet or platelet-vessel-wall interactions.[13] A recent study of a mouse model of kidney failure showed that moderate CKD was associated with a hypercoagulation state, whereas severe CKD was associated with a risk of bleeding.[14] This seemingly incompatible combination in CKD—"more thrombosis, more bleeding"—constitutes a huge challenge in nephrology research and complicates treatment with antithrombotic drugs (such as oral anticoagulants and antiplatelet agents) in these patients.[15]

Moreover, patients with CKD (and especially those with advanced CKD) are under-represented in randomized controlled clinical trials of oral anticoagulants and antiplatelet agents. Although antithrombotic drugs have a well-established risk/benefit ratio in the general population, conflicting results have been published for patients with CKD,[16–22] in whom major bleeding is the prime safety

concern.[16,23,24] Furthermore, there is a lack of data on the putative pharmacodynamic interactions between antiplatelet agents and oral anticoagulants with regard to the bleeding risk in patients with moderate to advanced CKD.

In addition to the bleeding risk, several studies have reported anticoagulant-induced acute kidney injury (AKI) caused by subclinical glomerular hemorrhage.[25–27] It has also been suggested that exposure to oral anticoagulants might be associated with an accelerated decline in kidney function in these patients.[28,29]

The primary objective of the present study was to assess the impact of (i) oral antithrombotics and (ii) the interactions between oral anticoagulants and antiplatelet agents on the occurrence of serious adverse events, such as bleeding episodes requiring an emergency department visit or hospital admission, AKI, and CKD progression. The secondary objective was, in the subgroup of patients with an indication for oral anticoagulants, to determine the incidence of thromboembolic events and bleeding events as a function of whether these drugs were actually prescribed or not.

METHODS

Study design and participants

CKD-REIN is a prospective cohort study carried out in 40 nationally representative nephrology outpatient facilities in France. Details of the study protocol have been published elsewhere.[30] Briefly, the main inclusion criteria are age 18 years or over, a confirmed diagnosis of moderate or advanced CKD, an estimated glomerular filtration rate (eGFR) less than 60 ml/min per 1.73 m^2, and the absence of dialysis or transplantation. A total of 3033 patients have been included in the CKD-REIN study. After the exclusion of 11 patients with missing prescription data, the present analysis covered 3022 patients (Figure 1). The study protocol was approved by the institutional review board at the French National Institute of Health and Medical Research (INSERM; reference: IRB00003888). The study was registered at ClinicalTrials.gov (NCT03381950).

Information

Trained clinical research associates collected data from patient interviews and medical records at baseline and then annually. The patients' characteristics (age, sex, smoking status, alcohol use, and body mass index) were recorded, and the patients were screened for a history of hypertension, diabetes, cardiovascular disease, dyslipidemia, or AKI, as defined previously.[30] Serum levels of creatinine, albumin, and hemoglobin, and urine levels of albumin or total protein were measured. We used the Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) equation to estimate the GFR.[31] Anemia was defined as a blood hemoglobin level below 120 g/L for women and below 130 g/L for men. Medication Global treatment adherence was evaluated with the Girerd score.[32]

Patients were asked to bring (i) all their drug prescriptions from the previous 3 months (regardless of the prescribing physician) to their inclusion appointment, and (ii) all prescriptions for the year to each annual follow-up appointment. Accordingly, drug prescriptions were continuously recorded

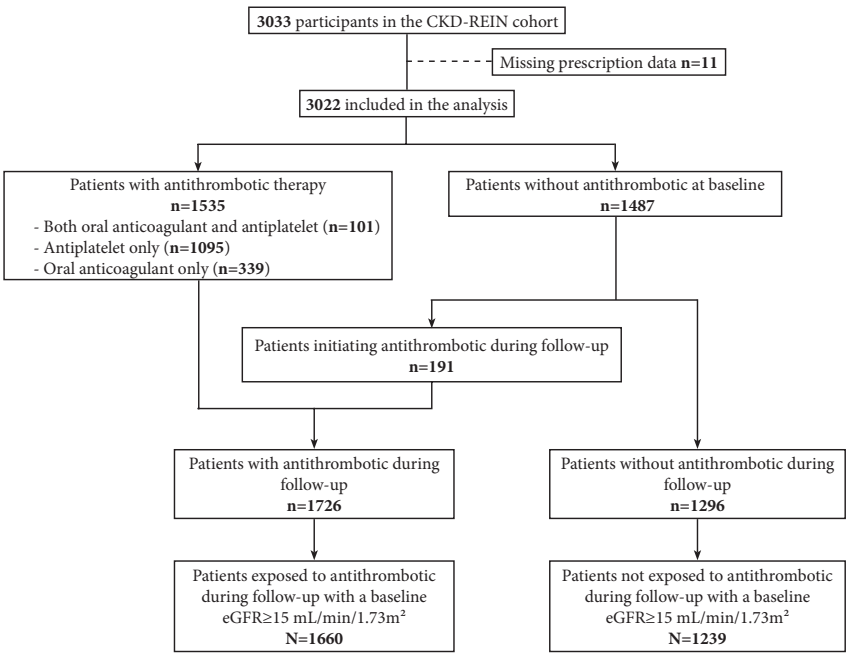

FIGURE 1 Study flow chart. CKD-REIN, chronic kidney disease study; eGFR, estimated glomerular filtration rate

from 3 months preceding inclusion through the end of the follow-up period. A specific electronic medication form linked to the international Anatomical Therapeutic Chemical (ATC) thesaurus[33] was used to code each drug prescription with regard to the brand name, international nonproprietary name, ATC class, unit dose, pharmaceutical formulation, administration route, initiation date, discontinuation date, and (if noted in the database) the reason for discontinuation. When the exact initiation or discontinuation date was not known, it was imputed as the date halfway through the period between the previous prescription and the following prescription.

Oral antithrombotic agents encompassed oral anticoagulants (ATC classes B01AA [vitamin K antagonists {VKAs}], B01AE [direct thrombin inhibitors], and B01AF [direct factor Xa inhibitors]) and antiplatelet agents (B01AC, and N02BA01 when the dose level of acetylsalicylic acid was below 160 mg).

Atrial fibrillation, valvulopathy, artificial heart valves, deep vein thrombosis, and pulmonary embolism at baseline were considered as indications for an anticoagulant. Ischemic and thromboembolic events (ischemic stroke, transient ischemic attack, pulmonary embolism, and deep vein thrombosis) were identified through hospitalization causes.

A modified HAS-BLED score (based on hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, elderly age, and drugs/alcohol concomitantly but not on the international normalized ratio, which was not measured in the present study)[34] was computed for patients with an indication for anticoagulants.

Study outcomes

The study outcomes were the first bleeding event leading to an emergency department visit or hospital admission, the first major bleeding event, the first episode of AKI, and progression to kidney failure.

Bleeding events were identified through hospitalization causes, which were coded by a physician according to the 10th revision of the International Classification of Diseases (ICD-10; Table S1). A sensitivity analysis (restricted to major bleeding events) was performed. A bleeding event was considered to be major if the bleeding led to death, occurred in a critical area or organ (i.e., intracranial, intraspinal, intra-ocular, retroperitoneal, intra-articular, pericardial, or intramuscular hemorrhages), caused a loss of at least 20 g/L of hemoglobin, or required transfusion of at least two red blood cell units, as defined by the International Society on Thrombosis and Hemostasis (ISTH).[35]

Episodes of AKI during follow-up were identified and recorded (i) by the clinical research associate during the annual medical visit, and (ii) by a physician examining all hospital reports. All reported episodes of AKI were reviewed by a committee of expert nephrologists. The episode was confirmed if the serum creatinine value had risen by at least 50% over a 7-day period or by at least 26 μmol/L over a 48 h period (according to the Kidney Disease: Improving Global Outcomes [KDIGO] 2012 definition).

Kidney failure (defined as initiation of dialysis or preemptive transplantation) was identified from medical records or by linkage with the French National Kidney Failure Registry.[36] Deaths before kidney failure (concurrent events) were identified from medical records or reported by family members at the annual follow-up visit.

Statistical analyses

The baseline characteristics were described for the overall population ($N = 3022$) and the subgroups (the presence or absence of oral antithrombotic treatment) and reported as the median (interquartile range [IQR]) for quantitative variables and as the percentage (frequency) for qualitative variables. Data from patients with and without prescriptions of oral antithrombotic were compared using Student's *t*-test, Fisher's exact test, or the χ^2 test.

Incidence rates for each event were computed for periods when patients were treated (or not) with oral antithrombotics. We used cause-specific Cox proportional hazard models to investigate characteristics associated with the risk of bleeding, AKI, and progression to kidney failure. Exposure to anticoagulant and antiplatelet agents were treated as time-dependent covariates. Otherwise, baseline data were used. Data were censored on the date of the patient's third annual follow-up visit, the date of last news before the third annual follow-up visit, the date of kidney failure, or the date of death, whichever occurred first (i.e., for competing events). The variables used in the models were selected after a literature review.[37–39] Variables with a p value greater than 0.10 in the crude model were excluded from the multivariate analyses. Age and sex were forced into the final model. Patients with an eGFR less than 15 ml/min/1.73 m² were excluded from the analysis of progression to kidney failure. For all the Cox models, the interaction between anticoagulant and antiplatelet variables was tested. If the interaction was statistically significant, antithrombotic prescriptions were studied in four categories: (i) no oral antithrombotics, (ii) an antiplatelet agent only, (iii) an oral anticoagulant only, and (iv) an oral anticoagulant and an antiplatelet agent. If the interaction was not statistically significant, oral anticoagulants and antiplatelet agents were considered as independent factors in models. For all three outcomes, we systematically tested interactions with eGFR levels (i.e., <30 or ≥30 ml/min/1.73 m^2). Hazard ratios (HRs) are presented with their 95% confidence interval (CI). The validity of all models (the proportional hazard assumption) was checked by testing the Schoenfeld residuals.

An exploratory analysis was performed on the subset of patients with at least one indication for anticoagulation. Incidence rates (95% CI) for ischemic, thromboembolic, and bleeding events were calculated for periods when patients were being treated (or not) with oral antithrombotics.

To deal with missing data, multiple imputations were performed (fully conditional specification method,[40] 10 datasets and 10 iterations) on the patient characteristics from Table 1, educational level, serum creatinine level, systolic and diastolic blood pressure, baseline heparin level, and

TABLE 1 The baseline characteristics of the study population

		Prescription of oral antithrombotic at baseline			
	All patients (n = 3022)	**Yes (n = 1535)**	**No (n = 1487)**	**p value**	**Imputed data (n = 3022)**
Age (years)	69 (60–76)	72 (66–79)	64 (53–72)	<0.0001	0%
Men	65.5%	73.3%	57.4%	<0.0001	0%
Smoking status				<0.0001	1%
Smoker	11.9%	10.0%	13.8%		
Nonsmoker	41.3%	34.7%	48.0%		
Ex-smoker	46.9%	55.3%	38.2%		
Alcohol abuse	1.4%	1.6%	1.2%	0.49	3%
eGFR (ml/min/1.73 m^2)	32.9 ± 12.2	32.4 ± 11.6	33.4 ± 12.7	0.03	0%
BMI (kg/m^2)	28.7 ± 5.9	29.7 ± 5.7	27.7 ± 5.9	<0.0001	2%
Serum albumin (g/L)	40.2 ± 4.3	40.0 ± 4.2	40.4 ± 4.3	0.01	19%
Proteinuria/creatininuria ratio				0.95	11%
A1: Normal to mildly increased	27.8%	27.7%	28.0%		
A2: Moderately increased	31.4%	31.3%	31.6%		
A3: Severely increased	40.7%	41.0%	40.4%		
Anemia	40.8%	45.6%	35.9%	<0.0001	1%
Heart failure	13.0%	21.8%	3.9%	<0.0001	0.3%
Coronary heart disease	24.7%	44.2%	4.5%	<0.0001	2%
Peripheral arterial disease	13.2%	22.1%	4.1%	<0.0001	2%
Stroke history	7.1%	11.6%	2.4%	<0.0001	2%
Transient ischemic attack history	3.6%	6.8%	0.3%	<0.0001	2%
Cerebral hemorrhage history	0.6%	0.5%	0.6%	0.79	2%
Gastrointestinal bleeding history	4.4%	4.9%	3.8%	0.18	6%
Cirrhosis history	2.2%	2.2%	2.1%	0.78	6%
Hypertension	90.7%	94.7%	86.5%	<0.0001	0.1%
Dyslipidemia	73.5%	85.8%	60.8%	<0.0001	0.2%
Diabetes	43.0%	56.4%	29.2%	<0.0001	0.2%
Acute kidney injury history	23.5%	25.6%	21.3%	0.006	8%
Number of drugs/patients at baseline	8 (5–10)	9 (7–12)	6 (4–8)	<0.0001	0%
Treatment adherence				<0.0001	1%
Good	37.8%	33.8%	41.9%		
Poor	62.2%	66.2%	58.1%		
Lipid modifying agents	63.1%	77.2%	48.6%	<0.0001	0%
Renin-angiotensin system inhibitors	75.8%	76.7%	75.0%	0.28	0%
Proton pump inhibitors	32.8%	41.2%	24.1%	<0.0001	0%
Diuretics	53.1%	65.0%	40.8%	<0.0001	0%
Nonsteroidal anti-inflammatory drugs	1.4%	1.1%	1.7%	0.14	0%
Selective serotonin reuptake inhibitors	4.6%	4.5%	4.8%	0.71	0%

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate, based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

prescriptions of antidiabetic agents and allopurinol. The data patterns suggested that the assumption whereby data were missing at random was plausible. Indicators in Table 1 and Cox model regression coefficients were estimated separately in each imputed dataset and combined according to Rubin's rules.[41] Statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC) and R software (version 4.0.2; Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of the patients and antithrombotic agents

Of the 3022 patients, 1535 (51%) had a prescription for one or more oral antithrombotic agents at baseline (339 with anticoagulants, 1095 with antiplatelet agents, and 101 with both; Figure 1, Table 1). On average, patients taking an oral antithrombotic at baseline were significantly older, more likely to be men, had more comorbidities, and were taking a greater number of drugs at baseline. The baseline eGFR was lower in patients taking antithrombotic agents than in patients not taking antithrombotic agents.

During a median (IQR) follow-up period of 3.0 (IQR, 2.8–3.1) years, 99 (3%) patients not treated at baseline were initiated treatment with an oral anticoagulant. Hence, a total of 539 (18%) patients received an anticoagulant during the follow-up (Figure S2a). Only 49 patients received a direct oral anticoagulant (DOAC) during follow-up. Treatment with an antiplatelet agent was initiated in 191 patients during the follow-up period (Figure S2b).

Bleeding events

During the first 3 years of follow-up, 152 patients had at least one bleeding event requiring an emergency department visit or a hospital stay, and 24 patients experienced more than one bleeding event. One third of the bleeding events were gastrointestinal hemorrhages ($n = 54$), 13% concerned the ear-nose-throat area ($n = 20$), and 7% were cerebral hemorrhages ($n = 11$; Figure 2). More than half of these events were major, according to the ISTH definition ($n = 79$).

The bleeding incidence rate was 1.2 per 100 person-years (PYs) for periods when patients were not treated with oral antithrombotics during the follow-up (47 events in 4036 PYs), versus 2.6 per 100 PYs for periods when patients were treated with oral antithrombotics during the follow-up (105 events in 3987 PYs; Table S2a).

The interaction between anticoagulants and antiplatelet agents was statistically significant ($p = 0.02$). After multiple adjustments, the risk of bleeding was significantly higher for patients treated with an oral anticoagulant only versus patients not treated with an oral antithrombotic agent (HR, 2.38, 95% CI, 1.45–3.89; Figure 3). This risk was even higher when patients had been prescribed both an anticoagulant and

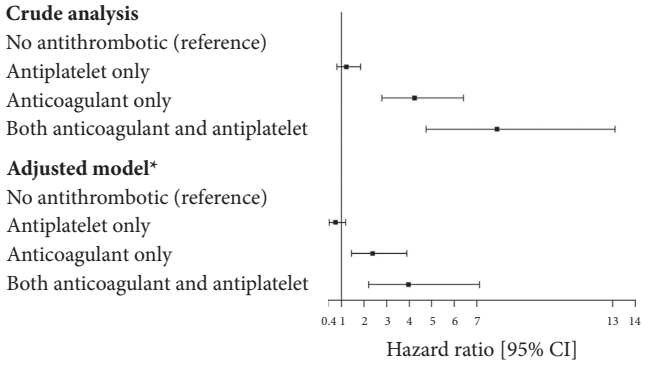

FIGURE 3 Crude and adjusted hazard ratios for bleeding events, according to the prescription of oral antithrombotic agents as a time-dependent variable in all patients. CI, confidence interval. *Adjusted for age, sex, estimated glomerular filtration rate (eGFR; <30 vs. ≥30 ml/min/1.73 m^2), serum albumin, cardiovascular history, diabetes, gastrointestinal bleeding history, and number of drugs per patient at baseline. Stroke history, cerebral hemorrhage history, alcohol abuse, lipid-modifying agent, and selective serotonin reuptake inhibitors were tested in a univariate analysis but did not meet the criteria for inclusion in the multivariable analysis ($p = 0.22$, 0.25, 0.44, 0.32, and 0.45, respectively). An interaction between antithrombotic treatment and eGFR was statistically significant ($p = 0.03$)

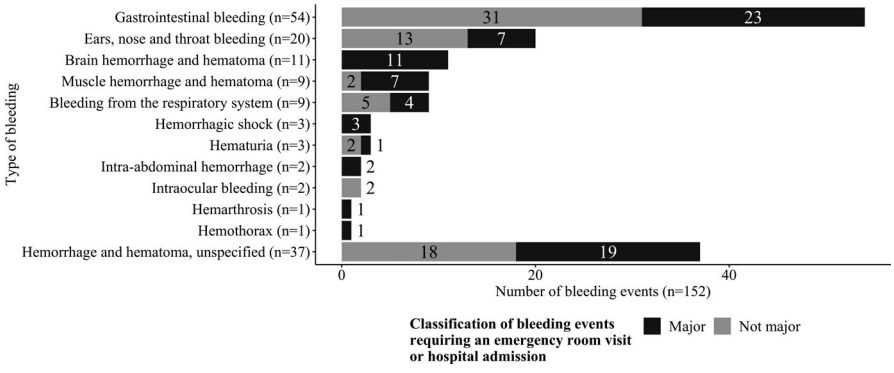

FIGURE 2 Description of the bleeding events requiring an emergency department visit or hospital admission, according to type of event and whether or not the event was major ($n = 152$)

an antiplatelet agent (HR, 3.96, 95% CI, 2.20–7.12). The only use of antiplatelet therapy was not associated with a higher risk of bleeding than for patients without any oral antithrombotic. Significant interaction was found with eGFR (HRs oral anticoagulant only: 2.62, 95% CI, 1.39–4.93 and HR, 1.91, 95% CI, 0.87–4.20 in patients with eGFR <30 vs ≥30 ml/min/1.73 m^2, and HR anticoagulant + antiplatelet: 5.76, 95% CI, 2.85–11.66 and HR, 1.54, 95% CI, 0.46–5.12 in patients with with eGFR <30 vs. ≥30 ml/min/1.73 m^2, interaction $p = 0.03$; Figure S2a).

A sensitivity analysis of major bleeding events gave similar results: HR, 3.40, 95% CI, 1.71–6.76 for anticoagulants only; HR, 6.57, 95% CI, 2.99–14.48 for a combination of anticoagulants and antiplatelet agents; HR, 0.66, 95% CI, 0.32–1.37 for antiplatelet agents only. Significant interaction was found with eGFR (HRs oral anticoagulant only: 2.96, 95% CI, 1.27–6.94 and HR, 3.96, 95% CI, 1.25–12.55 in patients with an eGFR <30 vs. ≥30 ml/min/1.73 m^2, and HR anticoagulant + antiplatelet: HR, 7.53, 95% CI, 2.98–18.99 and HR, 4.08, 95% CI, 0.81–20.44 in patients with an eGFR <30 vs. ≥30 ml/min/1.73 m^2, interaction $p < 0.0001$; Figure S2b).

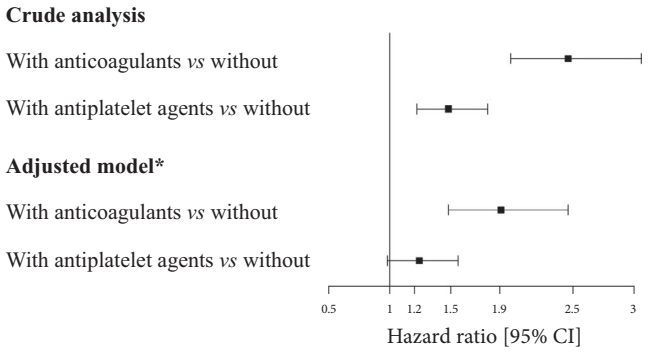

FIGURE 4 Crude and adjusted hazard ratios for acute kidney injury (AKI) events according to prescriptions of oral anticoagulant and antiplatelet agents as time-dependent variables in all patients. CI, confidence interval. *Adjusted for age, sex, estimated glomerular filtration rate (eGRF), serum albumin, anemia, proteinuria/creatininuria ratio, cardiovascular history, diabetes, history of AKI, number of drugs per patient at baseline, treatment adherence, renin-angiotensin system inhibitors at baseline, and proton pump inhibitors at baseline. Systolic blood pressure and nonsteroidal anti-inflammatory drug baseline prescriptions were tested in a univariate analysis but did not meet the criteria for inclusion in the multivariable analysis ($p = 0.18$ and $p = 0.22$, respectively). The interaction between oral anticoagulant and antiplatelet was not statistically significant ($p = 0.20$), as well as the interaction between oral anticoagulant and eGFR ($p = 0.30$)

Acute kidney injury

Of the 3022 included patients, 414 experienced at least one confirmed episode of AKI during the first 3 years of follow-up. The AKI incidence rate was 3.2 per 100 PYs for periods when patients were not treated with oral antithrombotics (126 AKIs for 3902 PYs) versus 7.7 per 100 PYs for periods when patients received oral antithrombotics (288 AKIs for 3749 PYs; Table S2a).

After adjustments for confounders, the risk of AKI was 1.9-fold higher in patients receiving anticoagulants than in those not receiving anticoagulant (HR, 1.91, 95% CI, 1.48–2.46; Figure 4). No significant interactions were found with an eGFR and antiplatelet agents. Antiplatelet therapy was not significantly associated with a higher risk of AKI, although a trend could be detected (HR, 1.24, 95% CI, 0.98–1.56).

Progression to kidney failure

At baseline, 2899 patients had an eGFR greater than or equal to 15 ml/min/1.73 m^2; of these, 57% ($n = 1660$) received an oral antithrombotic during the follow-up (Figure 1). During the first 3 years of follow-up, 270 patients progressed to kidney failure (i.e., dialysis or transplantation). The crude incidence rate was 3.4 per 100 PYs. When comparing periods with and without an oral antithrombotic, the difference in the incidence rate was small (3.3 and 3.4 per 100 PYs, respectively; Table S2a). No significant interactions were found with eGFR and antiplatelet agents.

Oral antithrombotic agents were not significantly associated with an increased risk of progression to kidney failure (Figure 5). The adjusted HR for patients receiving an oral anticoagulant was 1.37, 95% CI, 0.92–2.04 and the value in patients receiving an antiplatelet agent was HR, 1.22, 95% CI, 0.89–1.66.

Exploratory analysis of risks and benefits in patients with an indication for an oral anticoagulant

Of the 3022 patients included in the CKD-REIN study, 672 had at least one indication for an oral anticoagulant. Atrial fibrillation was the most frequently reported indication (Table S3). At baseline, 52% of these patients were actually receiving an oral anticoagulant, and around two in five of this subset were also receiving an antiplatelet (Table S4). Patients receiving an oral anticoagulant were older and were more likely to have comorbidities. Patients not treated with an oral anticoagulant had a significantly higher HAS-BLED score and more antiplatelet prescriptions than those treated with an oral anticoagulant ($p < 0.0001$; Table S4).

During the first 3 years of follow-up, 27 ischemic and thromboembolic events were reported (14 ischemic strokes,

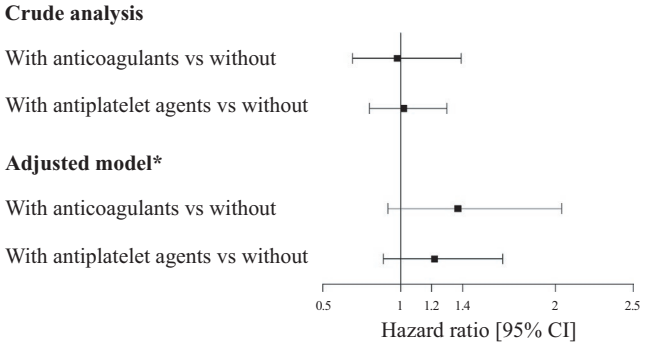

FIGURE 5 Crude and adjusted hazard ratios for kidney failure events according to prescriptions of oral anticoagulant and antiplatelet agents as time-dependent variables in patients with a baseline estimated glomerular filtration rate (eGFR) greater than or equal to 15 ml/min/1.73 m^2. CI, confidence interval. *Adjusted for age, sex, eGFR, body mass index, serum albumin, anemia, proteinuria/creatininuria ratio, systolic blood pressure, cardiovascular history, diabetes, history of acute kidney injury, number of drugs per patient at baseline, treatment adherence, renin-angiotensin system inhibitors at baseline, diuretics at baseline, and proton pump inhibitors at baseline. The interaction between oral anticoagulant and antiplatelet was not statistically significant ($p = 0.51$), as well as the interaction between oral anticoagulant and eGFR ($p = 0.30$)

3 transient ischemic attacks, and 10 cases of deep vein thrombosis or pulmonary embolism). The crude incidence rate was 1.6 per 100 PYs (27 events for 1718 PYs). This crude incidence rate was two times greater for periods when patients were not treated with an oral anticoagulant than for periods when patients were receiving an oral anticoagulant (Table S2b). The small number of events prevented us from performing a multivariable analysis.

During the same period, 70 bleeding events requiring an emergency department visit or hospital admission were reported in the subset of patients with an indication for an oral anticoagulant. Findings for bleeding events in this subgroup were consistent with those in the overall population (HR oral anticoagulant vs. no anticoagulant, 3.13, 95% CI, 1.74–5.64, but the interaction between antiplatelet and oral anticoagulant was not statistically significant (Tables S2b and S5).

DISCUSSION

In a large cohort of French patients with CKD, we found that almost a quarter of those treated with oral anticoagulants were also receiving antiplatelet drugs. The risk of bleeding in patients with CKD receiving an oral anticoagulant only was almost 2.5 times higher than in untreated patients and was four times higher when an oral anticoagulant and an antiplatelet agent were used concomitantly. The present large prospective CKD cohort study is the first of its kind, by its large number of included participants, to show that taking an oral anticoagulant is also associated with an increased risk of developing AKI. In contrast, taking an oral anticoagulant was not associated with progression to kidney failure.

In line with the observed prevalence of cardiovascular comorbidities, respectively, 15% and 40% of the study participants were being treated with oral anticoagulants and antiplatelet agents at baseline. It is noteworthy that when considering oral anticoagulants, VKAs were frequently used and prescriptions of DOACs were very rare. The pharmacokinetics and bioavailability of anticoagulants are altered in patients with CKD.[42] Furthermore, DOACs (but not VKAs) are mainly excreted by the kidneys.[43] The exclusion of patients with a creatinine clearance rate below 30 ml/min from clinical trials of DOAC and the need for DOAC dose adjustments according to the level of kidney function might lead to underprescription in these patients (relative to non-CKD populations).

Here, we focused on the risks associated with the use of oral antithrombotic drugs and, in particular, on the bleeding risk. In the present cohort, the bleeding risk was four times higher in patients receiving both oral anticoagulants and antiplatelet agents than in patients not receiving any antithrombotic agents; this finding highlights a pharmacodynamic interaction between the two drug classes. Our results are in line with a Danish national registry study,[16] in which the risk of bleeding was significantly higher in patients taking warfarin (alone or combined with aspirin) than in nontreated patients. However, the Danish study was retrospective, and CKD stage data were not reported. Other studies in populations of predialysis patients with CKD reported that an antithrombotic use is associated with a nonsignificant risk of bleeding.[17,18,20] Of note, we found a higher risk of bleeding and major bleeding in patients with eGFR less than 30 ml/min/1.73 m^2. In the same line, Limdi et al. found that compared to patients with eGFR greater than or equal to 60 ml/min/1.73 m^2, those with eGFR 30–44 ml/min/1.73 m^2 are at a twofold higher risk of hemorrhage and those with eGFR less than 30 ml/min/1.73 m^2 are at a 5.6-fold higher risk.[44] Our results are consistent with the findings in patients receiving hemodialysis,[45] in whom the prescription of oral anticoagulants is subject to debate[46]; some researchers have even suggested that these drugs should not be used in dialyzed patients because of their poor benefit/risk ratio.[47]

Our study is the first to show that taking an oral anticoagulant is associated with an increased risk of AKI in a large CKD cohort. Indeed, tubular nephropathies have recently been linked to use of the oral anticoagulants warfarin, fluindione, and dabigatran.[25] Patients with CKD are at greater risk of excessive anticoagulation, due to the negative impact of poor renal function on the clearance and metabolism of oral anticoagulants.[43,44] Excessive anticoagulation can lead to AKI resulting from glomerular bleeding and tubular obstruction caused by an accumulation of red blood cells.[26]

The diagnosis of anticoagulant-related nephropathy is based on a renal biopsy—an invasive test rarely performed in patients taking an anticoagulant. CKD is a risk factor for AKI and (probably) anticoagulant-related nephropathy.[26] Few studies have evaluated the association between taking oral anticoagulants and the occurrence of AKI in patients with moderate-to-severe CKD.[48,49] Most of the few available studies compared DOACs with VKAs.[50,51] Although the incidence of anticoagulant-related nephropathies is probably underestimated, the observation of marked hematuria before AKI should prompt the physician to consider this diagnosis.

Our analysis did not show an association between oral anticoagulant use and progression to kidney failure. Some researchers have hypothesized that anticoagulant use is associated with the progression of CKD. Individuals with CKD taking oral anticoagulants may experience repeated episodes of poorly identified clinical or subclinical glomerular bleeding, which could accelerate the fall over time in the eGFR. Furthermore, it is known that VKAs prevent gamma carboxylation of the matrix Gla protein (an inhibitor of vascular calcification) and thus hasten the appearance of arterial calcification.[52] In turn, arterial calcification might contribute to the progression of CKD. However, the literature data diverge with regard to the risk of CKD progression and the use of anticoagulants in patients with moderate-to-advanced CKD.[29,53] A large, retrospective study that included patients with stage three and four CKD, showed that disease progression (based on a change in eGFR over a median follow-up period of 1.5 years) was faster in patients treated with VKAs than in those who were not.[29] Although the assessment criteria were different, these results disagree with our present findings. In a 2-year study of 984 patients with CKD (eGFR: between 20 and 30 ml/min/1.73 m^2), VKA use was not associated with an accelerated decline in renal function or an earlier onset of dialysis.[53]

When choosing a treatment, the physician must take account of both risks and benefits. As shown here, the risks associated with oral anticoagulant treatment of patients with CKD appear to be elevated—especially for VKAs and antiplatelet agents. Only a few studies have sought to assess the benefit of oral anticoagulant treatment in the CKD population. Carrero et al. found a benefit of anticoagulants in predialysis patients with CKD after a myocardial infarction; there was a significant reduction in the risk of ischemic stroke.[20] In contrast, several studies have not found any significant benefits of anticoagulants in predialysis patients, although a general trend toward benefit was observed.[16–19,23] Among patients with an indication for oral anticoagulation in the CKD-REIN study, our exploratory analysis showed a nonsignificant protective trend (i.e., toward a reduction in the risk of thromboembolic events). However, the small number of events prevented us from adjusting this analysis. We also evaluated bleeding in the same subset; the risk was three times higher among patients actually treated with oral anticoagulants than in nontreated patients. One can therefore legitimately question the balance between the decrease risk of thromboembolic events and the increased risk of bleeding associated with antithrombotics (and especially oral anticoagulants), in this particular population. Furthermore, bleeding was not the only harmful event associated with oral anticoagulant prescription. When treating patients with CKD, it is important to evaluate other options (such as DOACs) with potentially high levels of efficacy and safety in the setting of kidney disease; this can only be confirmed by meticulous, prospective clinical investigation.

For patients with CKD with atrial fibrillation, the value of percutaneous left atrial appendage occlusion (to exclude the most prevalent source of thrombus formation) can be questioned because few studies have evaluated this method (reserved for patients with a high bleeding risk on oral anticoagulants) in the context of CKD.[54,55] Last, the benefit of concomitant use of oral anticoagulants and antiplatelet agents needs to be carefully assessed, given the major known risk.

The main strengths of this study lie in its prospective design and its large, well-characterized sample of patients with CKD. The longitudinally drug records (with start and stop dates) enabled us to take account of oral antithrombotic treatments as time-dependent covariates. Our analyses were not limited to one particular oral antithrombotic agent. Another strength relates to the fact that the sensitive, specific identification of events by experts greatly reduced the misclassification of the study outcomes. Last, comparison of the CKD-REIN database with the French national kidney failure registry enabled us to precisely identify kidney failure events.

Our study had some limitations. First, due to the low number of patients with DOAC prescriptions, we could not compare VKAs and DOACs. Second, our results were limited to the first event, which potentially skewed the exposure-event association. However, few patients presented repeated events during the first 3 years of follow-up. Third, we may not have captured all hospital admissions and in-hospital events. Given the low number of incident thromboembolic events during the first 3 years of the study, our analysis of the benefit of anticoagulants in patients with an indication for oral anticoagulation could only be carried out on an exploratory basis (i.e., as a crude analysis); a longer follow-up might have allowed us to perform an adjusted analysis. Finally, residual confounding is a further limitation, given that a number of unknown or unmeasured risk factors may have not been included in the analyses and might explain the observed associations. Confounding by indication could potentially overestimate the true risk. Finally, although prevalent user bias is a common bias encountered in pharmacoepidemiology studies, it mostly concerns drug efficacy evaluation. The inclusion of prevalent users may lead to an underestimation of the adverse effects

that occur at the beginning of treatment. Thus, we cannot rule out a possible underestimation of the risk.

In conclusion, treatment with oral antithrombotics should be initiated with caution in patients with CKD, and the benefit/risk ratio should be reassessed on a regular basis. Our results confirm the high risk of bleeding in patients with CKD treated with antithrombotics, and highlighted a notable interaction between oral anticoagulants and antiplatelet agents. The risk of AKI linked to oral anticoagulant prescriptions in patients with CKD warrants further investigation. The value of oral anticoagulant therapy in preventing the thromboembolic complications of atrial fibrillation in CKD can only be established in a randomized, controlled clinical trial.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

S.M.L., O.L., A.H., M.M., C.J., M.L., D.F., L.F, C.C., C.A., R.P.F, B.S., Z.A.M., and S.L. wrote the manuscript. S.M.L., S.L., Z.A.M., O.L., M.M., and B.S designed the research. S.M.L., S.L., Z.A.M., O.L., M.M., and B.S. performed the research. S.M.L., S.L., O.L., and M.M. analyzed the data.

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REFERENCES

1. Soliman EZ, Prineas RJ, Go AS, et al. Chronic kidney disease and prevalent atrial fibrillation: The Chronic Renal Insufficiency Cohort (CRIC). *Am Heart J*. 2010;159:1102-1107.
2. Alonso A, Lopez FL, Matsushita K, et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2011;123:2946-2953.
3. Kottgen A, Russell SD, Loehr LR, et al. Reduced kidney function as a risk factor for incident heart failure: the atherosclerosis risk in communities (ARIC) study. *J Am Soc Nephrol*. 2007;18:1307-1315.
4. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296-1305.
5. Piccini JP, Stevens SR, Chang Y, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation*. 2013;127:224-232.
6. Lau DH, Nattel S, Kalman JM, Sanders P. Sanders prashanthan modifiable risk factors and atrial fibrillation. *Circulation*. 2017;136:583-596.
7. Villain C, Metzger M, Combe C, et al. Prevalence of atheromatous and non-atheromatous cardiovascular disease by age in chronic kidney disease. *Nephrol Dial Transplant*. 2020;35:827-836.
8. Villain C, Liabeuf S, Metzger M, et al. Impact of age on cardiovascular drug use in patients with chronic kidney disease. *Clin. Kidney J*. 2020;13:199-207.
9. Shashar M, Francis J, Chitalia V. Thrombosis in the uremic milieu–emerging role of 'thrombolome'. *Semin Dial*. 2015;28:198-205.
10. Dou L, Poitevin S, Sallée M, et al. Aryl hydrocarbon receptor is activated in patients and mice with chronic kidney disease. *Kidney Int*. 2018;93:986-999.
11. Chitalia VC, Shivanna S, Martorell J, et al. Uremic serum and solutes increase post-vascular interventional thrombotic risk through altered stability of smooth muscle cell tissue factor. *Circulation*. 2013;127:365-376.
12. Addi T, Poitevin S, McKay N, et al. Mechanisms of tissue factor induction by the uremic toxin indole-3 acetic acid through aryl

hydrocarbon receptor/nuclear factor-kappa B signaling pathway in human endothelial cells. *Arch Toxicol*. 2019;93:121-136.
13. Schoorl M, Grooteman MPC, Bartels PCM, Nubé MJ. Aspects of platelet disturbances in haemodialysis patients. *Clin. Kidney J*. 2013;6:266-271.
14. Makhloufi C, Crescence L, Darbousset R, et al. Assessment of thrombotic and bleeding tendency in two mouse models of chronic kidney disease: adenine-diet and 5/6th nephrectomy. *TH Open*. 2020;4:e66-e76.
15. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS) The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5):373–498.
16. Olesen JB, Lip GYH, Kamper A-L, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med*. 2012;367:625-635.
17. Banerjee A, Fauchier L, Vourc'h P, et al. A prospective study of estimated glomerular filtration rate and outcomes in patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Chest*. 2014;145:1370-1382.
18. Chiu P-F, Huang C-H, Liou H-H, et al. Lower-dose warfarin delays renal progression and prolongs patient survival in patients with stage 3–5 chronic kidney disease and nonvalvular atrial fibrillation: a 12-year follow-up study. *Int J Clin Pharmacol Ther*. 2014;52:504-508.
19. Lai HM, Aronow WS, Kalen P, et al. Incidence of thromboembolic stroke and of major bleeding in patients with atrial fibrillation and chronic kidney disease treated with and without warfarin. *Int J Nephrol RenovASC Dis*. 2009;2:33-37.
20. Carrero JJ, Evans M, Szummer K, et al. Warfarin, kidney dysfunction, and outcomes following acute myocardial infarction in patients with atrial fibrillation. *JAMA*. 2014;311:919-928.
21. Major RW, Oozeerally I, Dawson S, et al. Aspirin and cardiovascular primary prevention in non-endstage chronic kidney disease: A meta-analysis. *Atherosclerosis*. 2016;251:177-182.
22. Palmer SC, DiMicco L, Razavian M, et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2012;156:445-459.
23. Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. Stroke, major bleeding, and mortality outcomes in warfarin users with atrial fibrillation and chronic kidney disease: a meta-analysis of observational studies. *Chest*. 2016;149:951-959.
24. Laville SM, Gras-Champel V, Moragny J, et al. Adverse drug reactions in patients with CKD. *Clin J Am Soc Nephrol*. 2020;15(8):1090-1102.
25. Golbin L, Vigneau C, Touchard G, et al. Warfarin-related nephropathy induced by three different vitamin K antagonists: analysis of 13 biopsy-proven cases. *Clin Kidney J*. 2017;10:381-388.
26. Brodsky SV, Satoskar A, Chen J, et al. Acute kidney injury during warfarin therapy associated with obstructive tubular red blood cell casts: a report of 9 cases. *Am J Kidney Dis*. 2009;54:1121-1126.
27. Kabir A, Nadasdy T, Nadasdy G, Hebert LA. An unusual cause of gross hematuria and transient ARF in an SLE patient with warfarin coagulopathy. *Am J Kidney Dis*. 2004;43:757-760.
28. Böhm M, Ezekowitz MD, Connolly SJ, et al. Changes in renal function in patients with atrial fibrillation: an analysis from the RE-LY Trial. *J Am Coll Cardiol*. 2015;65:2481-2493.
29. Posch F, Ay C, Stöger H, Kreutz R, Beyer-Westendorf J. Exposure to vitamin K antagonists and kidney function decline in patients with atrial fibrillation and chronic kidney disease. *Res Pract Thromb Haemost*. 2019;3:207-216.
30. Stengel B, Metzger M, Combe C, et al. Risk profile, quality of life and care of patients with moderate and advanced CKD: The French CKD-REIN Cohort Study. *Nephrol Dial Transplant*. 2019;34:277-286.
31. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604-612.
32. Girerd X, Radauceanu A, Achard JM, et al. Evaluation of patient compliance among hypertensive patients treated by specialists. *Arch Mal Coeur Vaiss*. 2001;94:839-842.
33. World Health Organization Collaborating Centre for Drug Statistics Methodology, Oslo Guidelines for ATC classification and DDD assignment 2016, 20th Edition (2016). <www.whocc.no/atc_ddd_index/>.
34. King A. HAS-BLED—a new risk score to predict bleeding in patients with AF. *Nat Rev Cardiol*. 2011;8:64.
35. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692-694.
36. Couchoud C, Stengel B, Landais P, et al. The renal epidemiology and information network (REIN): a new registry for end-stage renal disease in France. *Nephrol Dial Transplant*. 2006;21:411-418.
37. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093-1100.
38. Thongprayoon C, Hansrivijit P, Kovvuru K, et al. Diagnostics, risk factors, treatment and outcomes of acute kidney injury in a new paradigm. *J Clin Med*. 2020;9:1104.
39. Levin A, Djurdjev O, Beaulieu M, Er L. Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. *Am J Kidney Dis*. 2008;52:661-671.
40. Van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res*. 2007;16:219-242.
41. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. Hoboken, NJ: John Wiley & Sons; 2004.
42. Dreisbach AW, Lertora JJL. The effect of chronic renal failure on drug metabolism and transport. *Expert Opin Drug Metab Toxicol*. 2008;4:1065-1074.
43. Harder S, Graff J. Novel oral anticoagulants: clinical pharmacology, indications and practical considerations. *Eur J Clin Pharmacol*. 2013;69:1617-1633.
44. Limdi NA, Nolin TD, Booth SL, et al. Influence of kidney function on risk of supratherapeutic international normalized ratio-related hemorrhage in warfarin users: a prospective cohort study. *Am J Kidney Dis*. 2015;65:701-709.
45. Collette C, Clerc-Urmès I, Laborde-Castérot H, et al. Antiplatelet and oral anticoagulant therapies in chronic hemodialysis patients: prescribing practices and bleeding risk. *Pharmacoepidemiol Drug Saf*. 2016;25:935-943.

46. Burlacu A, Genovesi S, Ortiz A, et al. Pros and cons of antithrombotic therapy in end-stage kidney disease: a 2019 update. *Nephrol Dial Transplant*. 2019;34:923-933.
47. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J*. 2018;39:1330-1393.
48. An JN, Ahn SY, Yoon C-H, et al. The occurrence of warfarin-related nephropathy and effects on renal and patient outcomes in Korean patients. *PLoS One*. 2013;8:e57661.
49. Brodsky SV, Nadasdy T, Rovin BH, et al. Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. *Kidney Int*. 2011;80:181-189.
50. Shin J-I, Luo S, Alexander GC, et al. Direct oral anticoagulants and risk of acute kidney injury in patients with atrial fibrillation. *J Am Coll Cardiol*. 2018;71:251-252.
51. Chan Y-H, Yeh Y-H, See L-C, et al. Acute kidney injury in Asians with atrial fibrillation treated with dabigatran or warfarin. *J Am Coll Cardiol*. 2016;68:2272-2283.
52. Bennis Y, Vengadessane S, Bodeau S, et al. Vascular calcifications, the hidden side effects of vitamin K antagonists [in French]. *Therapie*. 2016;71:355-363.
53. Voskamp PW, Dekker FW, Rookmaaker MB, et al. Vitamin K antagonist use and renal function in pre-dialysis patients. *Clin Epidemiol*. 2018;10:623-630.
54. Piccini JP, Sievert H, Patel MR. Left atrial appendage occlusion: rationale, evidence, devices, and patient selection. *Eur Heart J*. 2017;38:869-876.
55. Kefer J, Tzikas A, Freixa X, et al. Impact of chronic kidney disease on left atrial appendage occlusion for stroke prevention in patients with atrial fibrillation. *Int J Cardiol*. 2016;207:335-340.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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