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Prescription of Direct Oral Anticoagulants to Patients With Moderate-to-Advanced CKD: Too Little or Just Right?



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Chronic kidney disease (CKD) is associated with an increased risk of cardiovascular disease in general and a broad spectrum of cardiac rhythm disorders (including atrial fibrillation [AF]) in particular. Although there are treatment options for many of these disorders, management is often more complex and more restricted in a CKD setting than in a non-CKD setting.¹ The risk-benefit ratio for oral anticoagulants is particularly difficult to judge in CKD patients, because of increased risks of both thromboembolic episodes and bleeding events. For many years, vitamin K antagonists (VKAs, including warfarin) constituted the cornerstone of oral anticoagulation in AF. Following a number of pivotal trials, 4 direct oral anticoagulants (DOACs) have been approved for use in non-valvular AF since 2010 (Supplementary Table S1) and have now supplanted VKAs in non-CKD patients. In contrast to VKAs, the DOACs were evaluated in randomized clinical trials (RCTs) and have included CKD patients.^{2,S1–S4}

Following *post hoc* analyses of the RCTs of DOACs in CKD patients performed between 2011 and 2016, a 2018 Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference stated that DOACs could be recommended in patients with an estimated glomerular filtration rate between 30 and 50 ml/min per 1.73 m² (i.e., stage 3 CKD), with a view to preventing stroke.¹

However, multinational data on the implementation of DOAC treatment in real-world nephrology practice among CKD patients are currently lacking.

The ongoing international CKD Outcomes and Practice Patterns Study (CKDopps)³ was established to provide insights into treatments, clinical practice, and clinical outcomes in patients with CKD stages 3 to 5. In the present analysis, we report on prescription patterns for oral anticoagulants in general and VKAs versus DOACs in particular.

RESULTS

Baseline Characteristics

This analysis included data from CKDopps, an ongoing, international, prospective cohort study of adult non-dialysis patients with an estimated glomerular filtration rate <60 ml/min per 1.73 m².³ Participants were selected from national samples of nephrologist-run CKD clinics in Brazil, France, Germany, and the USA between January 2013 and April 2019. Patients were enrolled between 2014 and 2017 in Brazil, 2013 and 2017 in the USA, 2013 and 2019 in Germany, and between 2013 and 2016 in France. Of the 8149 patients enrolled, 7040 had complete data on drug prescriptions at baseline, and 1060 (15%) of these had at least 1

Table 1. Baseline characteristics of the study population

	Total (<i>N</i> = 7040)	Oral anticoagulant at baseline		Type of oral anticoagulant		Imputed data, % (<i>N</i> = 7040)
		No (<i>n</i> = 5980)	Yes (<i>n</i> = 1060)	Vitamin K antagonist (<i>n</i> = 973)	DOAC (<i>n</i> = 87)	
Age at baseline (yr), median (IQR)	71 (62–78)	70 (61–78)	75 (69–81)	75 (69–80)	77 (73–83)	0
≥75 yr	39	36	54	52	70	
Male	59	58	65	66	57	0
eGFR at baseline (mL/min per 1.73 m ²), mean (SD)	29.5 (11.6)	29.6 (11.8)	29.3 (10.7)	29.2 (10.8)	29.9 (9.7)	0
CKD stage at enrollment						0
Stage 2 and 3A	12	13	11	10	13	
Stage 3B	26	26	26	27	18	
Stage 4	56	55	61	60	69	
Stage 5	6	6	3	3	0	
Hypertension	92	92	93	93	93	0.1
Diabetes	47	46	53	52	63	0.1
History of atrial fibrillation	8	3	37	37	34	1
History of ischemic stroke	3	3	6	6	4	1
History of transient ischemic attack	3	2	5	6	1	2
History of cerebral hemorrhage	1	0	1	1	0	2
Alcohol abuse within the past 12 mo	1	1	2	2	1	2
History of cirrhosis of the liver	2	2	3	3	3	3
Congestive heart failure	14	11	32	32	30	0.4
History of gastrointestinal bleeding	3	3	5	5	2	3
NSAID	5	5	4	4	9	17
Diuretic	64	61	82	81	87	0
ACE inhibitor	34	34	34	35	30	0
Angiotensin receptor blockers	41	41	38	37	48	0
Calcium-channel blocker	48	49	43	43	43	0
Beta blocker	54	51	68	68	77	0
Ezetimibe	5	5	6	6	3	0
Statins	57	56	61	61	59	0
Glucose lowering medications	31	30	35	33	47	0
Proton pump inhibitors	34	33	44	43	52	0
Selective serotonin reuptake inhibitors	6	6	6	6	8	0
Aspirin	38	42	19	19	13	0
Clopidogrel	9	9	5	5	7	0
Type of DOAC						0
Direct factor Xa inhibitor					93	
Direct thrombin inhibitor					7	

ACE, angiotensin-converting enzyme; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drugs. Unless otherwise noted, values are in percentage.

prescription of an oral anticoagulant (Table 1). The proportion of patients with at least 1 prescription of an oral anticoagulant was 3% in Brazil, 11% in the USA, 20% in Germany, and 15% in France.

Vitamin K antagonists were the most frequently prescribed oral anticoagulants (92%), whereas only 87 of the 1060 patients (8%) were on DOACs (81 on a direct factor Xa inhibitor and 6 on a direct thrombin inhibitor). A low DOAC prescription rate was observed at baseline in France, the USA, Brazil, and Germany for all CKD stages (Supplementary Figure S1). The patients' baseline characteristics (overall and according to the prescribed type of oral anticoagulant) are summarized in Table 1 and Supplementary Table S2. Among the 1060 patients on oral anticoagulants, 37% had a history of atrial fibrillation, 6% had a history of stroke, and 5% had a history of transient ischemic attack.

Follow-up Data

The CKDopps is ongoing, and at least 3 years of prospective follow-up (for the USA and Brazil) or 5 years (for France and Germany) are planned. A total of 6559 patients had data on oral anticoagulant prescriptions during the CKDopps follow-up period; 481 patients had no follow-up data and so were excluded from the subsequent analysis. Over a median follow-up period of 3 years (interquartile range, 1.5–4.6), 5280 of the patients never received an oral anticoagulant, 990 were already on an oral anticoagulant at baseline, and 289 patients initiated at least 1 new prescription of an oral anticoagulant. Thus, 1279 patients were exposed to oral anticoagulant during the follow-up period (Figure 1). Figure 2 shows the increase in DOAC prescriptions (as a percentage of all oral anticoagulant prescriptions) over the course of the

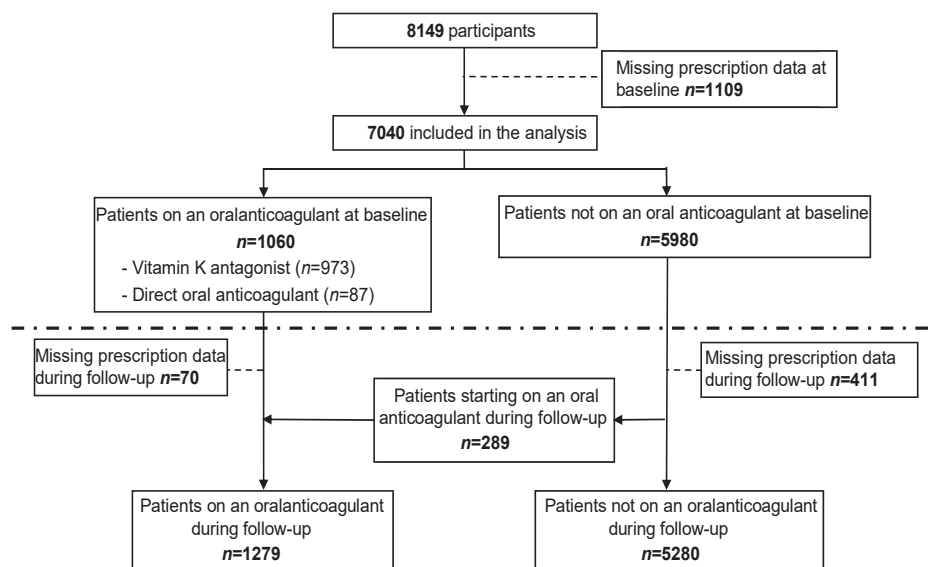


Figure 1. Study flowchart.

study. Among patients receiving a VKA at baseline and who had data on medication prescriptions between 2013 and 2019, 43 switched to a DOAC (Supplementary Table S3). Among the 289 incident

oral anticoagulant users, 183 started on VKAs and 106 started on DOACs (4 in 2013, 4 in 2014, 14 in 2015, 19 in 2016, 28 in 2017, 16 in 2018, 19 in 2019, and 2 in 2020). Hence, DOAC initiation appears to have become

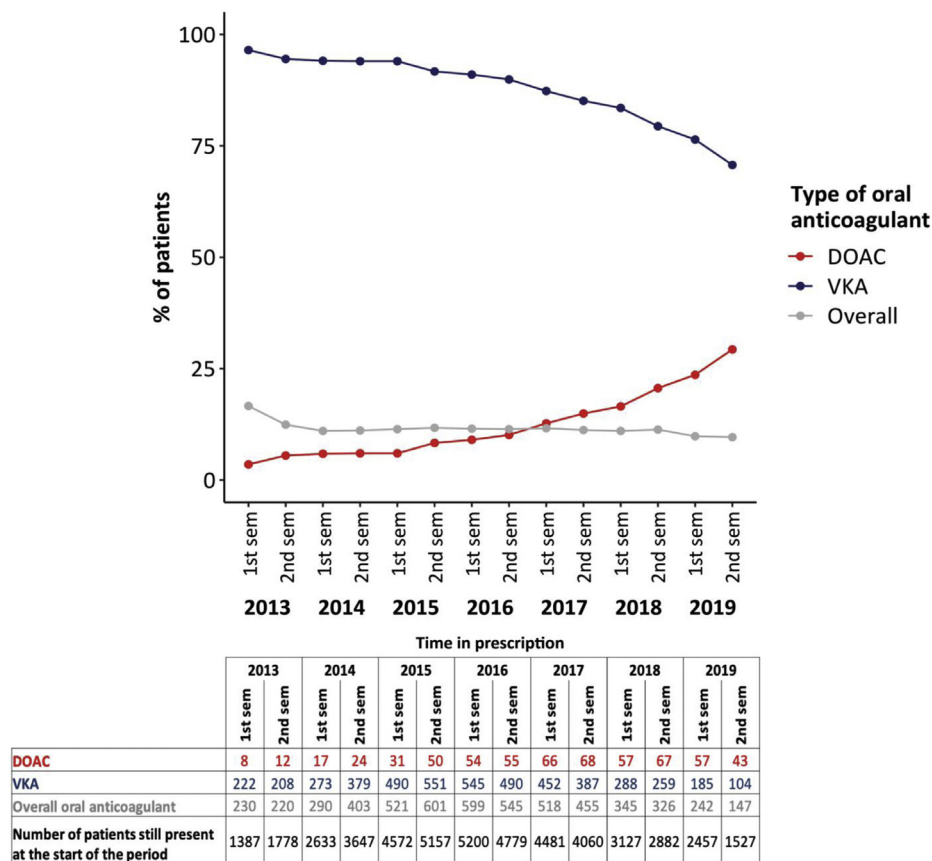


Figure 2. Time trends in oral anticoagulant use. At each time point, the number of patients receiving a VKA (or a DOAC) was divided by the total number of patients receiving an oral anticoagulant. The percentage of patients receiving an oral anticoagulant is shown in gray; the denominator is the number of patients still present at the start of the studied period. DOAC, direct oral anticoagulant; Sem, semester; VKA, vitamin K antagonist.

more frequent after 2015 (Supplementary Table S4). Among the 106 patients having started on DOACs, 103 started on direct Xa factor inhibitors and 3 started on direct thrombin inhibitors.

Discussion

In a large, international, prospective cohort study, we observed low use of DOACs (relative to VKAs) in nondialysis patients with moderate to severe CKD—even though there was an upward trend in DOAC prescription over the course of the study.

In non-CKD patients, DOACs (other than the historical VKA class) now constitute the cornerstone of oral anticoagulation in nonvalvular AF. However, evidence in CKD patients is scarce and hard to interpret. In fact, the efficacy and safety results for oral anticoagulants (both VKAs and DOACs) in stroke prevention in stage 4, 5, and 5D CKD patients are contradictory.^{4,5} In contrast, the data argue in favor of DOAC use by CKD stage 2 and 3 patients.⁴

However, our analysis of an international cohort showed that the proportion of patients receiving DOACs was low in all 4 countries studied. This low proportion contrasts with the highlights of the recent 2018 KDIGO Controversies Conference, stating that (on the basis of pivotal RCTs) DOACs are (i) not inferior to warfarin in patients with a Cockcroft-Gault estimated creatinine clearance of 30 to 50 mL/min (25–50 mL/min for apixaban)¹ and (ii) safer than warfarin. In RCTs that compared warfarin with DOACs, DOACs were associated with an ~50% reduction in the risk of intracranial hemorrhage. Among patients with an estimated creatinine clearance between 25 and 50 mL/min, treatment with apixaban and edoxaban was associated with significantly fewer major bleeding events.⁶ Even though the DOAC prescription rate tended to increase over the course of the present study, we consider that nephrologists should be aware of this marked, low level of use. In contrast, DOACs are far more frequently prescribed than VKAs in populations other than CKD patients.^{7,8} We hypothesize that the relative underuse of DOACs in CKD patients is due to (i) the lack of evidence for DOAC prescription in patients with an estimated glomerular filtration rate below 30 mL/min per 1.73 m² (i.e., prescription might be limited if the physician fears that renal function may worsen), (ii) the cost and insurance coverage that might differ for VKAs versus DOACs, and (iii) the need for the DOAC dose to be adjusted to the level of kidney function. Yao et al.'s recent study of 1473 patients with AF and a kidney-related indication for dose reduction found that 633 (43%) were potentially overdosed.⁹ With regard to oral anticoagulant prescriptions in the 4 countries studied here, we observed a very low prescription rate

in Brazil; this might be due to differences in insurance coverage and thus patient care.

In view of the dissemination of RCT results and guidelines, we expected to see a general increase in DOAC initiation among incident prescriptions of oral anticoagulants in the CKDopps study. We conclude that specific guidelines on anticoagulation management in CKD patients are necessary.

Our study had a number of strengths. First, we analyzed a large, ongoing, diverse, international cohort of patients with a broad range of kidney function levels. Second, we collected comprehensive, detailed, longitudinal data. Third, this is the first study to have described the prescription of VKAs and DOACs in nondialysis CKD patients. The study also had some limitations. First, it is possible that some of the oral anticoagulant prescriptions assessed here were issued before the KDIGO guidelines. However, the results of RCTs in CKD patients had already been published before the start of the study period. Second, the study design prevented us from collecting certain types of data, such as the indication for oral anticoagulants, the reasons for treatment switches, and the CHA2DS2-VASc score. Third, the inclusion period was very long; given that the CKDopps study is ongoing, we had fewer patient data for 2019 and 2020 than for earlier years.

Using international CKDopps data, we observed a low prescription rate for DOACs (relative to VKAs) in CKD stage 3 to 5 patients. This low prescription rate was not in line with the RCT results and the international guidelines. In view of the risk of significant adverse events associated with VKAs, the prescription of DOACs should be encouraged—particularly for CKD stage 3 patients. Our present findings might be of value in the design of subsequent clinical studies and thus might help to improve the quality of AF management among nondialysis CKD patients.

DISCLOSURE

BB, CT, RP, and BR are employees of Arbor Research Collaborative for Health. MW is a former employee and consultant for Arbor Research Collaborative for Health.

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AUTHOR CONTRIBUTIONS

SL, RP, and ZAM designed the study; SML analyzed the data; SL drafted the manuscript; SML, BB, CT, BS, BR, RP, and ZAM revised the article; and all authors approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

Supplementary Methods.

Table S1. Dates of marketing authorizations for DOACs in France and Germany (regulator: European Medicines Agency), the USA (regulator: Food and Drug Administration), and Brazil (regulator: ANVISA), by indication.

Table S2. The baseline HAS-BLED score in patients with atrial fibrillation.

Table S3. Description of patients who switched from a vitamin K antagonist to a direct oral anticoagulant during follow-up.

Table S4. Incident oral anticoagulant, by year.

Figure S1. Oral anticoagulants at baseline, by CKD stage and by country.

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