

# Non-bleeding Adverse Events with the Use of Direct Oral Anticoagulants: A Sequence Symmetry Analysis

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Published online: 30 April 2018  
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## Abstract

**Introduction** Postmarketing pharmacovigilance reports have raised concerns about non-bleeding adverse events associated with direct oral anticoagulants (DOACs), but only limited results are available from large claims databases.

**Objective** The aim of this study was to assess the potential association between DOAC initiation and the onset of four types of non-bleeding adverse events by sequence symmetry analysis (SSA).

**Methods** SSA was performed using nationwide data from the French National Healthcare databases (*Régime Général*, 50 million beneficiaries) to assess a cohort of 386,081 DOAC new users for the first occurrence of four types of non-bleeding outcomes: renal, hepatic, skin outcomes identified by using hospitalization discharge diagnoses, and gastrointestinal outcomes by using medication

reimbursement. Asymmetry in the distribution of each investigated outcome occurring before and after initiation of DOAC therapy was used to test the association between DOAC therapy and these outcomes. SSA inherently controls for time-constant confounders, and adjusted sequence ratios were computed after correcting for temporal trends. Negative (glaucoma) and positive (bleeding, depressive disorders) control outcomes were used and analyses were replicated on a cohort of 310,195 patients initiating a vitamin K antagonist (VKA).

**Results** This study demonstrated the expected positive association between either DOAC or VKA therapy and hospitalised bleeding and initiation of antidepressant therapy, while no association was observed between either DOAC or VKA therapy and initiation of antiglaucoma medications. For DOAC therapy, signals were the associations with hepatic outcomes, including acute liver injury [for the 3-month time window,  $aSR_3 = 2.71$ , 95% confidence interval (CI) 1.79–4.52]; gastrointestinal outcomes, including initiation of drugs for constipation and antiemetic drugs ( $aSR_3 = 1.31$ , 95% CI 1.27–1.36; and 1.17, 95% CI 1.12–1.22, respectively); and kidney diseases ( $aSR_3 = 1.33$ , 95% CI 1.29–1.37).

**Conclusion** Results of this nationwide study suggest that DOACs are associated with rare but severe liver injury and more frequent gastrointestinal disorders. A low risk of kidney injury with DOAC therapy can also not be excluded.

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s40264-018-0668-9>) contains supplementary material, which is available to authorized users.

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### Key Points

Results from this sequence symmetry analysis (SSA) using the French healthcare databases highlight the importance of non-bleeding adverse events in DOAC new users.

DOAC therapy may be associated with rare but severe liver injury and more frequent gastrointestinal disorders.

Channeling bias should be taken into account when interpreting results from SSA of a tested medication for which a therapeutic alternative exists.

## 1 Introduction

The use of direct oral anticoagulants (DOACs) has increased dramatically worldwide over the last 5 years, with a corresponding economic burden on healthcare systems [1–4]. This rapid uptake of DOAC use is mainly related to the lifelong prescription of these agents for the prevention of stroke in patients with non-valvular atrial fibrillation (AF) as a more convenient, fixed-dose alternative to vitamin K antagonists (VKAs). Compared with VKAs, DOACs do not require regular laboratory monitoring of patients and allow once-daily (rivaroxaban, apixaban, edoxaban) or twice-daily (dabigatran) dosing instead of multiple dose adjustments [5, 6]. European guidelines have recently expressed a preference for DOACs over VKAs for stroke prevention in non-valvular AF patients [7]. Considering the important clinical role of oral anticoagulants (OACs), the declining use of VKAs, and the increasing prevalence of AF with ageing of the population, DOAC prescription is therefore expected to continue to increase over the next years [8]. Continuous and careful monitoring of their safety profile is therefore needed. Large administrative databases provide a timely opportunity to perform signal detection and investigate adverse reactions.

The relative safety of DOACs versus warfarin in non-valvular AF patients [9–11], or versus heparin in the treatment and prevention of recurrence of venous thromboembolism [12–14], has been demonstrated in large-scale randomized clinical trials (RCTs), and has been confirmed globally by observational studies [15, 16]; however, both clinical trials and observational studies have mainly focussed on bleeding adverse events to date [17]. Postmarketing data, including pharmacovigilance reports [18] and case reports, have raised concerns about other, albeit rarer, non-bleeding

adverse events that could not be detected by RCTs due to intrinsic limitations, such as small sample size and short follow-up. Renal and hepatic adverse events are among the emerging DOAC safety issues [17]. Rare but severe skin adverse events, such as vasculitis, have also been reported in dabigatran-treated patients [19–21]. Furthermore, non-bleeding adverse events, including gastrointestinal symptoms such as dyspepsia, reported in dabigatran-treated patients [22–24], have been found to be one of the main reasons for permanent DOAC discontinuation.

At the request of the pharmacovigilance department of the French Medicines Agency (ANSM), we investigated a possible association between DOAC (dabigatran, rivaroxaban, apixaban) use and these potential non-bleeding adverse events by using data from the French Healthcare databases [25]. The sequence symmetry analysis (SSA) method [26, 27] has been shown to be a complementary tool to support other pharmacovigilance methods based on spontaneous reporting systems due to its high specificity for detecting adverse events using claims data [28, 29]. As this self-adjusted method is easy to process and allows concomitant investigation of different clinical entities within a limited timeframe, irrespective of the characteristics of the event and exposure [30], SSA was applied to test the potential association between DOAC initiation and the onset of four predefined types of non-bleeding adverse events.

## 2 Methods

### 2.1 Data Sources

French national health insurance (*Assurance Maladie*) covers the entire French population and is divided into several specific schemes according to beneficiaries' occupational sector, with the largest scheme being '*Régime général*' (approximately 50 million beneficiaries).

This study was conducted using data from the French health insurance system database (SNIIRAM, *Système national d'information inter-régimes de l'assurance maladie*) linked to the French hospital discharge database (PMSI, *Programme de médicalisation des systèmes d'information*). The SNIIRAM database contains individualised, anonymous, and comprehensive data on health spending reimbursements. Demographic data include date of birth, sex, and vital status. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification and packaging of each product is identified by means of a national specific pack identifier code providing information on the name of the product, active ingredient and dose in each pill, number of pills, and route of administration, but not the prescribed dose.

The PMSI database provides detailed medical information on all hospitalizations in France. The medical indication for drug reimbursements and the results of medical procedures or laboratory tests are not available in these databases. However, medical diagnosis information is available from two independent sources encoded according to the International Classification of Diseases, 10th edition (ICD-10): (1) diagnoses corresponding to patient eligibility for 100% reimbursement of severe and costly long-term diseases (LTDs) and disability, such as AF, coronary heart disease, certain debilitating diseases (such as multiple sclerosis, inflammatory bowel disease or rheumatoid arthritis), HIV infection, cancer, etc.; and (2) discharge diagnoses from hospitalization data. The SNIIRAM-PMSI databases also indicate medical procedures performed in the ambulatory setting or during a hospital stay.

The French healthcare databases have been previously described and used in epidemiology research, including pharmacoepidemiological studies [25, 31].

This research was authorised by the French Data Protection Agency (CNIL, Commission Nationale de l'Informatique et des Libertés).

## 2.2 Outcomes of Interest

Four groups of potential adverse events (renal, hepatic, skin, and gastrointestinal) were investigated. For each investigated group, outcomes were defined by using either hospitalization discharge diagnoses (renal, hepatic, and skin outcomes) or medication reimbursement (gastrointestinal outcomes) as proxies of these adverse events. Detailed definitions of these outcomes are provided in electronic supplementary material (ESM) 1.

## 2.3 Sequence Symmetry Analysis

### 2.3.1 Rationale

SSA is a case-only design based on the rationale that if a medication causes an adverse event, this medication will be prescribed more often before than after occurrence of this event [26, 27]. Asymmetry in the distribution of this outcome of interest before and after initiation of a tested medication is therefore used to assess the association between this medication and an outcome of interest. Outcomes can be identified either by medication prescription/reimbursement or hospitalization in healthcare databases. The advantages and pitfalls of this method have been recently described in detail [32].

### 2.3.2 Study Population

A cohort of patients who initiated treatment with dabigatran, rivaroxaban or apixaban between 1 January 2013 and

31 December 2015 (inclusion period) was identified from *Régime général* reimbursement data. Patients' index date was the date of the first DOAC reimbursement (the date on which the prescription was filled) during this period.

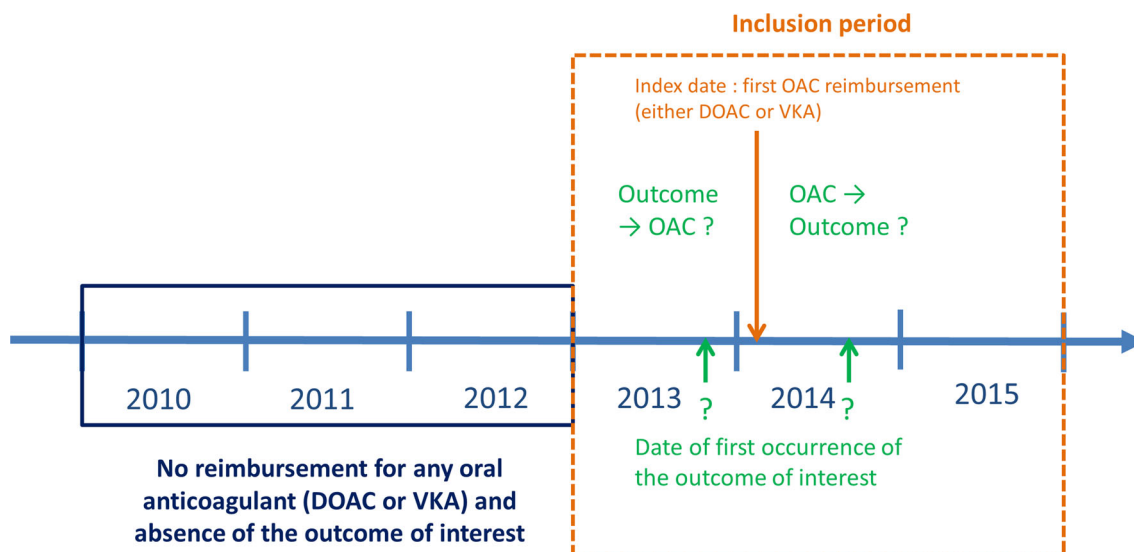
As usual in SSA, for each definition of each outcome of interest, only patients presenting both the outcome and initiating DOAC therapy were included, i.e. those meeting the following criteria: (1) having continuous *Régime général* health insurance coverage during the 2010–2015 period: at least one reimbursement each year related to *Régime général* coverage or death during this period; (2) being a DOAC new user: at least one reimbursement for DOACs (ATC: B01AE07 for dabigatran, B01AF01 for rivaroxaban, and B01AF02 for apixaban; edoxaban was not available in France during the inclusion period and was therefore not considered in this SSA) during the inclusion period and no reimbursement for any oral anticoagulant during the 2010–2012 period; and (3) presenting the outcome of interest: occurrence during the inclusion period and no occurrence during the 2010–2012 period. For each patient, only the date of the first time the outcome occurred during the inclusion period was considered in the analysis (Fig. 1).

Only the first DOAC reimbursement was considered and the patient was assigned to the OAC group corresponding to this first reimbursement.

### 2.3.3 Data Analysis

A separate SSA was performed for each definition of the outcome of interest. Patients were classified according to the temporal sequence (outcome → DOAC or DOAC → outcome) between the DOAC first reimbursement and the date of occurrence of the first outcome of interest during the time window considered. Patients who experienced the outcome of interest on the same day as the prescription of DOAC therapy were excluded from the analysis. Three time windows (on either side of the index date) were tested to search for the adverse event: 3 months (90 days), 6 months (180 days), and 12 months (360 days) [27].

The asymmetry of sequences was measured by calculating a crude sequence ratio (cSR) as the ratio of the number of patients who initiated DOAC therapy before the outcome over the number of patients for whom the outcome occurred before the initiation of DOAC therapy. To take into account possible changes in both outcome and DOAC prescription trends in the background population during each time window that would confound the cSR, a null-effect sequence ratio (nSR) was then calculated, as described by Tsiropoulous et al. [27]. An adjusted sequence ratio (aSR) was then computed by dividing the cSR by the nSR. Ninety-five percent confidence intervals (95% CIs) were calculated for the aSR by using a normal



**Fig. 1** Schematic representation of sequence symmetry analysis study design for a given outcome of interest. *DOAC* direct oral anticoagulant, *OAC* oral anticoagulant, *VKA* vitamin K antagonist

approximation to the binomial distribution [33]. A positive association between DOAC exposure and the investigated outcome was considered as significant when the lower limit of the 95% CI of the aSR was  $> 1$ . Significant positive associations were considered valid when they were consistent over the three time windows investigated; results in which a significant positive association was observed when the length of the time window was extended were therefore not considered to be valid.

Analyses were performed for the entire cohort of DOAC new users, and separately for each of the three DOACs.

A subgroup analysis was carried out in patients with AF; patients with a history of deep vein thrombosis, pulmonary embolism or lower-limb orthopaedic procedures were excluded from the initial cohort.

All analyses were performed using SAS software version 9.2 (SAS Institute, Inc., Cary, NC, USA).

#### 2.3.4 Sensitivity Analysis

Changes in underlying use and reimbursement trends were taken into account by computing an aSR. However, other possible sources of bias may exist with the SSA design, such as (1) detection bias that occurs when patients are more likely to receive DOAC therapy after having experienced the event of interest, as the disease requiring DOAC prescription may have been discovered on this occasion; and (2) situations in which events alter the probability of exposure, resulting in inverse causation bias [26, 32]. Two sensitivity analyses were therefore performed.

First, outcomes considered as ‘control’ outcomes were used to validate the method for OAC therapy [29]. As OAC

therapy is known to cause bleeding, this outcome was used as a positive control outcome. As glaucoma appeared to be unrelated to the prescription of OACs, hospitalization and medication for glaucoma were used as negative control outcomes. Finally, as a relationship between cardiovascular drugs and depression was described in the first study using this method [26], analyses were replicated using major depressive disorders as another positive control outcome.

Second, as an alternative and active comparator to DOAC therapy, VKA therapy (ATC: B01AA, fluindione, warfarin, acenocoumarol) was used as an aid to better identify the source of potential bias in DOAC analyses [34]. An SSA was replicated for each definition of the four outcomes in a cohort of VKA new users by using the same design and study population definitions as described above. Detailed definitions of these control outcomes are provided in ESM 1.

## 3 Results

### 3.1 Baseline Characteristics of Eligible Patients

A total of 696,276 OAC new users were eligible for inclusion in the SSA. Their baseline characteristics are displayed on Table 1. DOAC new users were younger and less severe than VKA new users and DOAC therapy was more often prescribed by private cardiologists.

### 3.2 Potential Adverse Events

Table 2 summarizes the results of SSA for DOAC and VKA new users, providing, for each definition of each

**Table 1** Baseline characteristics of eligible patients according to the oral anticoagulant treatment group

Characteristics (%) <sup>a</sup>	VKA new users (N = 310,195)	DOAC new users			
		Total (N = 386,081)	Dabigatran (N = 67,889)	Rivaroxaban (N = 254,816)	Apixaban (N = 63,376)
Male sex	142,434 (45.9)	186,289 (48.2)	33,293 (49.0)	121,525 (47.7)	31,471 (49.7)
Age, years [mean (SD)]	71.3 (15.8)	68.5 (14.1)	71.0 (12.4)	66.8 (14.7)	72.7 (11.8)
Age groups, years					
< 65	88,564 (28.6)	129,003 (33.4)	18,287 (26.9)	96,763 (38.0)	13,953 (22.0)
65–74	63,123 (20.4)	108,884 (28.2)	19,525 (28.8)	70,934 (27.8)	18,425 (29.1)
75–79	42,210 (13.6)	57,364 (14.9)	11,474 (16.9)	35,159 (13.8)	10,731 (16.9)
≥ 80	116,298 (37.5)	90,830 (23.5)	18,603 (27.4)	51,960 (20.4)	20,267 (32.0)
First prescriber's specialty					
Private cardiologist	30,448 (9.8)	88,557 (23.0)	17,244 (25.1)	51,144 (20.1)	20,169 (31.8)
Hospital practitioner	150,214 (48.5)	136,857 (35.5)	24,673 (36.4)	86,097 (33.8)	26,087 (41.2)
General practitioner	118,147 (38.1)	116,865 (30.3)	16,242 (23.9)	88,175 (34.6)	12,448 (19.7)
Other private specialists	11,178 (3.6)	43,502 (11.3)	9675 (14.3)	29,199 (11.4)	4628 (7.3)
Comorbidities <sup>b</sup>					
At least one LTD	222,287 (71.7)	210,453 (54.5)	40,453 (59.6)	128,263 (50.3)	41,737 (65.9)
Severe heart diseases <sup>c</sup>	58,261 (18.8)	59,276 (15.4)	13,016 (19.2)	31,979 (12.5)	14,281 (22.5)
Coronary heart diseases	39,515 (12.7)	33,825 (8.8)	6507 (9.6)	19,629 (7.7)	7689 (12.1)
Diabetes	52,320 (16.9)	51,059 (13.2)	9889 (14.6)	30,829 (12.1)	10,341 (16.3)
Neoplasia	52,866 (17.0)	50,790 (13.2)	9184 (13.5)	32,191 (12.6)	9415 (14.9)
Psychiatric disorders	15,541 (5.0)	14,779 (3.8)	2202 (3.2)	10,573 (4.1)	2004 (3.2)

DOAC direct oral anticoagulant, SD standard deviation, VKA vitamin K antagonist, LTD long-term disease

<sup>a</sup>Dichotomous variables are expressed as *N* (%), and continuous variables are expressed as mean (SD)

<sup>b</sup>Comorbidities were defined using information on severe and costly LTDs only (in France, a patient can only obtain LTD status when requested by a physician; the LTD registration allows patients to be fully reimbursed for health expenditures related to this LTD)

<sup>c</sup>Severe heart diseases: severe heart failure, cardiac arrhythmias, and congenital or valvular heart diseases

investigated outcome, the number of patients with 'outcome → OAC' or 'OAC → outcome' sequences and the resulting aSR. cSR and nSR estimates for all outcomes are reported in ESM 2.

Valid and significant positive associations with DOAC therapy were observed in three of the four investigated outcome groups, i.e. in the renal, hepatic and gastrointestinal outcomes groups.

Hospitalizations for kidney diseases, acute kidney failure and glomerular diseases were more likely to occur after DOAC initiation than before (aSR<sub>3</sub> = 2.36, 95% CI 1.96–2.88, for acute kidney failure). However, this significant positive association contrasted with the strong inverse association observed for VKA therapy (aSR<sub>3</sub> = 0.64, 95% CI 0.59–0.70, for acute kidney failure).

Significant positive association between DOAC therapy and toxic liver disease was found with the 3-month time

window (aSR<sub>3</sub> = 2.48, 95% CI 1.32–5.94) and with acute liver injury irrespective of the time window considered (aSR<sub>3</sub> = 2.71, 95% CI 1.79–4.52). On the contrary, no association was observed between VKA therapy initiation and these two hepatic outcomes (aSR<sub>3</sub> = 0.87, 95% CI 0.60–1.25, for toxic liver disease; and aSR<sub>3</sub> = 0.84, 95% CI 0.66–1.06, for acute liver injury). These temporal asymmetries were only found among rivaroxaban and apixaban new users.

After excluding drugs for acid-related disorders, such as proton pump inhibitors, the initiation of drugs for functional gastrointestinal disorders, such as antiemetic drugs or drugs for constipation, was significantly more likely after, rather than before, initiation of DOAC therapy. Overall, an almost 25% increased risk following DOAC initiation was consistently found for the three time windows. No asymmetry, or only slight asymmetry, was

**Table 2** Results from sequence symmetry analyses for patients initiating OAC therapy according to the type of OAC, definition of outcome and time-window exposure

Types of outcomes	Type of OAC	Time windows						
		3 months		6 months		12 months		
		OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>	OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>	OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>	
Control outcomes	Bleeding (hospitalizations)	DOACs	2446/916	2.68 (2.49–2.90)	3759/1395	2.71 (2.55–2.88)	5657/2095	2.71 (2.58–2.85)
		Dabigatran	406/158	2.26 (1.90–2.74)	675/228	2.31 (2.00–2.70)	1106/316	2.22 (1.97–2.53)
		Rivaroxaban	1741/591	2.95 (2.70–3.25)	2618/894	2.93 (2.72–3.17)	3886/1342	2.88 (2.71–3.07)
		Apixaban	299/167	2.09 (1.74–2.54)	466/273	2.29 (1.97–2.66)	665/437	2.61 (2.32–2.95)
		VKAs	4131/2629	1.54 (1.46–1.61)	6237/3646	1.64 (1.57–1.71)	9054/4691	1.79 (1.73–1.86)
	Glaucoma (hospitalizations)	DOACs	44/45	1.01 (0.66–1.53)	78/77	1.05 (0.77–1.44)	128/139	0.95 (0.75–1.21)
		Dabigatran	9/11	0.75 (0.28–1.83)	21/15	1.15 (0.60–2.38)	31/20	1.03 (0.60–1.91)
		Rivaroxaban	28/21	1.36 (0.78–2.51)	46/42	1.13 (0.74–1.73)	80/83	0.99 (0.72–1.34)
		Apixaban	7/13	0.64 (0.20–1.51)	11/20	0.76 (0.32–1.51)	17/36	0.83 (0.43–1.43)
		VKAs	26/43	0.60 (0.35–0.96)	59/76	0.76 (0.54–1.07)	100/120	0.79 (0.61–1.03)
Glaucoma (medications)	DOACs	1264/1347	0.96 (0.89–1.03)	2536/2540	1.02 (0.97–1.08)	4701/4772	1.01 (0.97–1.05)	
	Dabigatran	267/269	0.90 (0.76–1.07)	530/440	0.97 (0.86–1.11)	1037/732	0.93 (0.84–1.02)	
	Rivaroxaban	756/813	0.94 (0.86–1.04)	1575/1580	1.02 (0.95–1.09)	3002/2978	1.02 (0.97–1.07)	
	Apixaban	241/263	1.08 (0.91–1.29)	430/518	1.12 (0.99–1.28)	661/1060	1.08 (0.98–1.19)	
	VKAs	1040/1103	0.93 (0.85–1.01)	2081/2168	0.93 (0.88–0.99)	3861/3951	0.92 (0.88–0.96)	

Table 2 continued

Types of outcomes	Type of OAC	Time windows					
		3 months		6 months		12 months	
		OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>	OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>	OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>
Major depressive disorders (medications)	DOACs	4032/3221	1.29 (1.23–1.35)	6882/5648	1.28 (1.24–1.33)	11,112/9501	1.26 (1.23–1.30)
	Dabigatran	774/553	1.27 (1.14–1.42)	1335/929	1.17 (1.08–1.27)	2306/1382	1.13 (1.06–1.21)
	Rivaroxaban	2611/2130	1.26 (1.19–1.34)	4485/3717	1.26 (1.21–1.32)	7318/6361	1.23 (1.19–1.27)
	Apixaban	646/538	1.44 (1.28–1.61)	1060/1002	1.48 (1.36–1.62)	1485/1757	1.57 (1.47–1.69)
	VKAs	4383/3816	1.15 (1.10–1.20)	7418/6490	1.15 (1.11–1.19)	11,471/10,267	1.12 (1.09–1.15)
Renal outcomes (hospitalizations)							
Kidney diseases	DOACs	10,707/8264	1.33 (1.29–1.37)	15,008/11,020	1.42 (1.39–1.46)	20,401/14,783	1.48 (1.45–1.51)
	Dabigatran	2495/1632	1.37 (1.29–1.46)	3445/2069	1.35 (1.28–1.43)	4837/2563	1.29 (1.23–1.35)
	Rivaroxaban	6057/4930	1.26 (1.21–1.30)	8706/6645	1.37 (1.32–1.41)	12,025/8944	1.43 (1.39–1.47)
	Apixaban	2153/1698	1.51 (1.42–1.61)	2854/2300	1.73 (1.64–1.83)	3534/3270	1.97 (1.88–2.06)
	VKAs	9986/12,698	0.78 (0.76–0.80)	14,209/17,652	0.80 (0.79–0.82)	19,267/23,123	0.83 (0.81–0.85)
Acute kidney failure	DOACs	308/157	2.36 (1.96–2.88)	491/220	2.97 (2.54–3.5)	754/304	3.65 (3.21–4.19)
	Dabigatran	43/19	2.86 (1.74–5.33)	83/25	4.48 (2.99–7.53)	149/35	5.52 (3.96–8.42)
	Rivaroxaban	199/97	2.46 (1.94–3.17)	305/142	2.85 (2.35–3.5)	460/194	3.52 (2.99–4.19)
	Apixaban	66/41	1.90 (1.30–2.87)	103/53	2.63 (1.92–3.75)	144/75	3.30 (2.52–4.43)
	VKAs	903/1699	0.64 (0.59–0.70)	1324/2183	0.82 (0.76–0.88)	1903/2590	1.15 (1.08–1.22)

Table 2 continued

Types of outcomes	Type of OAC	Time windows					
		3 months		6 months		12 months	
		OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>	OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>	OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>
Glomerular diseases	DOACs	45/23	2.34 (1.46–4.10)	89/30	3.90 (2.66–6.23)	144/43	4.82 (3.52–7.05)
	Dabigatran	5/2	3.09	17/2	11.1	35/5	8.79 (4.26–54.54)
	Rivaroxaban	33/20	1.95 (1.15–3.61)	59/25	3.07 (1.99–5.21)	91/33	3.97 (2.74–6.20)
	Apixaban	7/1	7.90	13/3	5.42	18/5	5.35 (2.36–28.94)
	VKAs	147/594	0.30 (0.25–0.36)	203/696	0.40 (0.34–0.46)	304/784	0.62 (0.54–0.70)
Renal tubulo-interstitial diseases	DOACs	378/554	0.79 (0.69–0.89)	646/768	1.03 (0.93–1.14)	1030/1025	1.30 (1.19–1.41)
	Dabigatran	65/74	0.95 (0.68–1.33)	110/100	1.13 (0.86–1.49)	191/131	1.28 (1.03–1.61)
	Rivaroxaban	254/376	0.76 (0.65–0.89)	429/530	0.96 (0.85–1.09)	685/693	1.23 (1.11–1.37)
	Apixaban	59/103	0.68 (0.48–0.92)	107/137	1.06 (0.82–1.36)	154/200	1.34 (1.09–1.66)
	VKAs	811/1541	0.61 (0.56–0.66)	1352/1982	0.84 (0.79–0.90)	2093/2471	1.13 (1.07–1.20)
Hepatic outcomes (hospitalizations)	DOACs	27/11	2.48 (1.32–5.94)	37/23	1.60 (0.97–2.83)	51/33	1.52 (0.99–2.42)
	Dabigatran	3/3	0.89 (0.10–7.97)	7/3	1.81 (0.55–47.8)	8/3	1.65 (0.54–64.45)
	Rivaroxaban	17/7	2.44 (1.12–8.15)	21/18	1.16 (0.61–2.26)	33/25	1.28 (0.77–2.23)
	Apixaban	7/1	8.24	9/2	6.00	10/5	3.39 (1.27–16.17)
	VKAs	56/63	0.87 (0.60–1.25)	81/93	0.83 (0.61–1.11)	112/115	0.88 (0.68–1.14)
Toxic liver disease							



Table 2 continued

Types of outcomes	Type of OAC	Time windows					
		3 months		6 months		12 months	
		OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>	OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>	OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>
Acute liver injury	DOACs	70/26	2.71 (1.79–4.52)	90/42	2.14 (1.51–3.18)	133/53	2.47 (1.83–3.49)
	Dabigatran	9/5	1.59 (0.57–7.46)	17/6	2.21 (0.99–8.78)	24/6	2.49 (1.19–10.32)
	Rivaroxaban	46/17	2.71 (1.64–5.26)	54/29	1.85 (1.20–3.03)	84/38	2.15 (1.50–3.27)
	Apixaban	15/4	4.38 (1.80–41.76)	19/7	3.61 (1.70–12.15)	25/9	4.69 (2.40–12.81)
	VKAs	129/150	0.84 (0.66–1.06)	199/209	0.90 (0.74–1.10)	308/268	1.04 (0.88–1.23)
Disorders of the gallbladder and biliary tract	DOACs	563/805	0.71 (0.63–0.79)	1033/1171	0.89 (0.82–0.97)	1698/1657	1.03 (0.96–1.10)
	Dabigatran	104/142	0.65 (0.50–0.83)	175/198	0.69 (0.57–0.85)	314/248	0.80 (0.68–0.95)
	Rivaroxaban	364/513	0.72 (0.62–0.82)	684/746	0.92 (0.83–1.02)	1147/1061	1.08 (0.99–1.17)
	Apixaban	95/150	0.74 (0.57–0.96)	174/226	1.04 (0.85–1.26)	237/347	1.18 (1.00–1.39)
	VKAs	634/1461	0.43 (0.39–0.47)	1111/1921	0.56 (0.52–0.60)	1861/2462	0.70 (0.66–0.74)
Skin outcomes (hospitalizations) Skin diseases	DOACs	405/387	1.05 (0.91–1.21)	649/590	1.10 (0.98–1.23)	1018/852	1.20 (1.09–1.31)
	Dabigatran	78/56	1.22 (0.87–1.74)	127/87	1.12 (0.86–1.49)	196/115	1.07 (0.86–1.36)
	Rivaroxaban	267/276	0.97 (0.82–1.15)	430/420	1.02 (0.89–1.17)	690/601	1.14 (1.02–1.27)
	Apixaban	60/54	1.30 (0.90–1.89)	92/82	1.50 (1.12–2.03)	132/135	1.68 (1.32–2.14)
	VKAs	568/882	0.63 (0.56–0.70)	879/1257	0.67 (0.61–0.73)	1347/1636	0.76 (0.71–0.82)

Table 2 continued

Types of outcomes	Type of OAC	Time windows					
		3 months		6 months		12 months	
		OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>	OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>	OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>
Vasculitis (composite)	DOACs	91/84	1.10 (0.81–1.48)	173/160	1.08 (0.87–1.34)	299/258	1.14 (0.96–1.34)
	Dabigatran	23/18	1.14 (0.62–2.22)	40/26	1.22 (0.75–2.07)	63/36	1.10 (0.74–1.71)
	Rivaroxaban	50/46	1.10 (0.73–1.65)	102/99	1.03 (0.78–1.36)	191/164	1.13 (0.92–1.39)
	Apixaban	17/20	1.00 (0.50–1.92)	30/35	1.13 (0.68–1.85)	44/58	1.25 (0.83–1.85)
	VKAs	98/171	0.56 (0.43–0.71)	171/258	0.63 (0.52–0.76)	307/363	0.76 (0.65–0.89)
Vasculitis and unspecified arteritis	DOACs	8/9	0.92 (0.31–2.51)	14/16	0.92 (0.42–1.90)	21/20	1.12 (0.60–2.12)
	Dabigatran	1/0	–	2/0	–	5/0	–
	Rivaroxaban	5/7	0.74 (0.16–2.36)	10/13	0.80 (0.32–1.84)	13/16	0.86 (0.39–1.80)
Urticaria and erythema	Apixaban	2/2	1.2 (0.01–118.39)	2/3	0.92	3/4	1.40 (0.12–7.23)
	VKAs	18/33	0.55 (0.29–0.94)	25/46	0.54 (0.32–0.86)	34/56	0.61 (0.38–0.91)
	DOACs	54/45	1.23 (0.83–1.84)	89/62	1.48 (1.08–2.08)	134/88	1.60 (1.23–2.12)
	Dabigatran	9/9	0.89 (0.33–2.42)	21/15	1.12 (0.59–2.33)	32/17	1.26 (0.73–2.47)
	Rivaroxaban	35/30	1.19 (0.73–1.98)	55/40	1.42 (0.95–2.17)	82/59	1.45 (1.05–2.06)
Vasculitis and unspecified arteritis	Apixaban	10/6	1.98 (0.75–7.44)	13/7	2.55 (1.08–8.35)	20/12	2.97 (1.50–6.82)
	VKAs	55/109	0.5 (0.35–0.68)	79/143	0.54 (0.41–0.71)	116/174	0.65 (0.51–0.82)

Table 2 continued

Types of outcomes	Type of OAC	Time windows					
		3 months		6 months		12 months	
		OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>	OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>	OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>
Allergic purpura	DOACs	14/10	1.46 (0.66–3.71)	20/12	1.78 (0.90–4.09)	34/16	2.33 (1.35–4.66)
	Dabigatran	5/3	1.52 (0.37–22.15)	6/3	1.65 (0.46–31.63)	8/5	1.09 (0.37–4.99)
	Rivaroxaban	6/7	0.89 (0.24–2.84)	11/9	1.30 (0.53–3.52)	21/11	2.07 (1.05–4.97)
	Apixaban	3/0	–	3/0	–	5/0	–
	VKAs	14/22	0.64 (0.30–1.23)	27/32	0.86 (0.50–1.43)	43/36	1.21 (0.78–1.91)
Gastrointestinal outcomes (medications)	DOACs	4131/5332	0.88 (0.85–0.92)	6585/8950	0.92 (0.89–0.95)	10,025/14,891	0.95 (0.92–0.97)
	Dabigatran	917/961	1.00 (0.91–1.09)	1468/1568	0.95 (0.88–1.02)	2272/2321	0.89 (0.84–0.95)
	Rivaroxaban	2652/3669	0.82 (0.78–0.86)	4275/6129	0.86 (0.83–0.90)	6598/10,279	0.90 (0.87–0.93)
	Apixaban	561/701	1.03 (0.92–1.15)	840/1252	1.07 (0.98–1.17)	1152/2288	1.18 (1.10–1.26)
	VKAs	3152/5647	0.62 (0.59–0.64)	4869/8831	0.65 (0.63–0.67)	7286/13,539	0.69 (0.67–0.71)
Composite without drugs for acid-related disorders	DOACs	7119/6641	1.21 (1.17–1.25)	11,556/11,460	1.23 (1.20–1.26)	18,302/19,462	1.26 (1.24–1.29)
	Dabigatran	1436/1265	1.18 (1.1–1.28)	2368/2071	1.14 (1.08–1.21)	3987/3136	1.12 (1.07–1.17)
	Rivaroxaban	4733/4365	1.22 (1.17–1.27)	7673/7617	1.22 (1.18–1.26)	12,153/13,064	1.24 (1.21–1.27)
	Apixaban	949/1009	1.19 (1.09–1.3)	1513/1769	1.33 (1.24–1.43)	2158/3258	1.47 (1.39–1.55)
	VKAs	6836/7380	1.02 (0.98–1.05)	10,640/11,950	1.04 (1.01–1.06)	15,955/19,087	1.05 (1.02–1.07)

Table 2 continued

Types of outcomes	Type of OAC	Time windows					
		3 months	6 months	12 months			
		OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>	OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>	OAC → Outcome/ Outcome → OAC	aSR (95% CI) <sup>a</sup>
Antiemetic drugs	DOACs	4947/4831	1.17 (1.12–1.22)	8045/8304	1.20 (1.16–1.24)	12,998/14,082	1.25 (1.22–1.28)
	Dabigatran	1002/913	1.19 (1.09–1.3)	1618/1516	1.12 (1.05–1.20)	2760/2270	1.11 (1.05–1.17)
	Rivaroxaban	3293/3226	1.16 (1.1–1.21)	5396/5599	1.18 (1.14–1.23)	8770/9598	1.23 (1.20–1.27)
	Apixaban	649/692	1.17 (1.05–1.3)	1028/1187	1.33 (1.22–1.44)	1464/2211	1.45 (1.36–1.55)
	VKAs	5072/5738	0.98 (0.95–1.02)	8016/9484	1.00 (0.97–1.03)	12,500/15,199	1.05 (1.03–1.08)
Drugs for constipation	DOACs	8674/6947	1.31 (1.27–1.36)	14,177/12,169	1.27 (1.23–1.3)	22,592/20,520	1.25 (1.22–1.27)
	Dabigatran	1620/1190	1.27 (1.18–1.37)	2749/1964	1.20 (1.13–1.27)	4703/3009	1.13 (1.08–1.19)
	Rivaroxaban	5791/4661	1.30 (1.25–1.36)	9416/8183	1.24 (1.21–1.28)	15,051/13,846	1.22 (1.20–1.25)
	Apixaban	1260/1093	1.39 (1.29–1.51)	2009/2019	1.42 (1.34–1.51)	2833/3661	1.48 (1.41–1.56)
	VKAs	8988/7999	1.15 (1.11–1.18)	14,185/13,261	1.10 (1.08–1.13)	21,625/21,093	1.07 (1.05–1.09)

aSR adjusted sequence ratio, CI confidence interval, OAC oral anticoagulant, DOAC direct oral anticoagulant, VKA vitamin K antagonist

<sup>a</sup>Confidence intervals are not given in the case of very small numbers of pairs

observed between VKA therapy and the initiation of these drugs.

A total of 168,807 DOAC and 122,925 VKA AF new users were eligible for inclusion in the subgroup analysis of patients with AF. Consistent results were obtained when analysis was restricted to AF patients with regard to the significant positive associations found in patients with no restriction of indication. However, the initiation of antiemetic drugs or drugs for constipation was also found to be significantly more likely after, rather than before, initiation of VKA therapy in AF patients (see ESM 3).

### 3.3 Control Outcomes

Results of SSA for the control outcomes are also reported in Table 2. Hospitalization for bleeding was consistently nearly threefold more likely to occur after DOAC initiation than before [aSR for the 3-month time window (aSR<sub>3</sub>) = 2.68, 95% CI 2.49–2.90] over the three time windows used. The same applies to VKA therapy, albeit to a lesser extent (aSR<sub>3</sub> = 1.54, 95% CI 1.46–1.61).

No significant positive association was observed between DOACs and the initiation of antiglaucoma preparations, or with hospitalization for glaucoma (aSR<sub>3</sub> = 0.96, 95% CI 0.89–1.03; and 1.01, 95% CI 0.66–1.53, respectively), while inverse associations were observed for VKA new users with hospitalization for glaucoma for the 3-month time window only (aSR<sub>3</sub> = 0.6, 95% CI 0.35–0.96), and, to a lesser extent, with initiation of antiglaucoma preparations for the 6- and 12-month time windows (aSR<sub>6</sub> = 0.93, 95% CI 0.88–0.99; and aSR<sub>12</sub> = 0.92, 95% CI 0.88–0.96, respectively).

A significant positive association was observed between either DOAC or VKA therapy initiation and antidepressant initiation, irrespective of the type of OAC or the time window considered.

## 4 Discussion

### 4.1 Utilization of Sequence Symmetry Analysis on the French Healthcare Database for Monitoring Direct Oral Anticoagulant Adverse Events

This analysis, based on reimbursement data for approximately 390,000 DOAC new users and 310,000 VKA new users in 2013–2015, showed an association between OAC therapies and the well-known and specific increased bleeding risk, as well as an association between these cardiovascular drugs and depression, in line with the initial paper describing this method [26]. This suggests that this method can be used to monitor OAC adverse events in the

French healthcare databases. However, if no association was observed between DOAC initiation and hospitalization for glaucoma, a negative control outcome, VKA therapy was associated with a tendency for reduction of hospitalization for glaucoma, and this association was significant when considering the 3-month time window (40% decreased risk of hospitalization for glaucoma). A weaker association was also observed between VKA therapy and bleeding compared with DOAC therapy. These unexpected results may reflect inverse causation as bleeding events may have altered the probability of OAC exposure in opposite directions for DOACs versus VKAs, which can be explained by channeling. Channeling bias occurs when drug therapies with similar therapeutic indications are preferentially prescribed to groups of patients with different baseline prognoses [35, 36]. Numerous studies, including studies based on French data [37], have indeed described the overall channeling of DOAC therapy over VKA therapy toward a younger and healthier population, with VKAs becoming the preferred OAC therapy for patients with a higher risk of stroke and bleeding [38–40]. Consequently, patients with a history of bleeding are more likely to receive VKAs than DOACs, increasing the number of sequences of ‘bleeding → OAC’ initiation among VKA new users compared with DOAC new users. In addition, as VKA patients were older and had more severe disease than DOAC new users, and were therefore more likely to be hospitalized than DOAC new users, results from the VKA cohort may be more sensitive to detection bias [32]. These biases are particularly likely for hospitalized renal outcomes; according to their respective summary of product characteristics, DOAC dose reduction may be necessary in patients with moderate-to-severe renal impairment. As the extent of anticoagulation by DOAC therapy cannot be monitored, it is likely that this factor led prescribers to preferentially prescribe a VKA to patients with a recent history of renal outcomes rather than a DOAC, as reported elsewhere [41]. This selection in clinical practice, combined with the use of hospitalization data to define renal outcomes, may explain the strong spurious protective association observed in VKA new users, and, reciprocally, the strong and positive association observed with DOAC therapy. However, a risk of kidney injury, albeit low, cannot be excluded with DOAC therapy [42–44].

### 4.2 Potential Adverse Events: Main Findings and Comparison with Postmarketing Literature

This study suggests that DOAC therapy is associated with rare but severe toxic liver diseases and more frequent non-bleeding gastrointestinal disorders. Channeling bias for OAC prescribing has been shown to be mostly related to

the stroke and bleeding risks of patients. It is also unlikely that other sources of bias, particularly detection bias, could fully explain these associations. All DOACs undergo varying degrees of hepatic metabolism, with much lower hepatic metabolism for dabigatran [45]. Patients with acute liver disease were excluded from the landmark RCTs, but transient elevation of transaminase enzymes was reported to be uncommon during these trials [9–11]. A meta-analysis of RCT data concluded that DOACs were not associated with an increased risk of drug-induced liver injury (DILI) [46]. Data on the risk of DILI with DOACs are mostly derived from postmarketing experience, including case reports/case series [17, 47–49] and a pharmacovigilance study [50]. In a recent cohort study on the MarketScan Commercial and Medicare databases, dabigatran was associated with the lowest risk of liver injury compared with rivaroxaban and apixaban new users [51]. The results of this study are therefore consistent with the postmarketing literature [50, 52], which suggests that DOACs, especially rivaroxaban, can cause DILI. Overall, our results and the published literature advocate the monitoring of patients' liver function in the first months following DOAC initiation, especially in the presence of pre-existing liver conditions or concomitant intake of hepatotoxic agents.

DOAC therapy was associated with the initiation of drugs for functional gastrointestinal disorders when drugs for acid-related disorders were excluded from the outcome definition. To date, non-bleeding gastrointestinal disorders have mostly been reported to be uncommon, especially with dabigatran use [22, 53]; however, dyspepsia and esophagitis are now increasingly recognized complications of dabigatran use [54]. It has been suggested that the tartaric acid component of dabigatran hard capsules is responsible for increased mucosal irritation; however, the report of a case of *esophagitis dissecans superficialis* with rivaroxaban that does not contain this excipient suggests a mechanism that might be common to all DOAC drugs [55]. Moreover, a recent review on the use of rivaroxaban for venous thromboembolism prophylaxis after total hip or knee replacement surgery found that pyrexia, vomiting, nausea and constipation were the most commonly reported treatment-emergent non-bleeding adverse events in rivaroxaban-treated patients [56]. Frequent gastrointestinal adverse effects should not be overlooked as they can be associated with considerable impairment of the patient's quality of life, and may also lead to discontinuation of DOAC therapy, as previously described [23, 57–59], with the corresponding risk of subsequent thromboembolism. However, the signals observed for gastrointestinal outcomes in this SSA may also correspond to non-specific symptoms of various diseases. Moreover, the prevalent population taking OAC therapy corresponds to

polymedicated elderly patients, and is therefore particularly vulnerable to nausea or constipation. Further field studies and registry research are therefore needed to investigate the prevalence and impact of this type of adverse event in DOAC-treated patients.

No valid and significant positive associations were observed for skin outcomes, despite cases having been reported for dabigatran-treated patients [21]. However, due to the lack of specific drug treatments, these rare adverse events could only be studied using hospitalization data, therefore limiting their identification, and claims data may not be relevant to properly study such outcomes.

Finally, a recent SSA performed in AF patients initiating dabigatran, rivaroxaban, or apixaban between 2011 and 2015 using the Danish registries found similar results in terms of potential adverse events associated with DOAC therapy for gastrointestinal symptoms, including nausea, vomiting or constipation, and acute renal failure [60].

### 4.3 Strengths and Limitations

In France, National Health Insurance covers the entire population and most people also subscribe to a private complementary health insurance plan. Selection bias related to the access of patients to more expensive DOAC therapy is therefore not an issue when using the French healthcare databases [31, 61]. In addition to being based on large nationwide healthcare databases, a major strength of this study is that SSA is able to overcome some of the pitfalls that can threaten the validity of other observational designs. The SSA design inherently controls for time-constant, patient-specific measured and unmeasured confounders, including sociodemographic characteristics, comorbidities, genetic and environmental factors, and healthcare-related behaviors [32]. The aSRs were corrected for time trends in the occurrence of exposure and events. For instance, for apixaban, the nSR estimates were smaller than 1, and this deviation grew with increasing length of the time window. In particular, this reflects the trend in apixaban prescribing because, in France, the indication of apixaban was extended to stroke prevention in January 2014, with a corresponding sharp increase in apixaban prescription during the period 2014 and 2015 of the inclusion period. However, for all DOACs, the nSR was close to 1 for most outcome definitions.

The definitions of the investigated outcomes were not strictly validated in our databases. However, recent studies assessing the quality of PMSI data, including ICD-10 codes, to identify healthcare outcomes have shown these data to be reliable for epidemiological purposes [62, 63].

Positive and negative control outcomes, and the use of the cohort of VKA new users as an active comparator, were used to guide interpretation of the results observed with

DOACs in an attempt to identify results that could have been affected by bias, which is clearly a strength of this study. Replicating the analysis in VKA new users actually showed that the results of SSA in DOAC new users may be prone to channeling bias. This risk of channeling bias should particularly affect analyses on outcomes related to reasons for channeling, namely when prior knowledge on adverse events (for instance, bleeding) and their related risk factors (for instance, renal impairment) can affect the probability of OAC exposure in opposite ways between VKAs and DOACs. Results from hepatic, skin and non-hospitalized gastrointestinal outcomes may therefore be less sensitive to this type of bias. As illustrated by bleeding outcome, SSA estimates of VKAs could be biased toward lower values, and estimates of DOACs could be biased toward higher values. Although restricting analyses to more comparable patients, i.e. AF patients, providing consistent results in terms of the positive associations observed in the whole population, SSA remains an initial and easy-to-implement method of detecting adverse events by using claims data. More studies using other designs, either avoiding or less sensitive to channeling, are therefore needed to test the associations observed in this study. Analyses in which outcomes are defined using hospitalization data might be more prone to detection bias, as suggested by the weaker inverse association observed between VKA therapy and the initiation of antiglaucoma medications, compared with hospitalization for glaucoma.

To minimize time-varying confounding and detection bias that may affect the SSA design [27, 32], we restricted the time window to a maximum of 12 months, and did not consider the significant positive associations observed when the length of the time window was extended to be valid, such as certain results observed for kidney or skin outcomes groups. Consequently, we were unable to capture adverse events that only occur after the first year of treatment; however, this 1 year-period may ensure an acceptable sensitivity and positive predictive value [32]. In addition, due to the high discontinuation and switch rates observed in OAC patients [64], longer time windows may not have been relevant.

## 5 Conclusions

Based on nationwide health data for DOAC new users, results from this SSA highlight the importance of non-bleeding adverse events in OAC patients, and suggest that DOACs are associated with rare but severe liver injury and more frequent gastrointestinal disorders. A low risk of kidney injury associated with DOAC therapy can also not be excluded. Pending further field studies to confirm these results, patients initiating DOAC therapy should be

informed and carefully monitored regarding the risk of hepatic and gastrointestinal adverse events.

**Acknowledgements** The authors thank Dr. Saul, medical translator, for assistance in writing the manuscript, and Dr. Emilie Sbidian, Department of Dermatology, Assistance Publique-Hôpitaux de Paris (APHP), for her contribution and expertise to defining skin outcomes on the French Healthcare databases.

## Compliance with Ethical Standards

**Funding** The authors received no funding.

**Conflicts of interest** Géric Maura, Cécile Billionnet, Alain Weill and Anke Neumann are employees of the French National Health Insurance (Cnam); Joël Coste is employed by the French National Health Insurance (CNAM); Antoine Pariente belongs to the French National Institute of Health and Medical Research (Inserm). None of the authors have any conflicts of interest that are directly relevant to the content of this study.

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