

ORIGINAL ARTICLE

Risk of major bleeding among users of direct oral anticoagulants combined with interacting drugs: A population-based nested case-control study

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Aims: To assess the association between concurrent use of potential pharmacokinetic or pharmacodynamic interacting drugs and major bleeding among direct oral anticoagulant (DOAC) users.

Methods: We performed a case-control study nested in a cohort of new users of DOACs (dabigatran etexilate, apixaban or rivaroxaban). Data were obtained from the UK Clinical Practice Research Datalink linked to Hospital Episode Statistics (2008–2015). Cases were patients hospitalized having a primary diagnosis of major bleeding. Up to 4 controls were matched on age, sex, index date and region. Odds ratios (ORs) for the risk of major bleeding were assessed by conditional logistic regression analysis and adjusted for well-known covariates for the risk of bleeding.

Results: We identified 393 patients with a major bleeding from a total of 23 492 new users of DOACs and 1494 matched controls. Most subjects were users of rivaroxaban (58.8%) on the index date. The concurrent use of pharmacodynamic interacting drugs was associated with an increased risk of major bleeding (21.6% of cases vs 13.5% of controls, adjusted odds ratio [aOR] 1.92; 95% confidence interval [CI], 1.40–2.66). For the antiplatelet drugs the aOR was 2.01 (95% CI, 1.29–3.11) and for the selective serotonin reuptake inhibitors the aOR was 1.68 (95% CI, 1.10–2.59). We found no increased risk of major bleeding for concurrent use of pharmacokinetic interacting drugs vs DOACs alone (45.0 vs 51.2%; aOR: 0.77; 95% CI: 0.53–1.10).

Conclusion: Among patients taking DOACs the concurrent use of antiplatelet drugs or selective serotonin reuptake inhibitors was associated with increased risk of major bleeding, while pharmacokinetic interacting drugs do not increase this risk.

KEYWORDS

apixaban, bleeding, dabigatran, drug interactions, rivaroxaban

1 | INTRODUCTION

Oral anticoagulants are recommended for the prevention and/or treatment of thromboembolic disorders including atrial fibrillation, deep venous thrombosis and pulmonary embolism, orthopaedic surgery and acute myocardial infarction. In recent years, direct oral anticoagulants (DOACs) such as dabigatran, apixaban, rivaroxaban and edoxaban have been introduced for thromboprophylaxis. Compared with vitamin K antagonists (VKAs), these drugs have a more predictable anticoagulant effect, without the need for routine monitoring.¹ DOACs also show lower risk of major bleeding and fatal bleeding than VKAs in randomized controlled trials.²⁻⁴ Despite the advantages of DOACs over VKAs, several uncertainties about their benefit-risk profile remain,⁵ such as concomitant use with potential drug-drug interaction. Several drugs could influence the safe use of DOACs via pharmacokinetic (PK) or pharmacodynamic (PD) interactions when used at the same time as DOACs.⁶⁻⁸

The absorption of DOACs is dependent on the **P-glycoprotein** (P-gp) system. P-gp inhibitors, such as verapamil, amiodarone and quinidine can increase plasma concentrations of DOACs,^{9,10} thereby enhancing the anticoagulant effect. **CYP3A4**-type cytochrome P450-dependent elimination is another factor involved in the metabolism of DOACs. Therefore, CYP3A4 inhibitors (e.g. verapamil) or inducers (e.g. rifampicin, carbamazepine) can influence plasma concentrations of DOACs and thereby increase bleeding risk or reduce effectiveness (less antithrombotic effect), respectively.

In addition to the PK interactions, there are other drugs that may increase bleeding risk via PD interactions such as antiplatelet drugs, nonsteroidal anti-inflammatory drugs (NSAIDs) and selective serotonin re-uptake inhibitors (SSRIs).¹¹⁻¹³ To date, it is not known what the clinical relevance of these drug-drug interactions is since only sporadic case reports and laboratory data of manufacturers are available.^{9,14} One recently conducted study from Taiwan reported that concurrent use of drugs with PK interactions in DOAC users with nonvalvular atrial fibrillation was associated with an increased risk of bleeding.⁸ However, it is unknown to what extent these findings can be replicated.

Therefore, the aim of our study was to evaluate the combined use of DOACs with potentially PK and PD interacting drugs on bleeding risk.

2 | METHODS

2.1 | Study design and data source

We performed a case-control study nested in a cohort of new users of DOACs (dabigatran etexilate, apixaban or rivaroxaban). Data were obtained from the Clinical Practice Research Datalink (CPRD) and linked to secondary care data from the Hospital Episode Statistics (HES).^{15,16} CPRD is a longitudinal research database that includes >14 million patient records provided by general practitioners throughout the UK. Data recorded in CPRD include demographics, symptoms and

What is already known about this subject

- Patients treated with direct oral anticoagulants (DOACs) commonly use potentially pharmacokinetic- and/or pharmacodynamic-interacting drugs. The magnitude of the effect of concurrent use of potentially interacting drugs on bleeding risk in daily practice is largely unknown.

What this study adds

- Antiplatelet drugs and selective serotonin reuptake inhibitors in combination with DOACs were both associated with a nearly doubling of the risk of major bleeding.
- Drugs that increase plasma levels of the DOACs by inhibition of CYP3A4 and/or P-glycoprotein do not increase the risk of major bleeding.

diagnoses, prescriptions, results of diagnostic investigations, referrals to specialists and secondary care settings, feedback from other care settings, and lifestyle, such as body mass index and smoking status. Use of the CPRD as a reliable data source has been well validated.^{15,17}

HES data include primary and contributory causes of patient admission to NHS hospitals in England.¹⁶ The data include patient demographics, and clinical and administrative details. Data are coded using the International Classification of Diseases (ICD)-10 classification. Approval of the study protocol was granted by the Independent Scientific Advisory Committee of the Medicines and Healthcare Products Regulatory Agency (protocol 17_257R).

2.2 | Definition of study cohort

We identified all patients with a first prescription for a DOAC between 1 January 2008 and 31 December 2015, who were age 18 years or older, had at least 1 year of history in CPRD prior to the date of this first prescription (to enable adequate assessment of incident use, as well as confounders) and were eligible for data linkage with HES. The duration of individual DOAC prescriptions was assessed by using information on the prescribed number of tablets and the dosage instruction. When such information was incomplete for the prescription, the median time between prescriptions was used. If only 1-3 prescriptions were available for an individual patient, the duration was based on the most frequently occurring estimated prescription duration for the drug in the study population. Subsequently, periods of current use were determined for each patient by constructing treatment episodes. A treatment episode was defined as a series of subsequent prescriptions for DOACs, independent of dose changes and constructed according to the method used in our previous study.¹⁸ We allowed for a 30-day permissible gap between the theoretical end date of 1 DOAC prescription and the subsequent

prescription. In case a subsequent prescription for the same drug was collected before the theoretical end date of a previous prescription, the number of overlapping days was added to the theoretical end date of the subsequent prescription. The number of overlapping days was maximized at 90 days. If a subsequent prescription within the same treatment episode was for another type of DOAC, the patient was considered to have switched therapy and the remaining tablet days from the prior prescription were disregarded. Patients were followed up to the date of admission for a major bleeding, the date they left the practice, died, or to the end of the study, whichever came first.

2.3 | Definition of cases and controls

Cases were defined as current users of DOACs with a first hospital admission related to major bleeding after DOAC start as identified by ICD-10 codes (Table A1). Major bleeding events were a composite of gastrointestinal, intracranial and other symptomatic bleeding in a critical area or organ defined use an adapted version of the definition of International Society on Thrombosis and Haemostasis.¹⁹ The date of the major bleeding event was defined as the index date. For each case, up to 4 controls were matched from the study cohort by means of incidence density sampling (controls could have an outcome of interest later) on sex, age (± 1 year), region and index date. Only controls that were using DOACs on the index date were eligible for inclusion.

2.4 | Exposure to drugs with potential interaction with DOACs

For both cases and controls, therapy records for potentially interacting drugs (Table 1) were identified. These interacting drugs were obtained from the Summary of Product Characteristics (SmPCs)¹¹⁻¹³ and the European Heart Rhythm Association Practical Guide.²⁰ In the latest guide,²¹ many anticancer drugs were listed as potential interacting drugs, but as these are prescribed in-hospital this information is not captured in CPRD and hence was not considered in this study. We classified interacting drugs into potentially PK-interacting drugs (inhibitors of P-gp and/or CYP3A4) and PD-interacting drugs (drugs that already enhance bleeding risk themselves). Drugs that can potentially cause both PK and PD interactions, including clopidogrel, ticagrelor, diclofenac and naproxen, were categorized into PD-interacting drugs because of their mild inhibitory effects on CYP3A4 and P-gp.^{11-13,22-24} We assumed concurrent use if a prescription was issued in a 30 days window prior to the index date (for antibiotics 14 days). A sensitivity analysis was performed using an extended time window of 60 days prior to the index date.

2.5 | Potential confounding factors

We included the following covariates, which are well known for the risk of bleeding: body mass index, smoking status, hypertension,

TABLE 1 List of drugs with potential interaction with direct oral anticoagulants as found to be coprescribed in the Clinical Practice Research Datalink database

Drugs with pharmacokinetic interaction		
Strong CYP3A4 and/or P-gp inhibitors	Moderate CYP3A4 and/or P-gp inhibitors	Drugs with pharmacodynamic interaction
Ketoconazole,	Amiodarone	Antiplatelet drugs
Cyclosporine	Posaconazole	Ticlopidine
Itraconazole	Quinidine	Clopidogrel*
Dronedarone	Verapamil	ASA
Tacrolimus	Digoxin	Ticagrelor
	Diltiazem	NSAIDs
	Simvastatin	SSRIs
	Atorvastatin	Fluoxetine
	Fluconazole	Paroxetine
	Clarithromycin	Citalopram
	Erythromycin	Escitalopram
		Sertraline
		Nefazodone
		SNRIs
		Venlafaxine
		Duloxetine

ASA, acetylsalicylic acid; NSAIDs, nonsteroidal anti-inflammatory drug; SSRIs, selective serotonin reuptake inhibitor; SNRIs, serotonin-norepinephrine reuptake inhibitor.

*Ticagrelor, and clopidogrel are also substrate of the P-glycoprotein transporter.

chronic kidney disease, hepatic impairment (moderate to severe), history of major bleeding, gastritis, cancer, peptic ulcer disease and thrombocytopenia in the year before the index date. We included all components of the HAS-BLED (hypertension, abnormal kidney or liver function, stroke, bleeding history, and alcohol use) score except international normalized ratio value, for which data in CPRD are incomplete. Furthermore, other comedication, not belonging to the group of direct potential interacting drugs, which include glucocorticoids, proton pump inhibitors and enzyme inducers (carbamazepine, phenytoin and rifampicin) were considered and were recorded in a 6-month period prior to the index date.

2.6 | Statistical analyses

Descriptive statistics were used to assess characteristics of cases and controls. Means and standard deviations are shown for continuous variables and proportions for categorical variables. Student *t* test for continuous variables and χ^2 test for categorical variables were used as appropriate. We compared the proportion of patients having DOAC dose adjustments between index date and the last prescription prior

to the index date. The proportion of patients with adjusted doses were compared by using χ^2 tests. The strength of the association between concurrent use of interacting drugs and risk of major bleeding was assessed using conditional logistic regression analysis for all DOACs together. For individual DOACs, the matching of cases and controls was discarded and therefore unconditional logistic regression analyses were used. Additionally, the associations were analysed for individual DOACs and when possible for different types of major bleeding. The associations were expressed as odds ratios (ORs) and 95% confidence intervals (95% CI). We adjusted for the above-mentioned potential confounders and type of DOAC. Additionally, when analysing the association of potentially PK-interacting drugs, we also adjusted for potentially PD-interacting drugs and vice versa. As mentioned above, a sensitivity analysis was performed using an extended time window of 60 days (instead of 30 days) prior to the index date. A 2-sided *P*-value of $<.05$ was considered statistically significant. Data analyses were performed using SAS version 9.4 (SAS institute).

3 | RESULTS

The study included 23 492 DOAC users aged 18 years or older initiating DOAC therapy between 2008 and 2015. Among these patients, we identified 393 cases with a first hospital admission for major bleeding and matched them to 1494 controls.

The characteristics of cases and controls are shown in Table 2. The mean age on the index date was 78.7 years (standard deviation 10.6), about 62% were men and most patients (73.5% of the cases vs 81.2% of the controls) used DOACs for the treatment of atrial fibrillation. In general, comorbidities were more prevalent among cases than among controls (Table 2). Use of comedication without potential interactions was common among both cases and controls, with controls using some of the statins (with no CYP3A4 and P-gp inhibition), angiotensin-converting-enzyme inhibitors and calcium channel blockers more frequently.

3.1 | Primary analysis

Table 3 shows that use of PK interacting drugs on the index date occurred in 45.0% of the cases and 51.2% of controls, yielding a crude OR of 0.78 (95% CI: 0.62–0.98). After adjustment for confounders, no statistically significant association with bleeding risk was found: OR 0.77 (95% CI: 0.53–1.10). The most frequently prescribed drugs with potential PK interactions with DOACs were simvastatin (cases vs controls: 19.3 vs 25.0%), followed by atorvastatin (cases vs controls: 15.0 vs 15.5%), and digoxin (cases vs controls: 13.7 vs 12.9%). When individual drugs were evaluated only verapamil and diltiazem reached statistically significant associations; however, there were very few exposed patients.

Concurrent use of drugs having PD interactions with DOACs (Table 3) was associated with a statistically significantly increased risk

of bleeding: adjusted OR of 1.92 (95% CI: 1.40–2.66). The most frequently used drugs in this group were antiplatelet drugs (adjusted OR 2.01, 95%CI: 1.29–3.11) and SSRIs (adjusted OR, 1.68, 95%CI: 1.10–2.59). Acetylsalicylic acid was the most frequently used antiplatelet drug (cases vs controls: 8.1 vs 4.4%). The prevalence of use of all interacting drugs is presented in Table A2.

3.2 | Secondary analysis

Analyses of potentially interacting drugs with individual DOACs showed that the results (point estimates) were not materially different from the analyses of the DOACs as a group, although some of the associations were no longer statistically significant (see Table 4 for PD drugs, and Table A3 for PK drugs). After stratification, only dabigatran had a statistically significant interaction with SSRIs; however, there this was not observed for apixaban and rivaroxaban. After stratification for different types of major bleeding only for gastrointestinal bleeding, the numbers were high enough to evaluate the risks of major bleeding for DOAC users combined with interacting drugs. It appeared that major bleeding risks were similar as found for all major bleedings together; however, the associations were no longer statistically significant (Table A3).

3.3 | Sensitivity analysis

Sensitivity analyses were conducted with an extended time window (prescription of potential interacting drugs within 60 days prior to the index date). Although more prescriptions for most of the interacting drugs were found (Table A4), results did not materially change (Tables A5 and A6).

3.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,^{25,26} and are permanently archived in the Concise Guide to PHARMACOLOGY 2018/19.²⁷

4 | DISCUSSION

In this nested case–control analysis using real-world primary care data, we found the risk of major bleeding leading to hospitalization of approximately increased by 100 and 70% when antiplatelet drugs or SSRIs, respectively, were combined with DOACs. For the drugs that inhibit CYP3A4 and/or P-gp, no increased bleeding risk was found.

Nearly half (45%) of the patients with a major bleeding admission in our study were using a drug that can potentially cause a PK interaction with DOACs on the index date. Simvastatin, atorvastatin and

TABLE 2 Characteristics of cases and controls

	Cases n = 393	Controls n = 1494	P-value
Age (y)			
Mean (SD)	78.7 (10.6)	78.7 (10.1)	.76
<75, n (%)	123 (31.3)	455 (30.5)	
≥75, n (%)	270 (68.7)	1039 (69.5)	
Sex, male, n (%)	243 (61.8)	932 (62.4)	.84
BMI (kg/m²), mean (SD)	27.3 (6.2)	27.5 (5.5)	.48
BMI missing (%)	19 (4.8)	51 (3.4)	
Smoking status, n (%)			.83
No	140 (35.6)	552 (37.0)	
Yes	32 (8.1)	127 (8.5)	
Former	221 (56.2)	813 (49.2)	
Type of DOAC			
Dabigatran	79 (20.1)	279 (18.7)	
Apixaban	53 (13.5)	366 (24.5)	
Rivaroxaban	261 (66.4)	849 (56.8)	
Indications			.003
Atrial fibrillation	289 (73.5)	1213 (81.2)	
DVT/PE	62 (15.8)	153 (10.2)	
Other	56 (14.2)	185 (12.4)	
Comorbidities*			
Congestive heart failure	85 (21.6)	238 (15.9)	.008
Diabetes	73 (18.6)	290 (19.4)	.71
Hypertension	256 (65.1)	1012 (67.7)	.33
COPD	73 (18.6)	165 (11)	<.001
Peripheral vascular disease	27 (6.9)	81 (5.4)	.27
Upper GI disease	35 (8.9)	103 (6.9)	.17
Chronic kidney disease	28 (7.1)	75 (5.0)	.10
Chronic kidney disease (missing)	14 (3.5)	46 (3.1)	-
Chronic liver disease	<5 ^d	<5	-
History of acute coronary disease	109 (27.7)	336 (22.5)	.03
History of bleeding	234 (59.5)	610 (40.8)	<.001
History of GI bleeding	93 (23.7)	212 (14.2)	<.001
History of intracranial bleeding	16 (4.1)	38 (2.5)	.11
Comedications**			
Beta-adrenergic receptor blockers	148 (37.7)	607 (40.6)	.29
ACEI	139 (35.4)	617 (41.3)	.03
Diuretics	127 (32.3)	474 (31.7)	.82
Calcium channel blockers	55 (14.0)	323 (21.6)	.001
Other statins***	145 (36.9)	648 (43.4)	.02
Proton pump inhibitors	174 (44.3)	611 (40.9)	.23

ACEI, angiotensin-converting-enzyme inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; DVT, deep venous thrombosis; GI: gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drug; PE, pulmonary embolism; SD, standard deviation.

*Comorbidities before the index date.

**Comedications other than potentially interacting drugs.

***Excluding the potentially interacting drugs simvastatin and atorvastatin.

TABLE 3 Major bleeding risk among patients taking direct oral anticoagulants (DOACs) with the concomitant use of potentially interacting drugs

Concurrent use of*	Cases (n = 393), n (%)	Controls (n = 1494), n (%)	Crude OR (95% CI)	Adjusted OR** (95% CI)
Drugs with PK interaction, n (%)	177 (45.0)	765 (51.2)	0.69 (0.62–0.98)	0.69 (0.53–0.90)
Amiodarone	7 (1.8)	40 (2.7)	0.66 (0.29–1.48)	0.67 (0.28–1.59)
Simvastatin	76 (19.3)	374 (25.0)	0.72 (0.54–0.95)	0.69 (0.42–1.13)
Atorvastatin	59 (15.0)	232 (15.5)	0.96 (0.71–1.31)	1.25 (0.83–1.88)
Verapamil	5 (1.3)	12 (0.8)	1.67 (0.59–4.73)	1.76 (0.58–5.35)
Digoxin	54 (13.7)	192 (12.9)	1.08 (0.78–1.50)	1.08 (0.75–1.55)
Diltiazem	7 (1.8)	69 (4.6)	0.37 (0.17–0.81)	0.26 (0.11–0.61)
Drugs with PD Interaction, n (%)	85 (21.6)	202 (13.5)	1.79 (1.34–2.40)	1.88 (1.36–2.61)
SSRIs	41 (10.4)	95 (6.4)	1.71 (1.14–2.54)	1.68 (1.10–2.59)
Antiplatelet drugs	41 (10.4)	90 (6.0)	1.79 (1.21–2.64)	2.01 (1.29–3.11)
ASA	28 (7.1)	62 (4.1)	1.76 (1.10–2.82)	1.94 (1.16–3.26)
CLOP	9 (2.3)	23 (1.5)	1.54 (0.70–3.41)	1.68 (0.71–3.97)
ASA + CLOP	<5	<5	**	***
NSAIDs	7 (1.8)	19 (1.3)	1.45 (0.60–3.54)	1.30 (0.50–3.41)

*All the concurrent used drugs with DOACs were compared to use DOACs but without use these drugs.

**Adjusted for smoking, history of major bleeding, history of stroke or transient ischaemic attack before the bleeding event, diabetes, hypertension, myocardial infarction, congestive heart failure, chronic renal disease, hepatic impairment, peripheral vascular disease, chronic pulmonary disease, peptic ulcer disease, cancer, co-medications before the index date medications (β -adrenergic receptor blockers, angiotensin-converting-enzyme inhibitors, non-P-gp inhibitor statins, proton pump inhibitors, and cytochrome P450 enzyme inducers). For analysing the association of potentially pharmacokinetic interacting drugs we also adjusted for potentially pharmacodynamic interacting drugs and vice versa. ASA: acetylsalicylic acid; CI: confidence interval; CLOP: clopidogrel; NSAIDs, nonsteroidal anti-inflammatory drug; OR: odds ratio; SSRIs, selective serotonin reuptake inhibitors.

***Suppressed due to <5 patients (Clinical Practice Research Datalink policy).

digoxin were the most commonly coadministered interacting drugs. It is reassuring that prescriptions of strong CYP3A4 and/or P-gp inhibitors such as antifungal azoles and cyclosporine, which are advised to be avoided in DOAC users,²⁸ were not found in this study.

We found a statistically significant, nearly 2-fold increased risk of major bleeding for drugs that pharmacodynamically interact with DOACs. Both antiplatelet drugs and SSRIs inhibit platelet aggregation and thus primary haemostasis, while the DOACs inhibit fibrin formation and thus secondary haemostasis. Similar increased risks in randomized controlled trials and observational studies were observed when antiplatelet drugs were combined with DOACs.^{12,29,30} The increased bleeding risk when combining SSRIs with DOACs has not been published before although there are warnings in the SmPCs of dabigatran and rivaroxaban.^{12,13} In line with our findings, for the combination of coumarins and SSRIs, an increased bleeding risk has been reported before.^{31,32}

An important finding in our study is that despite a substantial combined use of moderate CYP3A4 and/or P-gp inhibitors and DOACs and the well-known effect of these inhibitors to increase DOAC plasma levels, no increased major bleeding risk was observed. Also, in *posthoc* analyses of the combined use of amiodarone (moderate CYP3A4 inhibitor) with apixaban or rivaroxaban in the randomized trials ARISTOTLE³³ and ROCKET AF,³⁴ respectively, no significant interactions on bleeding risk were found. This discrepancy between confirmed PK interactions and clinically relevant major bleeding may indicate the limitations of PK data in predicting clinical outcomes.

Obviously, we cannot say anything about minor bleeding risks. In contrast to the probably limited impact of moderate CYP3A4 and/or P-gp inhibitors in bleeding risk as described above, other observational studies did report an increased risk for major bleedings when amiodarone, simvastatin or lovastatin were combined with DOACs.^{6,35} An explanation for these contrasting findings might be different behavior of prescribers to adjust (lower) the dose of DOACs when a PK-interacting drug is co-prescribed as advised in the SmPCs. In a preliminary analysis, we found that the proportion of lower dose of DOACs in patients concomitant use a CYP3A4 and/or P-gp inhibitor was lower compared to patients not using these inhibiting drugs (see in the Appendix Table A7). However, the proportion of patients who received a lower DOAC dose was low. Thus, the fact that we did not find an increased major bleeding risk when DOACs were combined with PK-interacting drugs cannot be explained by lowering of DOAC dosages. The unexpected decreased risk on major bleeding as found in our study when diltiazem was combined with DOACs is probably a chance finding due to a low number of patients exposed to diltiazem.

The rate of major bleeding observed here is lower than that reported in other studies.^{36–38} However, rates might not be comparable because we only included patients with hospital admissions related to major bleeding or due to differences in ICD codes used to identify major bleeding.

Although the combination of a platelet inhibitor and a DOAC increases the risk for major bleeding compared to DOACs alone or

TABLE 4 Major bleeding risk among patients using apixaban, dabigatran or rivaroxaban with the concomitant use of drugs with pharmacodynamics interaction

Concurrent use of *	Apixaban				Dabigatran				Rivaroxaban			
	Cases n (%)	Controls (n = 279), n (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)	Cases n (%)	Controls (n = 366), n (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)	Cases n (%)	Controls (n = 849), n (%)	Crude OR (95% CI)	Adjusted OR** (95% CI)
Interacting drugs	14 (26.4)	34 (12.2)	2.59 (1.27–5.25)	3.32 (1.43–7.71)	18 (22.8)	47 (12.8)	2.00 (1.09–3.68)	3.00 (1.48–6.1)	53 (20.3)	121 (14.3)	1.53 (1.07–2.19)	1.39 (0.93–2.06)
SSRIs	6 (11.3)	13 (4.7)	2.22 (0.60–8.21)	2.78 (0.78–9.91)	10 (12.7)	20 (5.5)	2.51 (1.12–5.59)	2.70 (1.09–6.70)	25 (9.6)	62 (7.3)	1.35 (0.83–2.19)	1.23 (0.73–2.07)
Antiplatelet drugs	6 (11.3)	19 (6.8)	2.30 (0.60–8.86)	2.07 (0.66–6.49)	9 (11.4)	24 (6.6)	1.83 (0.82–4.11)	2.81 (1.05–7.51)	26 (10.0)	47 (5.5)	1.89 (1.14–3.12)	1.69 (0.97–2.94)
ASA	<5	12 (4.3)	**	***	5 (6.3)	17 (4.6)	1.44 (0.51–4.02)	1.90 (0.58–6.25)	18 (6.9)	33 (3.9)	1.86 (1.03–3.37)	1.71 (0.89–3.29)
CLOP	<5	6 (2.2)	***	***	<5	6 (1.6)	1.63 (0.32–8.24)	3.05 (0.44–21.34)	6 (2.3)	11 (1.3)	1.86 (0.68–5.09)	1.66 (0.56–4.89)
ASA+ CLOP	0	<5	***	***	<5	<5	***	***	<5	<5	***	***
NSAIDs	<5	<5	***	***	<5	<5	***	***	<5	10 (1.2)	***	***

*All the concurrent used drugs with direct oral anticoagulants were compared with direct oral anticoagulant use without these drugs.

**Adjusted for age, gender, body mass index, smoking, history of major bleeding, history of stroke or transient ischaemic attack before the bleeding event, diabetes, hypertension, myocardial infarction, congestive heart failure, chronic renal disease, hepatic impairment, peripheral vascular disease, chronic pulmonary disease, peptic ulcer disease, cancer, comedication before the index date medications (β-adrenergic receptor blockers, angiotensin-converting-enzyme inhibitors, non-P-gp inhibitor statins, proton pump inhibitors, and cytochrome P450 enzyme inducers). For analysing the association of potentially pharmacokinetic interacting drugs we also adjusted for potentially pharmacodynamic interacting drugs and vice versa. ASA: acetylsalicylic acid; Ci: confidence interval; CLOP: clopidogrel; NSAIDs, nonsteroidal anti-inflammatory drug; OR: odds ratio; SSRIs, selective serotonin reuptake inhibitors.

***Suppressed due to <5 patients (Clinical Practice Research Datalink policy).

platelet inhibitors alone^{29,30} this increased risk is acceptable when a patient with atrial fibrillation develops an acute coronary syndrome²¹ and can be considered in a patient with a recent acute coronary syndrome.^{29,30} Such combination of a platelet inhibitor and a DOAC should be carefully considered depending on the bleeding risk of a patient (e.g. by using the HAS-BLED score). Also, the guidelines should be strictly followed when the platelet inhibitor or DOAC needs to be discontinued (e.g. discontinuation of the platelet inhibitor after 12 months after an acute coronary syndrome with stent placement). Based on our findings of the increased bleeding risks when a DOAC is combined with a SSRI, prescribers should try to prevent such a combination in patients with a high bleeding risk. For instance, by considering a tricyclic antidepressant in the case of depression. Although we did not find an increased risk of major bleeding when drugs that moderately inhibit CYP3A4 and/or P-gp are combined with a DOAC, we advise to strictly follow the dose recommendations in the SmPCs of the specific DOACs.

The strength of this study is that we used population-based data from a primary care setting, thereby reflecting the risk of major bleeding of the combined use of potentially interacting drugs with DOACs in daily practice. CPRD is well-renowned research database of which the medical information entered is monitored for validity and completeness. However, some limitations need to be addressed. Firstly, our study might not include all concurrent exposure to interacting drugs at the index date, as we defined concurrent use based on a prescription in a 30-day time window prior to the index date. However, sensitivity analyses, where we expanded this period to 60 days, provided similar results and therefore information bias caused by misclassification of the exposure is expected to be low. NSAIDs are available over the counter and therefore we expect misclassification to be present and therefore biased effect estimates in our study. Further research is necessary to evaluate the bleeding risk of the combined use of NSAIDs and DOACs. As we used the CPRD we might miss patients in the database who use a DOAC prescribed by hospital specialists. These patients probably have more complex diseases and treatments than patients prescribed DOACs by primary care physicians and therefore may have other bleeding risks when DOACs are combined with drugs known to interact with them. Furthermore, we did not have information on patient adherence and the identification of an adjustment of drug treatment can only be seen at the time a next prescription is issued. Due to the limited sample size it was only partly possible to evaluate subgroups stratified by type of bleeding (e.g. intracranial, gastrointestinal bleeding), type of DOAC (dabigatran, rivaroxaban, apixaban) and individual interacting drugs.

5 | CONCLUSION

Our study showed that drugs with PD interactions, mainly SSRIs and antiplatelet drugs, were used frequently in patients using DOACs and were associated with an increased risk of major bleeding. Although inhibitors of CYP3A4 and/or P-gp influence the PK of

DOACs we did not find that these drugs increased the risk of major bleeding.

COMPETING INTERESTS

The authors declare no conflict of interest.

CONTRIBUTORS

Y.Z. was involved in the conception and design of the study, statistical analysis and interpretation of data, drafting and critical revision of the manuscript. P.C.S. was involved in conception and design of the study, acquisition of data, critical revision of the manuscript, and supervision. H.G. was involved in conception and design of the study and critical revision of the manuscript. H.A.H. was involved in conception and design of the study and critical revision of the manuscript. A.H.M.Z. was involved in conception and design of the study and critical revision of the manuscript. Anthonius de Boer was involved in conception and design of the study, analysis and interpretation of data, critical revision of the manuscript and supervision.

DATA AVAILABILITY STATEMENT


CPRD policy does not allow data sharing of individual patient data.

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APPENDIX A

TABLE A1 International Classification of Diseases 10th revision (ICD-10) codes used to identify major bleeding cases

Condition	ICD-10 code
Major bleeding	
Haemorrhagic stroke/intracranial bleeding	I60 I61 I62
Extracranial or unclassified major bleeding	D62, J942, H113, H313, H356, H431 N02 N95 R04 R31 R58
Gastrointestinal bleeding	K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5 K92.0, K92.1, K92.2
Traumatic intercranial bleeding	S063C S064 S065 S066

TABLE A2 Interacting drugs prescribed to cases and controls on direct oral anticoagulant therapy in a 30-day time window prior to the index date

	Cases (n = 393) n (%)	Controls (n = 1494) n (%)
Concomitant use of at least 1 drug with PK interaction	177 (45.0)	765 (51.2)
Strong CYP3A4 and/or P-gp inhibitor comedication		
Ketoconazole	0	0
Cyclosporine	0	0
Itraconazole	0	1
Dronedarone	<5	<5
Tacrolimus	0	0
Moderate CYP3A4 and/or P-gp inhibitors		
Amiodarone	7 (1.8)	40 (2.7)
Posaconazole	0	0
Quinidine	0	0
Verapamil	5 (1.3)	12 (0.8)
Digoxin	54 (13.7)	192 (12.9)
Diltiazem	7 (1.8)	69 (4.6)
Simvastatin	76 (19.3)	374 (25.0)
Atorvastatin	59 (15.0)	232 (15.5)
Ticagrelor	<5	0
Fluconazole	<5	<5
Clarithromycin	<5	7 (0.5)
Erythromycin	<5	<5
Concomitant use of at least 1 drug with PD interaction	85 (21.6)	202 (13.5)
Antiplatelets	41 (10.4)	90 (6.0)
Ticlopidine	<5	0
Clopidogrel	13 (3.3)	27 (1.8)
Low-dose acetylsalicylic acid	32 (8.1)	66 (4.4)
NSAIDs	7 (1.8)	19 (1.3)
Diclofenac	0	0
Naproxen	<5	5 (0.3)

(Continues)

TABLE A2 (Continued)

	Cases (n = 393)	Controls (n = 1494)
	n (%)	n (%)
SSRIs*	41 (10.4)	95 (6.4)
SNRI	6 (1.5)	16 (1.1)
Enzyme inducers		
Rifampicin	0	0
Carbamazepine	<5	<5
Phenytoin	<5	<5
Other inducers	0	0

PK, pharmacokinetic; PD, pharmacodynamic; ACE, angiotensin-converting-enzyme; NSAIDs, nonsteroidal anti-inflammatory drug; SSRIs, Selective serotonin reuptake inhibitor; SNRIs, Serotonin-norepinephrine reuptake inhibitor.

*The SSRIs we assessed were fluoxetine, paroxetine, sertraline, citalopram, escitalopram, sertraline, and nefazodone. The SNRIs we assessed were venlafaxine and duloxetine.

All the cases <5 are according to the regulations of ISAC for CPRD database.

TABLE A3 Association between the concurrent use of potentially interacting drugs and DOACs and gastrointestinal bleeding

Concurrent use of	Cases (n = 157), n (%)	Controls (n = 594), n (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)	P-value
Drugs with PK interaction,	68 (43.3)	314 (52.9)	0.66 (0.45–0.95)	0.53 (0.26–1.06)	.07
Amiodarone	<5	19 (3.2)	**	**	**
Simvastatin	33 (21.0)	153 (25.8)	0.75 (0.49–1.16)	0.90 (0.47–1.72)	.75
Atorvastatin	22 (14.0)	87 (14.6)	0.95 (0.57–1.59)	1.11 (0.85–2.13)	.75
Verapamil	<5	<5	**	**	**
Digoxin	19 (12.1)	91 (15.3)	0.76 (0.45–1.30)	0.62 (0.34–1.13)	.12
Diltiazem	<5	26 (4.4)	**	**	**
Drugs with PD interaction	28 (17.8)	84 (14.1)	1.28 (0.80–2.07)	1.27 (0.75–2.12)	.37
SSRIs*	14 (8.9)	41 (6.9)	1.29 (0.67–2.48)	1.25 (0.62–2.53)	.5
Antiplatelet	14 (8.9)	38 (6.4)	1.40 (0.74–2.66)	1.39 (0.38–2.83)	.36
ASA	10 (6.4)	28 (4.7)	1.37 (0.65–2.88)	1.29 (0.57–2.92)	.55
CLOP	<5	8 (1.3)	1.93 (0.55–6.70)	2.48 (0.65–9.45)	.19
ASA+ CLOP	0	<5	**	**	**
NSAIDs	0	6 (1.0)	**	**	**

PK, pharmacokinetic; PD, pharmacodynamic; ACE, angiotensin-converting-enzyme; NSAIDs, nonsteroidal anti-inflammatory drug; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors.

*The SSRIs we assessed were fluoxetine, paroxetine, sertraline, citalopram, escitalopram, sertraline, and nefazodone. The SNRIs we assessed were venlafaxine and duloxetine.

**Suppressed due to <5 patients (CPRD policy).

TABLE A4 Interacting drugs prescribed to cases and controls on direct oral anticoagulant therapy in a 60-day time window prior to the index date

	Cases (n = 393)	Controls (n = 1494)
Concomitant use of	n (%)	n (%)
Concomitant use of at least 1 drug with PK interaction	224 (57.0)	936 (62.7)
Strong CYP3A4 and/or P-gp inhibitor comedication		
Ketoconazole,	0	0
Cyclosporine	0	0
Itraconazole	0	<5
Dronedarone	<5*	<5
Tacrolimus	0	0
Moderate CYP3A4 and/or P-gp inhibitors		
Amiodarone	10 (2.5)	51 (3.4)
Posaconazole	0	0
Quinidine	0	0
Verapamil	5 (1.3)	18 (1.2)
Digoxin	65 (16.5)	228 (15.3)
Diltiazem	11 (2.8)	82 (5.5)
Simvastatin	95 (24.2)	467 (31.3)
Atorvastatin	76 (19.3)	294 (19.7)
Ticagrelor	<5	<5
Fluconazole	0	0
Clarithromycin	0	0
Erythromycin	<5	9 (0.6)
Concomitant use at least 1 drug with PD interaction	123 (31.3)	278 (18.6)
Antiplatelets	70 (17.8)	146 (9.8)
Ticlopidine	0	0
Clopidogrel	23 (5.9)	40 (2.7)
Acetylsalicylic acid	55 (14.0)	110 (7.4)
NSAIDs	9 (2.3)	29 (1.9)
Diclofenac	<5	<5
Naproxen	5 (1.3)	11 (0.7)
SSRIs*	53 (13.5)	113 (7.6)
SNRI	8 (2.0)	17 (1.1)
Enzyme inducers		
Rifampicin	0	0
Carbamazepine	<5	<5
Phenytoin	<5	<5
Other inducers	0	0

PK, pharmacokinetic; PD, pharmacodynamic; ACE, angiotensin-converting-enzyme; NSAIDs, nonsteroidal anti-inflammatory drug; SSRIs, Selective serotonin reuptake inhibitor; SNRIs, Serotonin-norepinephrine reuptake inhibitor.

*The SSRIs we assessed were fluoxetine, paroxetine, sertraline, citalopram, escitalopram, sertraline, and nefazodone. The SNRIs we assessed were venlafaxine and duloxetine.

**According to CPRD policy, all cells having less than 5 patients are shown as "<5".

TABLE A5 Association between use of concomitant drugs in current users of DOACs and risk of major bleeding (Sensitivity 60days)

Concurrent use of*	Cases (n = 393), n (%)	Controls (n = 1494), n (%)	Crude OR (95% CI)	Adjusted OR** (95% CI)
Drugs with PK interaction, n (%)	224 (57.0)	936 (62.7)	0.80 (0.635–1.00)	0.94 (0.64–1.39)
Amiodarone	10 (2.5)	51 (3.4)	0.74 (0.38–1.48)	0.71 (0.34–1.48)
Simvastatin	95 (24.2)	467 (31.3)	0.71 (0.55–0.92)	0.84 (0.58–1.20)
Atorvastatin	76 (19.3)	294 (19.7)	1.00 (0.75–1.33)	1.18 (0.82–1.70)
Verapamil	5 (1.3)	18 (1.2)	1.11 (0.41–3.04)	1.94 (0.64–5.83)
Digoxin	65 (16.5)	228 (15.3)	1.09 (0.80–1.48)	1.06 (0.76–1.48)
Diltiazem	11 (2.8)	82 (5.5)	0.49 (0.26–0.94)	0.37 (0.18–0.74)
Drugs with PD interaction, n (%)	123 (31.3)	278 (18.6)	2.02 (1.56–2.61)	2.10 (1.58–2.78)
SSRIs	53 (13.5)	113 (7.6)	1.94 (1.35–2.79)	1.91 (1.29–2.83)
Antiplatelet drugs	70 (17.8)	146 (9.8)	1.97 (1.45–2.69)	2.00 (1.36–2.95)
ASA only	46 (11.7)	103 (6.9)	1.82 (1.25–2.64)	1.88 (1.25–2.84)
CLOP only	14 (3.6)	33 (2.2)	1.74 (0.92–3.30)	1.59 (0.78–3.21)
> 1 drug	9 (2.3)	7 (0.5)	5.26 (1.95–14.15)	6.19 (2.12–18.03)
NSAIDs	9 (2.3)	29 (1.9)	1.16 (0.54–2.48)	1.16 (0.51–2.64)

ASA, acetylsalicylic acid; CLOP, clopidogrel. PK, P-gP inhibitors or CYP3A4 inhibitors; PD, pharmacodynamic.

*All the concurrent used drugs with DOACs were compared to use DOACs but without use these drugs.

**Adjusted for smoking, alcohol abuse, history of stroke or transient ischaemic attack before the bleeding event, diabetes, hypertension, myocardial infarction, congestive heart failure, chronic renal disease, hepatic impairment, peripheral vascular disease, chronic pulmonary disease, peptic ulcer disease, cancer, comedications before the index date medications (β -adrenergic receptor blockers, angiotensin-converting-enzyme inhibitors, non-PgP inhibitor statins, proton pump inhibitors, and cytochrome P450 enzyme inducers). For evaluating the association between pharmacodynamic interacting drugs and the major bleeding, co-medications with potential pharmacokinetic interactions were adjusted for. For evaluating the association between the combination use of pharmacokinetic interactions and DOAC and the major bleeding, drugs with potential pharmacodynamic interactions were adjusted for.

***Suppressed due to <5 patients CPRD policy).

TABLE A6 Major bleeding risk among patients taking apixaban, dabigatran, or rivaroxaban with the concomitant use of drugs with pharmacokinetic interactions

Concurrent use of **	Apixaban				Dabigatran				Rivaroxaban			
	Cases (n = 79), n (%)	Controls (n = 366), n (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)	Cases (n = 79), n (%)	Controls (n = 366), n (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)	Cases (n = 79), n (%)	Controls (n = 366), n (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Drugs with PK interaction,	24 (45.3)	137 (49.1)	0.86 (0.48–1.55)	0.80 (0.37–1.73)	38(48.1)	201 (54.9)	0.76 (0.47–1.24)	0.61 (0.33–1.71)	115 (44.1)	427 (50.3)	0.78 (0.60–1.03)	0.73 (0.52–1.02)
Amiodarone	<5	10 (3.6)	***	***	<5	9 (2.5)	***	***	5 (1.9)	21 (2.5)	0.77 (0.29–2.06)	0.77 (0.27–2.19)
Simvastatin	8 (15.1)	58 (20.8)	0.68 (0.30–1.52)	0.77 (0.31–1.92)	13 (16.5)	95 (26.0)	0.56 (0.30–1.07)	0.42 (0.21–0.87)	55 (21.1)	221 (26.0)	1.03 (0.69–1.54)	0.74 (0.51–1.07)
Atorvastatin	9 (17.0)	52 (18.6)	0.89 (0.41–1.94)	0.61 (0.23–1.65)	14 (17.7)	66 (18.0)	0.98 (0.52–1.85)	1.05 (0.51–2.14)	225 (86.2)	735 (86.6)	1.10 (0.69–1.74)	1.10 (0.69–1.74)
Verapamil	<5	<5	-	-	0	<5	-	-	<5	6 (0.7)	***	***
Digoxin	9 (17.0)	34 (12.2)	1.47 (0.66–3.29)	1.72 (0.66–4.49)	11 (13.9)	56 (15.3)	0.90 (0.45–1.80)	0.88 (0.41–1.93)	34 (13.0)	102 (12.0)	1.10 (0.72–1.66)	1.09 (0.68–1.73)
Diltiazem	<5	<5	***	***	<5	24 (6.6)	***	***	6 (2.3)	33 (3.9)	0.58 (0.24–1.40)	0.68 (0.25–1.84)

ASA, acetylsalicylic acid; CLOP, clopidogrel, PK, P-gP inhibitors or CYP3A4 inhibitors.

*All the concurrent used drugs with DOACs were compared to use DOACs but without use these drugs.

Adjusted for smoking, alcohol abuse, history of stroke or transient ischaemic attack before the bleeding event, diabetes, hypertension, myocardial infarction, congestive heart failure, chronic renal disease, hepatic impairment, peripheral vascular disease, chronic pulmonary disease, peptic ulcer disease, cancer, comediations before the index date medications (β-adrenergic receptor blockers, angiotensin-converting-enzyme inhibitors, non-PgP inhibitor statins, proton pump inhibitors, and cytochrome P450 enzyme inducers). For evaluating the association between pharmacodynamic interacting drugs and the major bleeding, co-mediations with potential pharmacokinetic interactions were adjusted for. For evaluating the association between the combination use of pharmacokinetic interactions and DOAC and the major bleeding, drugs with potential pharmacodynamic interactions were adjusted for. ASA: acetylsalicylic acid; CLOP: clopidogrel, PK: P-gP inhibitors or CYP3A4 inhibitors; *Suppressed due to <5 patients (Regulations of ISAC for CPRD database).

TABLE A7 The proportion of patients with adjustment among DOAC users concomitant with interacting drugs

Concomitant with	Cases	Control	P-value
PK (n = 942; missing 235)	<i>n</i> = 140	<i>n</i> = 567	
With adjustment*; n (%)	23 (16.4)	67 (11.8)	.14
Dose increase	3 (2.1)	12 (2.1)	.98
Dose decrease	11 (6.4)	9 (1.9)	.004
Switch to other DOAC	11 (7.9)	44 (7.8)	.97
PD (n = 276; missing 73)	<i>n</i> = 67	<i>n</i> = 147	
With adjustment; n (%)	10 (14.9)	15 (10.2)	.32
Dose increase	2 (3.0)	4 (2.7)	.91
Dose decrease	2 (3.0)	3 (2.0)	.67
Switch to other DOAC	6 (9.0)	8 (5.4)	.34

PK, P-gP inhibitors or CYP3A4 inhibitors; PD, drugs with pharmacodynamic interaction.

*Adjustment include dose adjustment and switch to other DOACs.