Received: 23 February 2022 | Revised: 11 August 2022 | Accepted: 19 August 2022

DOI: 10.1111/bcp.15531

ORIGINAL ARTICLE

Bleeding events among patients concomitantly treated with direct oral anticoagulants and macrolide or fluoroquinolone antibiotics

Tatsuya Yagi[1] | Buster Mannheimer[2] | Johan Reutfors[1] | Johan Ursing[3] | Diego Hernan Giunta[1] | Helle Kieler[1] | Marie Linder[1]

[1]Department of Medicine Solna, Centre for Pharmacoepidemiology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

[2]Department of Clinical Science and Education at Södersjukhuset, Karolinska Institutet, Stockholm, Sweden

[3]Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden

Correspondence
Tatsuya Yagi, Department of Medicine Solna, Centre for Pharmacoepidemiology, Karolinska Institutet, Karolinska University Hospital, 17176 Stockholm, Sweden.
Email: yagi5922@hama-med.ac.jp

Funding information
T.Y. receives research funding from the Japanese Society of Clinical Pharmacology and Therapeutics as part of the Foreign Clinical Pharmacology Training Program, the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 19K16443 and Hamamatsu University School of Medicine.

Fluoroquinolones and macrolides may, due to a potential drug-drug interaction, increase the concentration of any concomitantly administered direct oral anticoagulant (DOAC) and thereby increase the risk of severe bleeding. However, clinical evidence for such an effect is scarce. The present study aimed to evaluate the association between the use of fluoroquinolones or macrolides and bleeding events in patients with concomitant DOAC use. This was a nationwide cohort study including 19 288 users of DOACs in 2008-2018 using information from Swedish national health registers. We compared the incidence of bleeding events associated with use of fluoroquinolones or macrolides using doxycycline as a negative control. Cox regression was used to calculate crude and adjusted hazard ratios (aHRs) in time windows of various length of follow-up after the start of antibiotic use. The incidence rates for fluoroquinolones and macrolides ranged from 12 to 24 and from 12 to 53 bleeding events per 100 000 patients in the investigated time windows. The aHRs (95% confidence interval) for use of fluoroquinolones and macrolides were 1.29 (0.69-2.44) and 2.60 (0.74-9.08) at the concomitant window, 1.31 (0.84-2.03) and 1.79 (0.75-4.29) at 30 days, and 1.34 (0.99-1.82) and 1.28 (0.62-2.65) at 150 days, respectively. With regard to fluoroquinolones, the present study suggests that the risk of bleeding when combined with DOACs, if any, is small. Codispensation of macrolides in patients on DOACs was not associated with an increased risk of bleeding. However, due to the small number of macrolide users, the results must be interpreted with caution.

KEYWORDS
bleeding, cohort study, direct anticoagulants, fluoroquinolones, macrolides

There was no principal investigator because our research is register-based using data that have already been collected.

1 | INTRODUCTION

Direct oral anticoagulants (DOACs) are widely used for the prevention and treatment of venous thromboembolism and to prevent ischemic stroke in patients with atrial fibrillation (AF).[1–4] Moreover, DOACs are used for noncancer-related deep vein thrombosis (DVT) and pulmonary embolism (PE) prophylaxis in patients who have undergone knee or hip replacements.[3] Unlike warfarin, DOACs do not require routine laboratory monitoring of the anticoagulant effect or dose adjustment. Although it has been suggested that drug-drug interactions, dietary interactions and adverse events may be fewer with DOACs than with warfarin, the risk of bleeding remains a safety concern, particularly considering the lack of a clear reversal strategy.[5,6] Four DOACs are currently available in Sweden: dabigatran, rivaroxaban, apixaban and edoxaban. They are all metabolized by **cytochrome p450 3a4 (CYP3A4)** and/or are substrates for the efflux transporter **P-glycoprotein (P-gp)** and therefore susceptible to interactions with drugs that affect these enzymes. However, the contributions of CYP3A4 and P-gp differ, and the drug interaction by concomitant use of drugs that inhibit or induce these enzymes and transporters shows differences between DOACs.[7–9]

Fluoroquinolones are widely used to treat urinary tract, gastrointestinal and respiratory infections.[10] The most commonly used fluoroquinolone in Sweden is ciprofloxacin, which is a moderate inhibitor of CYP3A4 and may also reduce the mRNA expression of CYP3A4 and P-gp by reducing the bacteria that produce hepatic secondary bile acids.[11–13] Fluoroquinolones may thus potentially increase the systemic levels of any DOAC, further increasing the risk of bleeding. However, data on potential clinical consequences are lacking.

Macrolides (erythromycin, clarithromycin and azithromycin) are antibiotics that are used extensively for a wide range of indications such as pneumonia caused by typical or atypical agents and *Helicobacter pylori* causing stomach ulcers. Since macrolides are inhibitors of CYP3A4 and P-gp inhibitors, they may increase the pharmacologic effect of a concomitantly ingested DOAC.[7,14,15] Azithromycin is a mild CYP3A4 and P-gp inhibitor, whereas erythromycin and clarithromycin are strong CYP3A4 and P-gp inhibitors.[14]

To date, two cohort studies have been conducted to investigate the association between bleeding events and the use of DOACs with concurrent use of antibiotics. A large Canadian cohort study comparing clarithromycin and azithromycin in elderly patients on DOACs found that macrolides may be associated with an increased risk of bleeding.[16] A Taiwanese cohort study, on the contrary, reported a low bleeding rate in patients with concomitant use of clarithromycin/erythromycin and DOACs compared with DOAC alone.[17,18] However, the association between concomitant use of fluoroquinolones or macrolides and adverse bleeding events in DOAC users have not been fully clarified in a large, unselected Western population of patients in routine clinical settings. Moreover, it is unclear how long the association remains after the concomitant antibiotic use. Investigating these associations will help to provide safe anticoagulant treatment for patients using antibiotics in clinical settings.

What is already known about this subject

- Fluoroquinolones may increase systemic levels of DOACs and increase the bleeding risk.
- A Canadian study comparing clarithromycin versus azithromycin in elderly patients on DOACs suggested macrolides may increase the bleeding risk.
- Low bleeding rate was found in patients with concomitant use of clarithromycin/erythromycin and DOACs compared with DOAC alone in Taiwan.

What this study adds

- The present study suggests that the risk of bleeding when combining DOACs with fluoroquinolones, if any, is small.
- Although the results in this regard may be interpreted with caution, codispensation of macrolides in patients on DOACs was not associated with an increased risk of bleeding.

The present study aimed to evaluate the association between bleeding events and concomitant use of DOACs with macrolides or fluoroquinolones compared with negative control drug.

2 | METHODS

2.1 | Study design

We performed a population-based cohort study of patients with concomitant use of DOAC and macrolides or fluoroquinolones compared to patients with concomitant use of DOAC and doxycycline (negative control) to evaluate the association with adverse bleeding events.

2.2 | Data sources

Data from the Swedish national registers were linked through the unique personal identification number assigned to each resident at birth or immigration. The Swedish National Board of Health and Welfare is responsible for the health registers used in this study. Data on medications were obtained from the Swedish Prescribed Drug Register (PDR).[19] The PDR is a nationwide register covering all filled prescriptions on the individual level for medications for the entire Swedish population since July 1, 2005. For each filled prescription, it includes the trade name, pharmaceutical form, strength and package size, number of packages, Anatomical Therapeutic Chemical (ATC) classification code, amounts in the defined daily dose (DDD), and the prescription date and date of filling the prescription. The PDR does

not include sales of nonprescription over-the-counter medicines or drugs administered without a personal prescription during hospitalizations and nursing home stays.

Clinical history and outcomes were obtained from the Swedish National Patient Register (NPR).[20] The NPR contains data from all hospital admissions in Sweden starting from 1987 and outpatient specialist visits since 2001. At each discharge, information is recorded about the patient's demographics, primary and secondary diagnoses, procedure codes, hospitals and wards, dates of admission and discharge. The diagnoses are coded by the International Classification of Diseases 10th Revision (ICD-10) since 1997 and procedures are coded according to Nordic Medico-Statistical Committee (NOMESCO) NCSP codes. Date of death was retrieved from the Cause of Death Register.[21] The Swedish Cause of Death Register comprises all deaths among Swedish residents, whether occurring in Sweden or abroad, and cause of death is recorded by ICD codes.

2.3 | Study population

The study population consisted of patients who were aged 18 years or older and filled their first prescription for any DOAC (ATC code), dabigatran (B01AE07), apixaban (B01AF02), rivaroxaban (B01AF01), or edoxaban (B01AF03), between January 1, 2008 and December 31, 2018. Hospitalized patients were implicitly excluded since we used only filled prescriptions as exposure. The date of filling the first DOAC prescription constituted the unique cohort entry date for each individual. The present study excluded individuals recorded with knee or hip joint replacement (NCSP codes NGB, NFB, NFC, NGC) within 6 months before the index date, since they are at a higher risk of bleeding, and the recommended treatment durations are shorter than for other DOAC indications.[3,22] The indications for DOACs were assessed by recorded diagnosis before the start of dispensing of DOACs.

Exposure to antibiotic agents was captured as filled prescriptions of either fluoroquinolones (ATC codes J01MA02, J01MA06, J01MA12, J01MA14), macrolides (ATC codes J01FA01, J01FA06, J01FA09, J01FA10) or doxycycline (ATC code J01AA02) during the first DOAC exposure. Doxycycline is an antibiotic with an extensive use that shares several indications with fluoroquinolones and macrolides, although it is most commonly used for acute exacerbation of chronic bronchitis and other respiratory tract infections.[23] In contrast, to the best of our knowledge, doxycycline does not share the potential of fluoroquinolones and macrolides to interact with DOACs.[24,25] We excluded patients with *H. pylori* treatment indication by identifying patients with concomitant use of the most common combinations for this indication: concurrent use of amoxicillin or metronidazole with clarithromycin, concomitant use of amoxicillin or metronidazole with levofloxacin, and those with concurrent use of metronidazole with doxycycline. If these combinations of antibiotics overlapped during clarithromycin, levofloxacin or doxycycline supply, we considered it a combination for the treatment of *H. pylori*.

Only the first continuous DOAC use episode for each individual was included in the analysis (not allowing switches between different DOACs). The use of antibiotics was assumed to start on the date of filling the prescription. Risk windows for the outcomes of interest were defined as the concomitant use window considering the duration of antibiotic use, as well as the concomitant window plus an extended window of six incremental lengths: 30, 60, 90, 120, 150 and 180 days (Figure 1). The present study considered the potential mechanism of CYP3A4/P-gp inhibition via changes in gut flora by administration of fluoroquinolones and evaluated extended windows of 30-180 days since Dethlefsen et al have reported that it takes about 2-5 months for a return to normal intestinal flora after the end of ciprofloxacin administration.[26]

2.4 | Exposure definition

Episodes of continuous use for DOACs were constructed by adding the durations of the filled prescriptions together. DDD is the assumed average maintenance dose per day for a drug used for its main

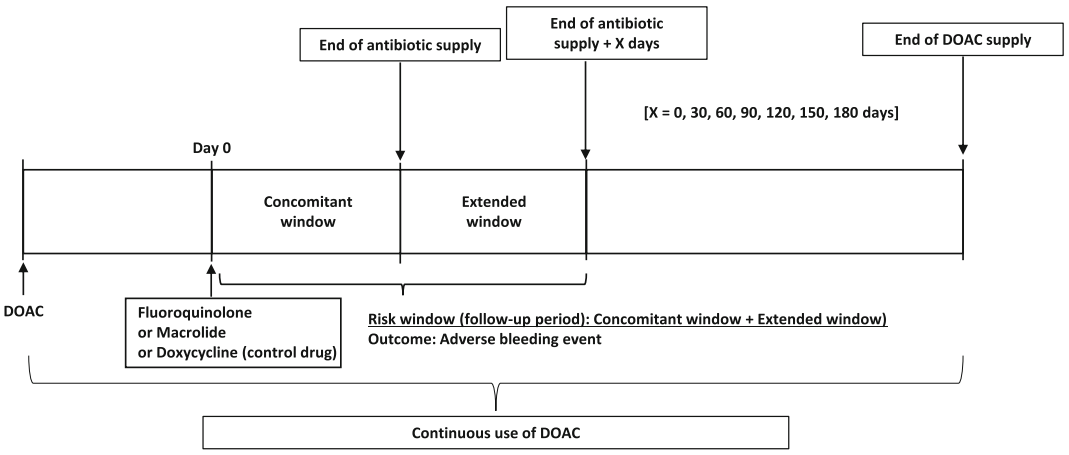

FIGURE 1 Illustration of the cohort design used in this study. DOAC, direct oral anticoagulants

indication in adults. The duration of each filled prescription was assumed to be equivalent to the number of filled DDDs augmented by 25% to account for missed tablets.[27] The continuous exposure episode lasted as long as the next filling was within the assumed duration of the previous filling. When the next filling was beyond the assumed duration, the continuous exposure episode ended at the date of the last filled prescription + 1.25 × number of DDDs. Regarding the concomitant use of antibiotics, only the first dispensation of an antibiotic (fluoroquinolones, macrolides or doxycycline) during the first continuous DOAC use episode was included in the analyses, and the dispensation date of the antibiotics was defined as day 0. In this study, dispensing of each antibiotic during continuous use of DOACs was defined as "concomitant use." Thus, "concomitant use" was "not dispensing on the same day," but overlapping supply. The period of concomitant use of antibiotics was defined as exposure episodes constructed by linking filled prescriptions within the allowable gap of 25% of DDD together. The end of follow-up of this cohort was death, end of study or end of antibiotic or DOAC supply and the start of an antibiotic from another group, that is, if an antibiotic (A) was prescribed during supply of an antibiotic (B) from a group of antibiotics other than B, only antibiotic B was included in this analysis and the prescription date of antibiotic A censored the follow-up time.

2.5 | Outcomes

We identified all clinically relevant bleeding events using the primary diagnoses for all hospital admissions from the NPR according to the following ICD-10 codes: intracranial bleeding (I60-I62), gastrointestinal bleeding (I850, I983, K226, K228, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K920-K922) and other bleeding (H431, D500, D629, J942, I312). We considered the admission date as the outcome date.

2.6 | Covariates and confounders

Potential confounders were identified by selecting the number of drugs that have clinically known pharmacokinetic interaction with DOACs such as CYP3A4/P-gp inhibitors/inducers (clarithromycin, erythromycin, isoniazid, HIV protease inhibitors, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole, carbamazepine, valproic acid, phenytoin, levetiracetam, amiodarone, amlodipine and rifampicin) or drugs and diagnoses associated with bleedings, such as nonsteroidal anti-inflammatory drugs, proton pump inhibitors, antiplatelet agents, selective serotonin reuptake inhibitors, alcohol-related diagnosis, bleeding history, cancer, chronic pulmonary disease, coagulation disorder, congestive heart failure, dementia, diabetes diagnosis, hypertension, ischemic heart disease, liver disease, mitral stenosis, obesity, renal disease, sepsis and urinary tract infection (Supporting Information Tables S1 and S2). The use of each medication was characterized based on the ATC codes recorded in the PDR using a 1-year look-back period whereas the comorbid diagnoses were identified based on ICD10 codes recorded in the NPR in the previous 5 years.

2.7 | Statistical analysis

Patient characteristics were described as absolute and relative frequencies for categorical variables and as means with standard deviations (SD) for continuous variables. We estimated cumulative incidences per 100 patients (%) and incidence rates by 100 000 person-days of exposure.

We estimated crude hazard ratios (HRs) and adjusted hazard ratios (aHR) with 95% confidence intervals (95% CI) using a Cox proportional regression model to evaluate the association between bleeding events and concomitant use of DOACs with macrolides or fluoroquinolones versus doxycycline. Covariates were assessed as fixed at baseline. For each time window, we considered the same risk time with doxycycline as the reference category. We adjusted HRs using age (≤75 years or age >75 years), gender, and the potential covariate and confounders. Patients were followed from the start of concomitant antibiotic use until the end of the risk window, death or the end of the study, whichever occurred first. We explored effect modification with a subgroup analysis by DOAC indication (atrial fibrillation, thromboembolism or others) and specific anticoagulants (dabigatran, apixaban, rivaroxaban or edoxaban).

All analyses and data management were performed using STATA/MP version 15.4 (STATA StataCorp LLC, Lakeway Drive College Station, Texas, USA) and SAS statistical software version 9.4 (SAS Institute, Cary, North Carolina, USA).

2.8 | Ethical approval

The Regional Ethics Committee at Karolinska Institutet (record no 2013/1850-31/1 and addendum 2016/2218-32) and the National Board of Health and Welfare approved the study.

2.9 | 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, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[28]

3 | RESULTS

A total of 335 198 new DOAC users were identified from January 1, 2008 to December 31, 2018. Patients who had undergone elective hip or knee replacement surgery within 6 months before the index date (n = 28 353), patients without a concomitant potentially interacting antibiotic (n = 287 272) and patients with possible *H. pylori*

infection (n = 285) were excluded. A total of 19 288 patients fulfilled the inclusion criteria: 9783 patients treated with fluoroquinolones, 764 with macrolides and 8741 with doxycycline (Figure 2). The two most commonly included DOACs were apixaban (n = 10 640, 55%) followed by rivaroxaban (n = 6342, 33%).

The mean age was 73 (SD 11) years with 69% of men in the fluoroquinolone group. In the macrolide group, the mean age was 67 (SD 14) years with a lower proportion of men (51%). The medians (25th, 75th percentiles) of antibiotics duration of fluoroquinolones, macrolides and doxycycline were 10 (8, 10), 5 (5, 10) and 10 (10, 15) days, respectively. All baseline characteristics at index date by antibiotic group are shown in Table 1.

In the concomitant use window, bleeding events occurred in 26 out of 9783 patients (0.27%, 95% CI 0.18-0.39) in the fluoroquinolone group, four out of 764 patients (0.52%, 95% CI 0.20-1.34) in the macrolide group and 23 of the 8741 patients (0.26%, 95% CI 0.18-0.39) in the doxycycline group. Cumulative incidence considering the extended window of 30 days was 0.6% (59/9783, 95% CI 0.47-0.78), 0.92% (7/764, 95% CI 0.44-1.88) and 0.49% (43/8741, 95% CI 0.37-0.66) for the fluoroquinolone, macrolide and doxycycline groups, respectively. Considering the longer extended window of 180 days, we observed a total of 134 bleeding events in the fluoroquinolone group, 10 in the macrolide group, and 88 in the doxycycline group.

The incidence rates of bleeding in each antibiotic group for each exposure window are presented in Table 2. In the considered time windows, the incidence rates ranged from 12 to 24 bleeding events per 100 000 person-days for fluoroquinolones, from 12 to 53 bleeding events per 100 000 person-days for macrolides, and from 8 to 19 bleeding events per 100 000 person-days for doxycycline.

The crude and aHR for bleeding events of concomitant use of fluoroquinolones and DOACs (0 days extension) were 1.17 (95% CI 0.67-2.08) and 1.29 (95% CI 0.69-2.44), respectively. During the extended windows following concomitant fluoroquinolone use, the aHR were 1.31 (95%CI: 0.84-2.03) at 30 days, 1.15 (95%CI 0.79-1.67) at 60 days, 1.34 (95%CI 0.99-1.82) at 150 days and 1.29 (95%CI 0.95-1.74) at 180 days. The crude and aHR for bleeding events of concomitant use of macrolides and DOACs (0 days extension) were 2.43 (95 %CI 0.72-8.23) and 2.60 (95% CI 0.74-9.08). During the extended window of concomitant macrolide use, the aHR were 1.79 (95% CI: 0.75-4.29) at 30 days, 1.34 (95% CI 0.57-3.15) at 60 days, 1.28 (95% CI 0.62-2.65) at 150 days and 1.23 (95% CI 0.60-2.54) at 180 days. The association measurements between use of fluoroquinolones or macrolides and DOACs with bleeding events compared to doxycycline are presented in Table 2.

Subgroup analysis by DOAC indication and by individual DOACs (dabigatran, apixaban and rivaroxaban) are presented in Table 3 and Supporting Information Table S4, respectively. All crude and aHRs were consistent with the primary analysis, except in patients treated for thromboembolism. In this subgroup, the aHRs for bleeding events in patients that had received fluoroquinolones and DAOCs were 1.93 (95%CI 1.01-3.68) and 1.83 (95%CI 1.01-3.30) for the extended windows of 120 and 150 days.

4 | DISCUSSION

The present nationwide cohort study using data obtained from the Swedish national health registers explored the association between bleeding events and concomitant use of fluoroquinolones or macrolides with DOACs. In a population-based cohort of over 10 000 individuals, we did not find any association between codispensed fluoroquinolones or macrolides and DOACs with bleeding events,

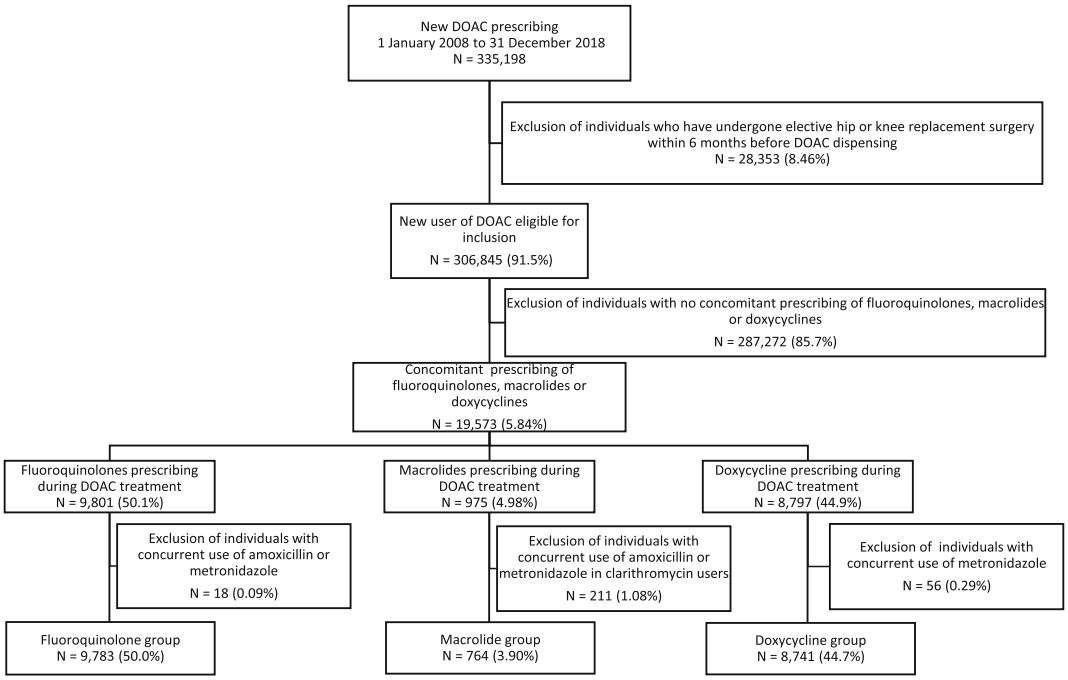

FIGURE 2 Identification of concurrent users of direct oral anticoagulants and fluoroquinolones or macrolides or doxycycline. DOAC, direct oral anticoagulants

TABLE 1 Characteristics, comorbidities and comedications at baseline among patients taking a DOAC, by antibiotic group

		Fluoroquinolones (N = 9783)		Macrolides (N = 764)		Doxycycline (N = 8741)	
Characteristic	**Value**	***N***	***P* (%)**	***N***	***P* (%)**	***N***	***P* (%)**
Age	Mean [SD] years	73	[11]	67	[14]	71	[10]
	18-49 years	289	(3.0)	83	(10.9)	338	(3.9)
	50-64 years	1352	(13.8)	157	(20.5)	1418	(16.2)
	65-79 years	5536	(56.6)	420	(55.0)	5289	(60.5)
	>80 years	2606	(26.6)	104	(13.6)	1696	(19.4)
Sex	Men	6740	(68.9)	388	(50.8)	4757	(54.4)
	Women	3043	(31.1)	376	(49.2)	3984	(45.6)
DOAC	Dabigatran	1039	(10.6)	88	(11.5)	1089	(12.5)
	Apixaban	5437	(55.6)	403	(52.7)	4800	(54.9)
	Rivaroxaban	3252	(33.2)	270	(35.3)	2820	(32.3)
	Edoxaban	55	(0.6)	3	(0.4)	32	(0.4)
DOAC indication	Atrial fibrillation	6533	(66.8)	441	(57.7)	6088	(69.6)
	Deep venous thrombosis	1211	(12.4)	111	(14.5)	942	(10.8)
	Pulmonary embolism	999	(10.2)	106	(13.9)	922	(10.5)
	Others/none	1040	(10.6)	106	(13.9)	789	(9.0)
Antibiotics duration	Median [25th, 75th percentiles] days	10	[8, 10]	5	[5, 10]	10	[10, 15]
	Mean [SD] days	10.9	[15.3]	9.9	[18.7]	14.0	[11.8]
Number of concomitant drugs							
• All	Median [25th, 75th percentiles]	5	[3, 7]	5	[3, 7]	5	[3, 7]
	1-3 drugs	2685	(27.4)	299	(39.1)	2472	(28.3)
	4-6 drugs	3935	(40.2)	315	(41.2)	3775	(43.2)
	7-9 drugs	2047	(20.9)	101	(13.2)	1722	(19.7)
	>10 drugs	838	(8.6)	46	(6.0)	619	(7.1)
• CYP3A4 inhibitor	1 drug	2132	(21.8)	56	(7.3)	2045	(23.4)
	2 drugs	229	(2.3)	30	(3.9)	205	(2.3)
	3 drugs	11	(0.1)	2	(0.3)	19	(0.2)
	4 drugs	2	(0.02)	0	(0)	1	(0.01)
• CYP3A4 inducer	1 drug	68	(0.7)	3	(0.4)	6	(0.07)
Comorbidities	Hypertension	4470	(45.7)	304	(39.8)	3796	(43.4)
	Ischemic heart disease	1770	(18.1)	118	(15.4)	1459	(16.7)
	Myocardial infarction	593	(6.1)	34	(4.5)	460	(5.3)
	Pacemaker	473	(4.8)	36	(4.7)	413	(4.7)
	Chronic heart failure	1552	(15.9)	100	(13.1)	1430	(16.4)
	Peripheral vascular disease	645	(6.6)	39	(5.1)	426	(4.9)
	Stroke	1504	(15.4)	87	(11.4)	983	(11.2)
	Coagulation disorder	229	(2.3)	22	(2.9)	222	(2.5)
	Bleeding history	372	(3.8)	30	(3.9)	259	(3.0)
	Cancer	2171	(22.2)	127	(16.6)	1394	(15.9)
	Chronic pulmonary disease	1092	(11.2)	162	(21.2)	2263	(25.9)
	Liver dysfunction	428	(4.4)	17	(2.2)	210	(2.4)
	Diabetes mellitus	1989	(20.3)	105	(13.7)	1330	(15.2)
	Rheumatic disease	507	(5.2)	47	(6.2)	476	(5.4)
	Obesity	359	(3.7)	30	(3.9)	360	(4.1)
	Tobacco use	160	(1.6)	12	(1.6)	291	(3.3)

TABLE 1 (Continued)

		Fluoroquinolones (N = 9783)		Macrolides (N = 764)		Doxycycline (N = 8741)	
Characteristic	**Value**	***N***	***P* (%)**	***N***	***P* (%)**	***N***	***P* (%)**
Pharmacologic treatments	ACE inhibitor/ARB	4233	(43.3)	292	(38.2)	4013	(45.9)
	Lipid-lowering agents	3109	(31.8)	200	(26.2)	2729	(31.2)
	Antiplatelet	1175	(12.0)	84	(11.0)	953	(10.9)
	Gastro protective agents	2572	(26.3)	218	(28.5)	2353	(26.9)
	Antidepressant	780	(8.0)	85	(11.1)	786	(9.0)
	Nonsteroid anti-inflammatory drugs	377	(3.9)	46	(6.0)	333	(3.8)
	Sulfamethoxazole/trimethoprim	84	(0.9)	8	(1.0)	21	(0.2)
	Metronidazole	663	(6.8)	7	(0.9)	20	(0.2)

Note: Indication is based on the recorded diagnosis in connection with filling a prescription with one of the DOAC drugs.
CYP3A4/P-gp inhibitors: clarithromycin, erythromycin, isoniazid, HIV protease inhibitors, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole, carbamazepine, valproic acid, phenytoin, levetiracetam, amiodarone, amlodipine.
CYP3A4/P-gp inducers: dexamethasone, omeprazole, rifabutin, bosentan, nafcillin, rifapentine, efavirenz, etravirine, emtricitabine, tenofovir, lamivudine, modafinil, rifampicin.
Number of concomitant drugs: ATC codes beginning with A01 (stomatological preparations), A02 (drugs for acid-related disorders), A07 (antidiarrheals, intestinal anti-inflammatory/anti-infective agents), A08 (antiobesity preparations, excluding diet products), A10 (drugs used in diabetes), B01 (antithrombotic agents), C (cardiovascular system), D01 (antifungals for dermatological use), D06 (antibiotics and chemotherapeutics for dermatological use), G01 (gynaecological anti-infectives and antiseptics), J01 (antibacterials for systemic use), J02 (antimycotics for systemic use), J04 (antimycobacterials), J05 (antivirals for systemic use), L04 (immunosuppressants), M01 (anti-inflammatory and antirheumatic products), N06 (psychoanaleptics), N07 (other nervous system drugs), P01 (antiprotozoals) and V06 (general nutrients).
Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; DOAC, direct oral anticoagulant; SD, standard deviation.
Parenthesis means % and square bracket means standard deviations.

compared to a negative control treatment with concomitant use of doxycycline and DOACs. Subgroup analysis by DOAC indication and by individual DOACs was consistent with the primary analysis, but with broader confidence intervals, as expected.

Previous animal studies have suggested that the fluoroquinolone ciprofloxacin may decrease the function of P-gp and CYP3A4, and consequently increase the risk of bleeding if combined with DOACs, which are substrates for these enzymes.[11,12,29,30] In addition, Dethlefsen et al reported that the time to return to normal intestinal flora after ciprofloxacin administration was about 2-5 months.[26] We did not observe an increased risk of bleeding events during or shortly after concomitant fluoroquinolone use and only a slight increased bleeding risk for up to 4-5 months after the concomitant use of fluoroquinolone in the thromboembolic disease subgroup analysis. Additionally, we would expect a higher risk of bleeding closer to the use of the antibiotic rather than after 4-5 months. The results thus suggest that intake of ciprofloxacin during DOAC treatment did not significantly increase the risk of major bleeding events in this population.

A Canadian population-based, retrospective cohort study by Hill et al explored the association between concomitant use of DOACs with two macrolides, clarithromycin (n = 6592) and azithromycin (n = 18 351), and the risk of hospitalizations caused by a major bleeding among adults of advanced age (over 66 years).[16] They estimated a higher cumulative incidence of bleeding in the extended window of 30 days amounting to 0.8% in patients using clarithromycin and 0.3% in patients using azithromycin, and a 1.7-fold consistently higher bleeding risk for clarithromycin users compared to azithromycin users. In our study, we explored antibiotic class-aggregated effects compared to doxycycline as a negative control in an unselected population with a broader range of ages. Our bleeding risk estimation was aggregated by antibiotic class and we did not explore the drug-specific risk of bleeding within each antibiotic class. The differences in the estimated risk of bleeding between studies may be explained by the differences between both study populations, including age distribution, comorbidities, anticoagulant indications and concomitant treatments.

The study by Chang et al used a retrospective cohort of 91 330 patients with nonvalvular atrial fibrillation diagnosis who filled a DOAC prescription in Taiwan to explore the effect on major bleeding events of concomitant use of clarithromycin or erythromycin compared to patients without these antibiotics.[17] They reported a lower bleeding rate for patients using either of these two antibiotics compared to DOACs alone, with an aHR of 0.60 (95% CI 0.48-0.75). An explanation put forward for this finding was that the treatment possibly leads to the eradication of *H. pylori*, reducing the risk of peptic ulcer bleeding by *H. pylori*, which in turn outweighed the potential bleeding risk brought by inhibiting CYP3A4 and P-gp. In our study, we excluded patients with filled prescriptions of macrolides compatible with recommended combinations to eradicate *H. pylori*. We also used a negative control to mitigate the confounding by indication effect. However, our sample size was considerable smaller, and consequently had lower precision and less power to detect small differences.

Bykov et al compared the case-crossover and the self-controlled case series designs to evaluate drug-drug interactions in adults, including the effect of the concomitant use of dabigatran and

TABLE 2 Hazard ratios for adverse bleeding events compared to doxycycline for concomitant window and extended windows of 30, 60, 90, 120, 150 and 180 days

Antibiotic	Extended window[a] (days)	Number of bleedings	Person-time (days)	Incidence rate (per 100 000 person-days)	Crude hazard ratio (95% CI)	Adjusted hazard ratio[b] (95% CI)
Fluoroquinolones (N = 9783)	0	26	106 510	24.4	1.17 (0.67-2.08)	1.29 (0.69-2.44)
	30	59	350 684	16.8	1.29 (0.87-1.92)	1.31 (0.84-2.03)
	60	86	550 998	15.6	1.38 (0.99-1.92)	1.15 (0.79-1.67)
	90	107	719 449	14.9	1.45 (1.07-1.96)	1.22 (0.87-1.71)
	120	116	863 170	13.4	1.48 (1.11-1.98)	1.31 (0.95-1.82)
	150	129	987 668	13.1	1.48 (1.12-1.98)	1.34 (0.99-1.82)
	180	134	1 096 141	12.2	1.46 (1.12-1.92)	1.29 (0.95-1.74)
Macrolides (N = 764)	0	4	7530	53.1	2.43 (0.72-8.23)	2.60 (0.74-9.08)
	30	7	26 245	26.7	1.74 (0.82-4.64)	1.79 (0.75-4.29)
	60	7	41 765	16.8	1.26 (0.54-2.91)	1.34 (0.57-3.15)
	90	8	55 017	14.5	1.27 (0.58-2.76)	1.15 (0.50-2.64)
	120	9	65 921	13.7	1.34 (0.65-2.79)	1.20 (0.55-2.64)
	150	10	75 259	13.3	1.36 (0.68-2.70)	1.28 (0.62-2.65)
	180	10	83 266	12.0	1.29 (0.65-2.56)	1.23 (0.60-2.54)
Doxycycline (N = 8741)	0	23	122 131	18.8	1.00 (ref)	1.00 (ref)
	30	43	343 757	12.5	1.00 (ref)	1.00 (ref)
	60	59	533 963	11.0	1.00 (ref)	1.00 (ref)
	90	70	699 982	10.0	1.00 (ref)	1.00 (ref)
	120	74	845 207	8.8	1.00 (ref)	1.00 (ref)
	150	84	974 369	8.6	1.00 (ref)	1.00 (ref)
	180	88	1 088 647	8.1	1.00 (ref)	1.00 (ref)

[a]The risk window where the outcome is captured equals the concomitant window plus the extended window.
[b]The adjusted hazard ratio is hazard ratio that adjusted for the potential confounders were identified by selecting the drugs that have clinically known pharmacokinetic interaction with direct oral anticoagulants such as CYP3A4/P-gp inhibitor/inducer, or drugs and diagnoses associated with bleedings, such as nonsteroidal anti-inflammatory drugs, proton pump inhibitors, antiplatelet agents, selective serotonin reuptake inhibitors, alcohol-related diagnosis, bleeding history, cancer, chronic pulmonary disease, coagulation disorder, congestive heart failure, dementia, diabetes diagnosis, hypertension, ischemic heart disease, liver disease, mitral stenosis, obesity, renal disease, sepsis and urinary tract infection.

clarithromycin on hospitalization for major bleeding.[9] Consistent with our results, using these two approaches they did not find any association between concomitant use and major bleeding, but they may have had low power due to a very small number of patients exposed to dabigatran and clarithromycin.

The nationwide coverage of the national Swedish healthcare registers yielded a large, unselected population of patients in routine clinical settings for detection of clinically relevant severe bleedings. However, our study has some limitations. Regarding the macrolide group, although the current study comprised the whole population of Sweden for more than 10 years, the number of bleedings was few, resulting in limited statistical power, particularly for some subgroup analyses. This affects primarily the conclusions related to the use of macrolides due to a relatively low prescription rate, as compared to fluoroquinolones.

Using information from the PDR, exposure was based on patients with a filled prescription only. Not having access to drugs administered to inpatients and nursing home residents without a prescription implicates a risk of misclassification of exposure. Furthermore, we had limited information for patient adherence to pharmaceutical treatment and duration of exposure, which could possibly lead to either an underestimation or an overestimation of outcomes. However, this problem may be limited since the vast majority of DOACs are prescribed to the patient. The proportion of DOAC users with adequate adherence was above 80% in a study from Sweden, Denmark, Scotland, Norway and Germany between 2011 and 2018.[31] This adherence estimation may be reasonably extrapolated to all of Sweden.

Regarding the reference drug, although not previously shown, doxycycline may theoretically impact the intestinal flora and potentially reduce bacteria that produce CYP3A4 and P-gp, which may decrease the effect with regard to the investigated drugs. If doxycycline also has the effect of decreasing CYP3A4 and P-gp according to its impact of the intestinal flora, our results may be underestimated. Moreover, although sharing several indications for its use, doxycycline indications do in part differ from the indications of each study drug. For example, fluoroquinolones are typically used for more severe infections compared to doxycycline. The present study did not include the information on antibiotic indications. Thus, although the present study used a negative control, the confounding from the antibiotic indication might not have been fully adjusted and fully corresponding

TABLE 3 Hazard ratios for adverse bleeding events compared with doxycycline in AF patients and compared with doxycycline in DVT/PE patients

Antibiotic	Extended window[a] (days)	Number of bleedings	Person-time (days)	Incidence rate (per 100 000 person-days)	Crude hazard ratio (95% CI)		Adjusted hazard ratio[b] (95% CI)	
Compared with doxycycline in AF patients								
Fluoroquinolones (N = 6533)	0	19	70 327	27.0	1.23	(0.64-2.36)	1.18	(0.57-2.46)
	30	40	235 716	17.0	1.17	(0.74-1.86)	1.09	(0.65-1.83)
	60	54	372 313	14.5	1.19	(0.80-1.78)	0.89	(0.57-1.40)
	90	69	488 553	14.1	1.35	(0.94-1.94)	1.06	(0.73-1.60)
	120	77	589 484	13.1	1.29	(0.91-1.84)	1.08	(0.73-1.59)
	150	82	678 441	12.1	1.38	(0.99-1.93)	1.15	(0.79-1.66)
	180	85	757 431	11.2	1.34	(0.97-1.87)	1.10	(0.76-1.58)
Macrolides (N = 441)	0	2	4067	49.2	2.44	(0.56-10.7)	2.53	(0.55-11.5)
	30	4	15 335	26.1	1.78	(0.63-5.03)	1.68	(0.58-4.86)
	60	4	24 870	16.1	1.29	(0.46-3.59)	1.30	(0.46-3.68)
	90	4	33 085	12.1	1.16	(0.42-3.21)	1.19	(0.42-3.36)
	120	4	39 853	10.0	1.07	(0.39-2.95)	1.16	(0.41-3.26)
	150	4	45 679	8.8	0.98	(0.36-2.71)	1.02	(0.37-2.86)
	180	4	50 669	7.9	0.93	(0.34-2.58)	0.99	(0.35-2.75)
Doxycycline (N = 6088)	0	18	85 094	21.2	1.00	(ref)	1.00	(ref)
	30	33	241 399	13.7	1.00	(ref)	1.00	(ref)
	60	45	376 314	12.0	1.00	(ref)	1.00	(ref)
	90	51	495 762	10.3	1.00	(ref)	1.00	(ref)
	120	55	601 275	9.1	1.00	(ref)	1.00	(ref)
	150	60	696 475	8.6	1.00	(ref)	1.00	(ref)
	180	63	782 014	8.1	1.00	(ref)	1.00	(ref)
Compared with doxycycline in DVT/PE patients								
Antibiotic	**Extended window[a] (days)**	**Number of bleedings**	**Person-time (days)**	**Incidence rate (per 100 000 person-days)**	**Crude hazard ratio (95% CI)**		**Adjusted hazard ratio[b] (95% CI)**	
Fluoroquinolones (N = 2210)	0	5	24 283	20.6	0.89	(0.22-3.55)	1.73	(0.33-8.99)
	30	17	80 125	21.2	1.70	(0.75-3.88)	2.04	(0.81-5.11)
	60	29	125 294	23.1	1.94	(1.00-3.75)	1.89	(0.91-3.42)
	90	34	162 296	20.9	1.72	(0.95-3.09)	1.61	(0.83-3.12)
	120	38	192 500	19.7	1.94	(1.10-3.46)	1.93	(1.01-3.68)
	150	41	217 502	18.9	1.71	(1.01-2.91)	1.83	(1.01-3.30)
	180	43	238 052	18.1	1.73	(1.03-2.91)	1.72	(0.97-3.07)
Macrolides (N = 217)	0	2	2498	80.1	3.30	(0.35-30.8)	4.69	(0.21-105.5)
	30	3	7688	39.0	2.09	(0.45-9.71)	2.15	(0.41-11.2)
	60	3	11 806	25.4	1.45	(0.33-6.45)	1.53	(0.31-7.73)
	90	4	15 240	26.2	1.70	(0.50-5.79)	0.93	(0.20-4.59)
	120	5	18 074	27.7	2.21	(0.74-6.57)	1.17	(0.28-4.56)
	150	6	20 465	29.3	2.32	(0.88-6.18)	1.49	(0.45-5.01)
	180	6	22 506	26.7	2.16	(0.82-5.70)	1.48	(0.45-4.81)
Doxycycline (N = 1864)	0	4	26 002	15.4	1.00	(ref)	1.00	(ref)
	30	9	72 517	12.4	1.00	(ref)	1.00	(ref)
	60	13	112 016	11.6	1.00	(ref)	1.00	(ref)
	90	17	145 254	11.7	1.00	(ref)	1.00	(ref)
	120	17	173 320	9.8	1.00	(ref)	1.00	(ref)

(Continues)

TABLE 3 (Continued)

Compared with doxycycline in DVT/PE patients						
Antibiotic	Extended window[a] (days)	Number of bleedings	Person-time (days)	Incidence rate (per 100 000 person-days)	Crude hazard ratio (95% CI)	Adjusted hazard ratio[b] (95% CI)
	150	21	197 121	10.7	1.00 (ref)	1.00 (ref)
	180	22	217 039	10.1	1.00 (ref)	1.00 (ref)

Abbreviations: AF, atrial fibrillation; CI, confidence interval; DVT/PE, deep venous thrombosis/pulmonary embolism.
[a]The risk window where the outcome is captured equals the concomitant window plus the extended window.
[b]The adjusted hazard ratio is hazard ratio that adjusted for the potential confounders were identified by selecting the drugs that have clinically known pharmacokinetic interaction with DOACs such as CYP3A4/P-gp inhibitor/inducer, or drugs and diagnoses associated with bleedings, such as nonsteroidal anti-inflammatory drugs, proton pump inhibitors, antiplatelet agents, selective serotonin reuptake inhibitors, alcohol-related diagnosis, bleeding history, cancer, chronic pulmonary disease, coagulation disorder, congestive heart failure, dementia, diabetes diagnosis, hypertension, ischemic heart disease, liver disease, mitral stenosis, obesity, renal disease, sepsis and urinary tract infection.

between fluoroquinolones or macrolides and doxycycline, and this may represent a source of bias. Although an obvious limitation, the effect would be an overestimation of the bleeding risk, but only a slight increased risk was found. As in all observational studies, there is a potential risk of residual confounding. We did not adjust for the use of other anticoagulants such as vitamin K antagonist and heparins since we assume that they are not used concomitantly. The level of antibiotic prescription is low in Sweden compared with many other European countries because Sweden has a strong position on and regulation of antibiotic use.[32] Thus, our results may not generalize to other populations with different antibiotic use regulations. The number of CYP3A4 substrates may have an influence on DOAC adverse bleeding events. However, our dataset does not include information on all dispensed drugs due to legal restrictions, and therefore we could not adjust for all concomitant use of CYP3A4 substrates. Since CYP3A enzymes (including CYP3A4) metabolize more than 45% of all drugs, we evaluated the number of concomitant medications that also included non-CYP3A4 substrates. Our dataset included only concomitant drug information on drugs from the classes stomatological preparations (ATC code beginning with A01), drugs for acid-related disorders (A02), antidiarrheals, intestinal anti-inflammatory/anti-infective agents (A07), anti-obesity preparations, excluding diet products (A08), drugs used in diabetes (A10), antithrombotic agents (B01), cardiovascular system (C), antifungals for dermatological use (D01), antibiotics and chemotherapeutics for dermatological use (D06), gynaecological anti-infectives and antiseptics (G01), antibacterials for systemic use (J01), antimycotics for systemic use (J02), antimycobacterials (J04), antivirals for systemic use (J05), immunosuppressants (L04), antiinflammatory and antirheumatic products (M01), psychoanaleptics (N06), other nervous system drugs (N07), antiprotozoals (P01) and general nutrients (V06). Although controversial, it cannot be ignored that the number of CYP3A4 substrates per se may reduce the clearance of drugs also metabolized by this enzyme. However, with data only including drugs defined as covariates of this study, we were not able to fully control for this possible bias.

In conclusion, co-dispensation of macrolides in patients treated with DOACs was not associated with an increased risk of bleeding compared to concomitant use of doxycycline. However, due to the small number of macrolide users, the results must be interpreted with caution. With regard to fluoroquinolones, the results suggest that the risk of bleeding when combined with DOACs compared to concomitant use of doxycycline, if any, is small.

ACKNOWLEDGEMENTS

The authors had editorial support from Caroline Öberg and database management support from Zoltan Thinsz at the Centre for Pharmacoepidemiology, Karolinska Institutet.

COMPETING INTERESTS

H.K., M.L., J.R. and D.H.G. are employed at the Centre for Pharmacoepidemiology, which receives grants from several pharmaceutical companies, regulatory authorities and contract research organizations for the performance of drug safety and drug utilization studies. B.M. and J.U. have nothing to disclose.

CONTRIBUTORS

T.Y. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design, and acquisition, analysis and interpretation of data: all authors. Drafting of the manuscript: T.Y. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: T.Y. and M.L. Support as clinician: B.M., J.R. and J.U. Administrative, technical and material support: J.R., D.H.G., H.K. and M.L. Supervision: J.R., D.H.G., H.K. and M.L.

DATA AVAILABILITY STATEMENT

Restrictions apply to the availability of the datasets generated and/or analysed during the current study, and so they are not publicly available due to confidentiality.

ORCID

Tatsuya Yagi https://orcid.org/0000-0003-1194-3568

REFERENCES

1. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2):e419S-e496S. doi:10.1378/chest.11-2301

2. Makam RCP, Hoaglin DC, McManus DD, et al. Efficacy and safety of direct oral anticoagulants approved for cardiovascular indications: Systematic review and meta-analysis. *PLoS ONE*. 2018;13(5): e0197583. doi:10.1371/journal.pone.0197583
3. Forster R, Stewart M. Anticoagulants (extended duration) for prevention of venous thromboembolism following total hip or knee replacement or hip fracture repair. *Cochrane Database Syst Rev*. 2016;3: Cd004179. doi:10.1002/14651858.CD004179.pub2
4. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardiothorac Surg*. 2016;50(5):e1-e88. doi:10.1093/ejcts/ezw313
5. Conway SE, Hwang AY, Ponte CD, Gums JG. Laboratory and clinical monitoring of direct acting oral anticoagulants: what clinicians need to know. *Pharmacotherapy*. 2017;37(2):236-248. doi:10.1002/phar.1884
6. Samuelson BT, Cuker A. Measurement and reversal of the direct oral anticoagulants. *Blood Rev*. 2017;31(1):77-84. doi:10.1016/j.blre.2016.08.006
7. Evans WE, McLeod HL. Pharmacogenomics—drug disposition, drug targets, and side effects. *N Engl J Med*. 2003;348(6):538-549. doi:10.1056/NEJMra020526
8. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. 2015;17(10):1467-1507. doi:10.1093/europace/euv309
9. Bykov K, Li H, Kim S, Vine SM, Lo Re V, 3rd, Gagne JJ. Drug-drug interaction surveillance study: comparing self-controlled designs in five empirical examples in real-world data. *Clin Pharmacol Ther*. 2021;109(5):1353-1360. doi:10.1002/cpt.2119
10. Chan T, Bunce PE. Fluoroquinolone antimicrobial drugs. *CMAJ*. 2017;189(17):E638. doi:10.1503/cmaj.160938
11. Hellwig T, Gulseth M. Pharmacokinetic and pharmacodynamic drug interactions with new oral anticoagulants: what do they mean for patients with atrial fibrillation? *Ann Pharmacother*. 2013;47(11):1478-1487. doi:10.1177/1060028013504741
12. Toda T, Saito N, Ikarashi N, et al. Intestinal flora induces the expression of Cyp3a in the mouse liver. *Xenobiotica*. 2009;39(4):323-334. doi:10.1080/00498250802651984
13. Toda T, Ohi K, Kudo T, et al. Ciprofloxacin suppresses Cyp3a in mouse liver by reducing lithocholic acid-producing intestinal flora. *Drug Metab Pharmacokinet*. 2009;24(3):201-208. doi:10.2133/dmpk.24.201
14. Macrolide Antibiotics. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
15. Dinos GP. The macrolide antibiotic renaissance. *Br J Pharmacol*. 2017;174(18):2967-2983. doi:10.1111/bph.13936
16. Hill K, Sucha E, Rhodes E, et al. Risk of hospitalization with hemorrhage among older adults taking clarithromycin vs azithromycin and direct oral anticoagulants. *JAMA Intern Med*. 2020;180(8):1052-1060. doi:10.1001/jamainternmed.2020.1835
17. Chang SH, Chou IJ, Yeh YH, et al. Association between use of non-vitamin K oral anticoagulants with and without concurrent medications and risk of major bleeding in nonvalvular atrial fibrillation. *JAMA*. 2017;318(13):1250-1259. doi:10.1001/jama.2017.13883
18. Wang CL, Wu VC, Chang KH, et al. Assessing major bleeding risk in atrial fibrillation patients concurrently taking non-vitamin K antagonist oral anticoagulants and antiepileptic drugs. *Eur Heart J Cardiovasc Pharmacother*. 2019;6(3):147-154. doi:10.1093/ehjcvp/pvz035
19. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf*. 2007;16(7):726-735. doi:10.1002/pds.1294
20. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11(1):450. doi:10.1186/1471-2458-11-450
21. Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. *Eur J Epidemiol*. 2017;32(9):765-773. doi:10.1007/s10654-017-0316-1
22. Rachidi S, Aldin ES, Greenberg C, Sachs B, Streiff M, Zeidan AM. The use of novel oral anticoagulants for thromboprophylaxis after elective major orthopedic surgery. *Expert Rev Hematol*. 2013;6(6):677-695. doi:10.1586/17474086.2013.853430
23. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7): e45-e67. doi:10.1164/rccm.201908-1581ST
24. Administration tFaD. Drug Development and Drug Interactions|Table of Substrates, Inhibitors and Inducers. 2020.
25. Flockhart DA, Thacker D, Mcdonald C, Desta Z. The Flockhart Cytochrome P450 Drug-Drug Interaction Table. In: Division of Clinical Pharmacology, Indiana University School of Medicine, 2021.
26. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc Natl Acad Sci USA*. 2011;108(Suppl 1):4554-4561. doi:10.1073/pnas.1000087107
27. Hudson M, Rahme E, Richard H, Pilote L. Comparison of measures of medication persistency using a prescription drug database. *Am Heart J*. 2007;153(1):59-65. doi:10.1016/j.ahj.2006.10.018
28. Alexander SP, Christopoulos A, Davenport AP, et al. The Concise Guide To PHARMACOLOGY 2021/22: G protein-coupled receptors. *Br J Pharmacol*. 2021;178(Suppl 1):S27-s156. doi:10.1111/bph.15538
29. Douros A, Grabowski K, Stahlmann R. Safety issues and drug-drug interactions with commonly used quinolones. *Expert Opin Drug Metab Toxicol*. 2015;11(1):25-39. doi:10.1517/17425255.2014.970166
30. Kuno T, Hirayama-Kurogi M, Ito S, Ohtsuki S. Effect of intestinal flora on protein expression of drug-metabolizing enzymes and transporters in the liver and kidney of germ-free and antibiotics-treated mice. *Mol Pharm*. 2016;13(8):2691-2701. doi:10.1021/acs.molpharmaceut.6b00259
31. Komen JJ, Pottegård A, Mantel-Teeuwisse AK, et al. Persistence and adherence to non-vitamin K antagonist oral anticoagulant treatment in patients with atrial fibrillation across five Western European countries. *EP Europace*. 2021;23(11):1722-1730. doi:10.1093/europace/euab091
32. Weist K, Muller A, Monnet D, Heuer O. Surveillance of antimicrobial consumption in Europe 2012. 2014. European Centre for Disease Prevention and Control, [online] Stockholm, Sweden. Available: http://ecdceuropaeu/en/publications/Publications/antimicrobial-consumptioneurope-esac-net-2012pdf [accessed 22-May-2015]

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Yagi T, Mannheimer B, Reutfors J, et al. Bleeding events among patients concomitantly treated with direct oral anticoagulants and macrolide or fluoroquinolone antibiotics. *Br J Clin Pharmacol*. 2023;89(2): 887-897. doi:10.1111/bcp.15531