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Risk of Hospitalization With Hemorrhage Among Older Adults Taking Clarithromycin vs Azithromycin and Direct Oral Anticoagulants

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IMPORTANCE Clarithromycin is a commonly prescribed antibiotic associated with higher levels of direct oral anticoagulants (DOACs) in the blood, with the potential to increase the risk of hemorrhage.

OBJECTIVE To assess the 30-day risk of a hospital admission with hemorrhage after coprescription of clarithromycin compared with azithromycin among older adults taking a DOAC.

DESIGN, SETTING, AND PARTICIPANTS This population-based, retrospective cohort study was conducted among adults of advanced age (mean [SD] age, 77.6 [7.2] years) who were newly coprescribed clarithromycin (n = 6592) vs azithromycin (n = 18 351) while taking a DOAC (dabigatran, apixaban, or rivaroxaban) in Ontario, Canada, from June 23, 2009, to December 31, 2016. Cox proportional hazards regression was used to examine the association between hemorrhage and antibiotic use (clarithromycin vs azithromycin). Statistical analysis was performed from December 23, 2019, to March 25, 2020.

MAIN OUTCOMES AND MEASURES Hospital admission with major hemorrhage (upper or lower gastrointestinal tract or intracranial). Outcomes were assessed within 30 days of a coprescription.

RESULTS Among the 24 943 patients (12 493 women; mean [SD] age, 77.6 [7.2] years) in the study, rivaroxaban was the most commonly prescribed DOAC (9972 patients [40.0%]), followed by apixaban (7953 [31.9%]) and dabigatran (7018 [28.1%]). Coprescribing clarithromycin vs azithromycin with a DOAC was associated with a higher risk of a hospital admission with major hemorrhage (51 of 6592 patients [0.77%] taking clarithromycin vs 79 of 18 351 patients [0.43%] taking azithromycin; adjusted hazard ratio, 1.71 [95% CI, 1.20-2.45]; absolute risk difference, 0.34%). Results were consistent in multiple additional analyses.

CONCLUSIONS AND RELEVANCE This study suggests that, among adults of advanced age taking a DOAC, concurrent use of clarithromycin compared with azithromycin was associated with a small but statistically significantly greater 30-day risk of hospital admission with major hemorrhage.

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Supplemental content

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Anticoagulant-associated hemorrhage is one of the most common adverse drug reactions requiring hospitalization among individuals of advanced age, with a 2-fold increase among those older than 75 years.[1] Identification and avoidance of dangerous drug-drug interactions are associated with a significant reduction in adverse events and improvement in evidence-based prescription patterns.

During the last decade, direct oral anticoagulants (DOACs) have supplanted traditional vitamin K antagonists as the anticoagulation drugs of choice.[2] Large phase 3 trials have demonstrated noninferiority or superiority of DOACs relative to traditional anticoagulants (warfarin) for effectiveness in stroke prevention for those who have atrial fibrillation and for prevention and treatment of venous thromboembolism.[3-11] Patient preferences for DOACs are based on their simplicity of use, with no need for routine bloodwork monitoring.[12] As such, recent guidelines recommend DOACs as the first-line agents for the prevention of stroke in patients with nonvalvular atrial fibrillation (strong recommendation; high-quality evidence) and the treatment of venous thromboembolism.[13,14] Direct oral anticoagulants have 2 predominant mechanisms of metabolism: P-glycoprotein (Pgp) cell transporters, which are involved in transcellular transportation, and the cytochrome P450 enzyme CYP3A4, which is involved in the metabolism in the human liver.[15] Dabigatran etexilate mesylate requires efflux transportation by the Pgp system but is independent of the cytochrome P450 enzyme system.[16] Apixaban and rivaroxaban are heavily reliant on the CYP3A4 enzyme complexes for hepatic metabolism.[17]

Despite the widespread adoption of DOACs, their safety and drug interaction profile are not fully understood. Medications, such as some antibiotics, that act on these pathways have the potential to alter DOAC metabolism or excretion and change serum levels.[18] Clarithromycin is a commonly prescribed macrolide antibiotic used in the treatment of respiratory infections, uncomplicated skin and soft tissue infections, nontuberculous mycobacterial infections, *Helicobacter pylori* eradication, and streptococcal pharyngitis.[19-22] It is a potent inhibitor of CYP3A4 and Pgp. Multiple pharmacokinetic studies have demonstrated that concomitant use of apixaban, rivaroxaban, or dabigatran with clarithromycin increases serum levels of DOACs by 20% to 100% and prolongs coagulation time.[23-33] In contrast, a similar and comparable macrolide class antibiotic, azithromycin, demonstrates minimal CYP3A4 and Pgp inhibition.[34] Although this interaction would imply that combined use of a DOAC and clarithromycin would increase adverse bleeding events, whether this is clinically relevant remains unknown, to our knowledge. Nevertheless, based on the pharmacokinetic data, warnings about the concurrent use of strong CYP3A4 inhibitors and a heightened hemorrhagic risk are included on DOAC product monographs.[35-37] In addition, recent treatment guidelines recommend DOAC dose adjustments with clarithromycin use or suggest selecting an alternative anticoagulation agent.[14,38-40]

Because knowledge of the risk of bleeding with concurrent DOACs and clarithromycin is limited, we examined whether the risk of bleeding was elevated among patients taking DOACs who were treated with concurrent clarithromycin compared with azithromycin. We hypothesized that concomitant DOAC and clarithromycin use would be associated with an elevated risk of hemorrhagic events.

Key Points

Question Is the concurrent use of clarithromycin among older adult patients taking direct oral anticoagulants associated with a higher 30-day risk of hospitalization for major hemorrhage compared with azithromycin?

Findings In this population-level cohort study of 24 943 older adults taking direct oral anticoagulants, clarithromycin was associated with an adjusted 1.71-fold higher rate of hospitalization (absolute risk difference, 0.34%) within 30 days for a major hemorrhage event compared with azithromycin.

Meaning The use of clarithromycin was associated with a high rate of hemorrhage among older adults taking direct oral anticoagulants compared with azithromycin and poses a potential drug-drug interaction.

Methods

Data Sources

We used deidentified, linked databases housed at the Institute for Clinical Sciences (ICES; see eTable 1 in the Supplement for description of databases used in this study). Demographic characteristics and vital status information were obtained from the Ontario Registered Persons Database. Medication information was obtained from the Ontario Drug Benefit Claims database. Ontario is Canada's largest province, with more than 13 million residents.[41] All citizens have access to universal public health care, with drug coverage for individuals older than 65 years. This database contains highly accurate records of all outpatient prescriptions dispensed to patients 65 years or older, with an error rate of less than 1%.[42] Diagnostic and procedural information from all hospitalizations was determined using the Canadian Institute for Health Information Discharge Abstract Database. Diagnostic information from emergency department visits was determined using the National Ambulatory Care Reporting System. Information was also obtained from the Ontario Health Insurance Plan database, which contains all claims for inpatient and outpatient physician services. Whenever possible, we defined patient characteristics and outcomes using validated codes. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. The study used deidentified data and patient consent was waived as per the Ontario Ministry of Health. The reporting of this study follows guidelines for observational studies (eTable 2 in the Supplement).[43]

Design and Setting

The study population included all adults in Ontario, Canada, 66 years or older from June 23, 2009 (the first date that DOACs were added to the Ontario Drug Formulary), to December 31, 2016 (eFigure 1 in the Supplement). Prescription drug information is available for all adults older than 65 years in Ontario; we initiated our cohort at 66 years to allow for a 1-year look-back period for existing medications. We identified an exposed cohort of individuals who received a new prescription for a DOAC (apixaban, dabigatran, or rivaroxaban). We then identified a subset of patients who received a prescription for clarithromycin (exposure of interest) or azithromycin (active comparator; eTable 3 in the Supplement). Azithromycin is also a macrolide class antimicrobial; however, it demonstrates very weak CYP3A4 and Pgp inhibition relative to clarithromycin.[18] It is a well-suited comparator for clarithromycin because it is prescribed to similar ambulatory patient populations in terms of characteristics, comorbid illnesses, medication use, cause of infection, prescribing physician, and hemorrhagic risk.[34] The antibiotic dispensing date served as the study index date, and patients with prior use of other potent CYP3A4 or Pgp inhibitors during the 90-day look-back period from index (medications included conazole antifungals, tacrolimus, cyclosporine, quinines, and rifampin [eTable 4 in the Supplement]) were excluded. Clarithromycin users (exposure group) were compared with azithromycin users with follow-up for the outcome of interest of up to 30 days after index date. Discontinuaton of the DOAC drug was defined as no refill within 1.5 times the original prescription length plus 90 days. Individuals undergoing dialysis or those who had received a kidney transplant were excluded.

Outcomes

The study outcome was a hospital admission or emergency department visit with major hemorrhage up to 30 days after dispensing of the study antibiotic (see eTable 5 in the Supplement for outcome definitions). The following types of hemorrhage were included in the outcome of major hemorrhage: upper or lower gastrointestinal, intracerebral, subarachnoid, and other nontraumatic intracranial (sensitivity, 94%; positive predictive value, 87%).[44] Hospitalizations with a diagnosis of hemorrhage were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) codes in the Canadian Institute for Health Information Discharge Abstract Database.

Study Design

We compared all patients taking DOACs who received a prescription for clarithromycin with all patients taking DOACs who received a prescription for azithromycin using a cohort study design. Potential confounders examined included demographic characteristics (age, sex, income, and place of residence), index year, comorbid illnesses (history of hemorrhage, hypertension, diabetes, stroke, atrial fibrillation, acute coronary syndrome, heart failure, coronary artery disease, coronary artery bypass grafting, percutaneous coronary intervention, peripheral vascular disease, and venous thromboembolism), health care use (numbers of hospitalizations and emergency department visits in the preceding 5 years), and medications (β-blockers, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, antiplatelet agents, selective serotonin reuptake inhibitors, and statins).

Additional Analyses

We conducted a number of additional analyses. First, we performed a self-controlled case series (SCCS), a variation of the case-control design in which all patients taking DOACs who experienced a hemorrhage (cases) would be examined for hemorrhage risk by comparing period(s) of exposure to clarithromycin vs period(s) of nonexposure[45] (eFigure 2 in the Supplement). The risk of hemorrhage would be compared within the same individual. Thereby, an individual serves as their own control, limiting confounding other than for time and potential time-varying characteristics, for which additional adjustment is performed. Further strengths of the SCCS study design include it allowing for recurrent exposures and/or repeated outcome events, it is well suited to short exposure periods, and it has been previously used specifically to examine drug interactions.[46-49] We identified time periods of exposure as 30 days from the dispensing date of a study antibiotic. Time periods of nonexposure were defined as all study time in which none of the study antibiotics were prescribed and the individual continued to take a DOAC. The DOAC prescription date was used as the start of follow-up, and individuals were followed up until death, DOAC discontinuation, or the maximum follow-up date. Second, we repeated all analyses using a liberal definition of hemorrhage that included any bleeding event or receipt of a blood transfusion with presentation to an emergency department or hospitalization. Third, we excluded those with a history of *H pylori* infection (3-year look back) because it is a common indication for clarithromycin and may predispose to gastrointestinal-related hemorrhage (identified by *ICD-10* code B96.81; positive predictive value, 97.4%).[50] Fourth, we repeated our models using inverse treatment probability weighting incorporating all covariates listed in **Table 1**, including duration of prior DOAC use. Fifth, we repeated our models examining fracture and the composite of depression and anxiety as negative outcomes. Sixth, we repeated our models in days 30 to 90 after antibiotic prescription to examine whether the association was attenuated after completion of the antibiotic course. Seventh, we repeated our models for individuals with known kidney function (using estimated glomerular filtration rate by the chronic kidney disease–epidemiology collaboration formula).

Statistical Analysis

Statistical analysis was performed from December 23, 2019, to March 25, 2020. For the cohort study, we used standardized differences to assess baseline characteristics by exposure status (clarithromycin vs azithromycin). Standardized differences describe differences between group mean values relative to the pooled SD and are less sensitive to large sample sizes than traditional hypothesis testing, and a significant difference is considered to be 10% or greater.[51] We examined the association of clarithromycin vs azithromycin exposure and hemorrhage using Cox proportional hazards regression models. Schoenfeld residuals were examined to test the proportionality assumption. Only the first hemorrhage event was considered. Models were adjusted for variables detected to be different by a standardized difference greater than 10% between the 2 groups. To examine for effect modification by DOAC type (apixaban, dabigatran, or rivaroxaban), separate models with interaction terms were examined. For the SCCS, we used conditional Poisson regression models to determine the rate ratio of hemorrhage during clarithromycin exposure compared with nonexposure periods, adjusting for time as a continuous variable.[45] Recurrent outcome events were included in the SCCS analysis. For the inverse probability treatment weighting, we calculated weights including all covariates listed in Table 1. We then used Cox proportional hazards regression models with the applied stabilized weights truncated at the first and 99th percentile. We conducted all analyses with SAS Enterprise software, version 7.1 (SAS Institute Inc). The 95% CIs that did not overlap with 1 were treated as statistically significant. All *P* values were from 2-sided tests and results were deemed statistically significant at $P < .05$.

Results

From a total of 24 943 unique patients taking DOACs, we identified 6592 (26.4%) who received clarithromycin and 18 351 (73.6%) who received azithromycin during the study period (Table 1). A total of 9025 patients (36.2%) were between 66 and 75 years of age, and 22 075 (88.5%) resided in urban centers. Concurrent antibiotic and DOAC use increased over time. The most common comorbidities were hypertension (21 657 [86.8%]) and diabetes (8827 [35.4%]). β-Blockers were

Table 1. Baseline Patient Characteristics for the Cohort Study Comparing Clarithromycin and Azithromycin Among Patients Taking DOACs

Characteristic	Patients, No. (%) Clarithromycin (n = 6592)	Patients, No. (%) Azithromycin (n = 18 351)	Standardized difference[a]
Female sex	3238 (49.1)	9255 (50.4)	0.03
Age group, y			
66-75	2523 (38.3)	6502 (35.4)	0.06
76-85	2850 (43.2)	7847 (42.8)	0.01
86-95	1177 (17.9)	3827 (20.9)	0.08
>95	42 (0.6)	175 (1.0)	0.04
Income quintiles			
1 (Low)	1362 (20.7)	4001 (21.8)	0.03
2	1336 (20.3)	3875 (21.1)	0.02
3	1345 (20.4)	3672 (20.0)	0.01
4	1243 (18.9)	3254 (17.7)	0.03
5 (High)	1287 (19.5)	3510 (19.1)	0.01
Rural residence	769 (11.7)	2099 (11.4)	0.01
Index year			
2009	9 (0.1)	6 (0.03)	0.04
2010	25 (0.4)	27 (0.1)	0.05
2011	41 (0.6)	23 (0.1)	0.08
2012	695 (10.5)	1176 (6.4)	0.15
2013	1537 (23.3)	2653 (14.5)	0.23
2014	1548 (23.5)	3798 (20.7)	0.07
2015	1394 (21.1)	4820 (26.3)	0.12
2016	1343 (20.4)	5848 (31.9)	0.26
Comorbid illness			
Prior hemorrhage			
Major	255 (3.9)	395 (2.2)	0.10
Any	545 (8.3)	1221 (6.7)	0.06
Hypertension	5651 (85.7)	16 006 (87.2)	0.04
Diabetes	2360 (35.8)	6467 (35.2)	0.01
Stroke or transient ischemic attack	208 (3.2)	652 (3.6)	0.02
Atrial fibrillation or flutter	1660 (25.2)	5260 (28.7)	0.08
Myocardial infarction	110 (1.7)	379 (2.1)	0.03
Heart failure	1479 (22.4)	4643 (25.3)	0.07
Coronary artery disease	1712 (26.0)	4871 (26.5)	0.01
Coronary artery bypass grafting	197 (3.0)	581 (3.2)	0.01
Percutaneous cardiac intervention	424 (6.4)	1315 (7.2)	0.03
Peripheral vascular disease	158 (2.4)	526 (2.9)	0.03
Venous thromboembolism	212 (3.2)	717 (3.9)	0.04
Health care use, median (IQR), No. of visits			
Hospitalizations	1 (1-2)	1 (1-2)	0.07
Emergency department visits	2 (1-3)	2 (1-3)	0.09
Medications			
β-Blocker	3794 (57.6)	10 642 (58.0)	0.01
NSAID	676 (10.3)	1547 (8.4)	0.06
Proton pump inhibitor	3332 (50.5)	7854 (42.8)	0.16
Antiplatelet agent	257 (3.9)	707 (3.9)	0.00
SSRI	862 (13.1)	2539 (13.8)	0.02
Statin	4082 (61.9)	11 758 (64.1)	0.04
DOAC			
Apixaban	1612 (24.5)	6341 (34.6)	0.22
Dabigatran	2224 (33.7)	4794 (26.1)	0.17
Rivaroxaban	2756 (41.8)	7216 (39.3)	0.05

(continued)

Table 1. Baseline Patient Characteristics for the Cohort Study Comparing Clarithromycin and Azithromycin Among Patients Taking DOACs (continued)

Characteristic	Patients, No. (%) Clarithromycin (n = 6592)	Azithromycin (n = 18 351)	Standardized difference[a]
DOAC daily dose, mean (SD), mg			
Apixaban	7.41 (2.8)	7.49 (4.7)	0.23
Dabigatran	256.94 (212.9)	250.31 (146.4)	0.04
Rivaroxaban	17.47 (3.5)	17.9 (6.7)	0.46
Time taking DOAC prior to antibiotic exposure, mean (SD), d	390.4 (367.1)	380.5 (360.1)	0.11
eGFR, mL/min/1.73 m^2			
>60	3546 (53.8)	9772 (53.3)	0.01
30-60	1983 (30.1)	5938 (32.4)	0.04
<30	103 (1.6)	331 (1.8)	0.02
Missing	960 (14.6)	2310 (12.6)	0.06

Abbreviations: DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate by chronic kidney disease–epidemiology collaboration equation; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

[a] Standardized differences greater than 0.1 are statistically significant.

Table 2. Thirty-Day Rate of Hemorrhage With Clarithromycin vs Azithromycin Among Patients Taking DOACs

Characteristic	No. of events	Cumulative incidence, %	HR (95% CI) Unadjusted	Adjusted
Major hemorrhage				
Clarithromycin	51/6592	0.77	1.81 (1.27-2.57)	1.71 (1.20-2.45)[a]
Azithromycin	79/18 351	0.43		
Any hemorrhage or receipt of pRBC transfusion				
Clarithromycin	109/6592	1.65	1.53 (1.21-1.93)	1.53 (1.21-1.94)[a]
Azithromycin	199/18 351	1.08		

Abbreviations: DOAC, direct oral anticoagulant; HR, hazard ratio; pRBC, packed red blood cell transfusion.

[a] Model adjusted for proton pump inhibitors, DOAC type, and daily DOAC dose.

prescribed for 14 436 patients (57.9%), and statins were prescribed for 15 840 patients (63.5%). There was little difference between the 2 groups, with the exceptions of index year of cohort entry, proton pump inhibitor use, mean daily DOAC dose, and DOAC type. Rivaroxaban was the most commonly used DOAC (9972 [40.0%]), followed by apixaban (7953 [31.9%]) and dabigatran (7018 [28.1%]). The mean (SD) daily dose of apixaban and rivaroxaban was lower among clarithromycin users than azithromycin users (apixaban, 7.41 [2.8] vs 7.49 [4.7] mg; rivaroxaban, 17.47 [3.5] vs 17.9 [6.7] mg), and the mean (SD) duration of DOAC use prior to antibiotic exposure was longer for azithromycin users than clarithromycin users (390 [0.11] vs 353 [0.11] days). Kidney function was measured for 21 673 patients (86.9%), with 8355 (33.5%) having a baseline estimated glomerular filtration rate of 60 mL/min/1.73m^2 or less, and did not differ between the 2 groups.

A total of 130 hemorrhagic events (0.52%) occurred within 30 days using the stringent outcome definition, and 308 hemorrhagic events (1.23%) occurred within 30 days using the more liberal outcome definition (**Table 2**). Major hemorrhage occurred in 51 of 6592 patients (0.77%) taking clarithromycin and 79 of 18 351 patients (0.43%) taking azithromycin. The crude incident rate for major hemorrhage was higher among patients taking clarithromycin compared with those taking azithromycin (95.9 [95% CI, 89.3-102.9] per 1000 person-years for clarithromycin users vs 53.1 [95% CI, 50.2-56.2] per 1000 person-years for azithromycin users). The higher rate with clarithromycin was consistent after adjustment for proton pump inhibitor use, DOAC type, and DOAC mean daily dose (hazard ratio [HR], 1.71 [95% CI, 1.20-2.45]). Neither outcome differed by DOAC type.

In additional analyses, we identified 744 major hemorrhage events among 647 unique individuals taking DOACs who were exposed to clarithromycin in the SCCS (**Table 3**). A total of 69 events occurred during periods of clarithromycin use, whereas 675 occurred during period of clarithromycin nonuse. More than one-third of patients had a history of major hemorrhage, a history of atrial fibrillation, diabetes, or cardiac disease. Use of β-blockers (396 [61.2%]), proton pump inhibitors (404 [62.4%]), and statins (411 [63.5%]) was frequent. The most commonly used DOAC was rivaroxaban (276 [42.7%]), followed by dabigtran (191 [29.5%]) and apixaban (180 [27.8%]). Major hemorrhagic events were associated with concurrent clarithromycin and DOAC use compared with DOAC use alone (rate ratio, 1.44 [95% CI, 1.08-1.92]) (**Table 4**).

Our findings were consistent using the more broad definition of hemorrhage in the cohort study (308 of 24 943 events [1.2%]; clarithromycin, 109 of 6592 events [1.7%]; azithromycin, 199 of 18 351 events [1.1%]), with a higher incident rate for hemorrhage with clarithromycin use (204.8 [95% CI, 191.3-219.7] vs 133.7 [95% CI, 127.0-140.8]) and in the SCCS (1760 total events; periods of clarithromycin use, 145 events; periods of clarithromycin nonuse, 1615 events; rate ratio, 1.64 [95% CI, 1.35-1.98]) and after exclusion of individuals with a history of *H pylori* infection (HR, 1.53 [95% CI, 1.21-1.95]) in the cohort study. Our findings were consistent in inverse probability of treatment weighting models (major hemorrhage: HR, 1.77 [95% CI, 1.20-2.59]; any hemorrhage: HR, 1.50 [95% CI,

Table 3. Baseline Characteristics of Patients Taking DOACs and Concurrent Clarithromycin With a Major Hemorrhage Event Included in a Self-controlled Case Series

Characteristic	Patients, No. (%) (n = 647)
Female sex	296 (45.7)
Age group, y	
66-75	190 (29.4)
76-85	296 (45.7)
86-95	153 (23.6)
>95	8 (1.2)
Income quintiles	
1 (Low)	138 (21.3)
2	136 (21.0)
3	151 (23.3)
4	116 (17.9)
5 (High)	106 (16.4)
Rural	138 (21.3)
Index year	
2011	Suppressed[a]
2012	79 (12.2)
2013	125 (19.3)
2014	160 (24.7)
2015	155 (24.0)
2016	125 (19.3)
Comorbid illness	
Major hemorrhage	227 (35.1)
Hypertension	568 (87.8)
Diabetes	243 (37.6)
Stroke or transient ischemic attack	33 (5.1)
Atrial fibrillation or flutter	263 (40.6)
Myocardial infarction	20 (3.1)
Heart failure	246 (38.0)
CAD, excluding angina	209 (32.3)
Coronary artery bypass grafting	36 (5.6)
Percutaneous coronary intervention	49 (7.6)
Peripheral vascular disease	28 (4.3)
Venous thromboembolism	21 (3.2)
Health care use, median (IQR), No. of visits	
Hospitalizations	1 (1-2)
Emergency department visits	2 (1-4)
Medications	
β-Blocker	396 (61.2)
NSAID	60 (9.3)
Proton pump inhibitor	404 (62.4)
Antiplatelet agent	43 (6.6)
SSRI	72 (11.1)
Statin	411 (63.5)
DOAC type	
Apixaban	180 (27.8)
Dabigatran	191 (29.5)
Rivaroxaban	276 (42.7)
DOAC daily dose, mean (SD), mg	
Apixaban	6.49 (2.31)
Dabigatran	236.64 (45.85)
Rivaroxaban	17.29 (3.52)

Abbreviations: CAD, coronary artery disease; DOAC, direct oral anticoagulant; IQR interquartile range; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

[a] Categories with fewer than 5 events were suppressed as per Institute for Clinical Sciences policy.

Table 4. Rate Ratio of Hemorrhage Events With Concurrent Clarithromycin and Direct Oral Anticoagulant Use From a Self-controlled Case Series

Outcome	No. of patients/No. of events	No. of events during periods taking clarithromycin/person-years taking clarithromycin	No. of events during periods without clarithromycin/person-years without clarithromycin	Rate ratio (95% CI)
Major hemorrhage	647/744	69/18 003	675/557 237	1.44 (1.08-1.92)
Any hemorrhage or receipt of pRBC transfusion	1491/1760	145/41 857	1615/1 460 379	1.64 (1.35-1.98)

Abbreviation: pRBC, packed red blood cell.

1.16-1.93]) (see eTable 6 in the Supplement for additional analyses). No association was identified with an antibiotic and either negative outcome (fracture: clarithromycin, 17 of 6592 events [0.3%]; azithromycin, 65 of 18 351 events [0.4%]; adjusted HR, 0.73 [95% CI, 0.43-1.73]; and anxiety and depression: clarithromycin, 11 of 6592 events [0.2%]; azithromycin, 35 of 18 351 events [0.2%]; adjusted HR, 0.87 [95% CI, 0.44-1.71]). When we examined the hemorrhage rate in days 30 to 90, the association was attenuated (major hemorrhage: HR, 1.13 [95% CI, 0.81-1.57]; any hemorrhage: HR, 1.05 [95% CI, 0.84-1.31]). Last, the association persisted in models accounting for kidney function (major hemorrhage: HR, 1.72 [95% CI, 1.17-2.52]; any hemorrhage: HR, 1.44 [95% CI, 1.12-1.86]).

Discussion

In a retrospective cohort study of patients taking DOACs, we found that the 30-day rate of hemorrhage requiring hospitalization or an emergency department visit after dispensing of clarithromycin was higher relative to azithromycin. Furthermore, the hemorrhage rate was similarly elevated when comparing periods of clarithromycin use with periods of nonuse within the same individual. These findings were consistent when a more broad-based definition for hemorrhage was used that included receipt of a blood transfusion, after excluding individuals with a history of *H pylori* infection, using alternative methods of controlling for confounding (inverse probability of treatment weighting), and limited to patients with known kidney function. No association was evident using negative controls or in the 30- to 90-day follow-up period after antibiotic administration. Our results suggest that the coadministration of clarithromycin and DOACs poses a small but significant drug-drug interaction and a higher clinical 30-day rate of hemorrhage.

To date, limited clinical evidence exists on the use of clarithromycin with DOACs. Fralick et al[23] reported a single case in which a patient taking rivaroxaban experienced spontaneous intracranial and pulmonary hemorrhages after being started on clarithromycin. The patient's anti-Xa level, measured more than 30 hours after the last reported dose of rivaroxaban, was 537 µg/L (normal 24-hour trough level, 8-150 µg/L), suggesting significantly elevated serum levels at the time of bleeding. Chang et al[52] evaluated the clinical risk of bleeding when DOACs were combined with other medications. With 4770 major bleeding events seen in the 91 330 patients who were taking a DOAC and followed up for 1 year, they found a paradoxical decreased adjusted incidence rate of bleeding in patients who received clarithromycin or erythromycin. The investigators postulated that this lower bleeding rate was the result of a decrease in gastrointestinal bleeding, secondary to clarithromycin use in the treatment of *H pylori* peptic ulcers, which may outweigh the increased risk of bleeding from elevated DOAC levels. However, this possibility was untested, discrepant with the existing pharmacokinetic evidence and potentially due to residual confounding, leading to further clinical uncertainty.[53]

With regard to the clinical significance of our study, to our knowledge, this is the largest study to date examining clinically relevant bleeding with concomitant use of DOACs and clarithromycin. We used 2 different but complementary study designs that demonstrated consistency. From a clinical perspective, the risk of major hemorrhage observed was less than 1.0% overall with clarithromycin use, with an absolute difference of 0.34% (roughly 1 in 300 exposures) between clarithromycin and azithromycin. Thereby, an individual's hemorrhage risk, indication for anticoagulation, and availability of a suitable antibiotic substitute need to be carefully considered. In scenarios in which DOAC and clarithromycin are concurrently administered, our findings suggest a potential role for monitoring DOAC levels to prevent supratherapeutic levels.

Direct oral anticoagulant levels appear to be consistently increased with concurrent clarithromycin use based on pharmacokinetic and pharmacodynamic studies.[15,24-26,29-33,36,37,53-56] For dabigatran, when combined with clarithromycin, the areas under the plasma concentration–time curves (AUCs) of dabigatran increased from 49% to 100%, and the peak serum concentrations of dabigatran increased from 60% to 80%. In the case of apixaban, increases were seen in both its AUC (60%) and peak serum concentration (30%). With rivaroxaban, a similar trend was seen with increases in both AUCs (50%-94%) and peak serum concentrations (40%-92%) with concomitant use of clarithromycin. Of the 3 DOACs evaluated, apixaban and rivaroxaban are dependent on CYP3A4 metabolism and should appear to pose more risk with clarithromycin exposure. We specifically examined for effect modification in our models and did not detect any difference in bleeding risk by DOAC. The inability to detect differences by DOAC types suggests that either there is no increased risk of hemorrhage with all 3 DOACs examined or, alternatively, there was an inability to detect differences owing to limited sample sizes.

Limitations

Our findings should be interpreted with the limitations of our study in mind. First, our population was composed exclusively of patients older than 66 years. Differences may exist between our patient cohort and a younger population. However, older patients are at a high risk for bleeding events given comorbidities, polypharmacy, and increased risk of falls.[57] Second, while our sample of patients exposed to DOACs and clarithromycin or azithromycin was quite large, the number of observed bleeding events in both groups was relatively small. Third, we did not examine for dosage adjustments in either DOACs or concurrent antibiotics at the time of prescription. Fourth, we excluded only potent CYP3A4 or Pgp inhibitors; other drugs with less potent inhibition may have been used. Fifth, unmeasured confounding may have occurred. Sixth, we identified patients based on prescription filling and are unable to make inferences on patient adherence to the medication. It was assumed that patients completed their full course of antibiotics and took their medications as prescribed, which may not have been true in all cases.

Conclusions

Among a large cohort of patients of advanced age (>66 years old) taking DOACs who were dispensed clarithromycin, there was a higher rate of hemorrhage requiring hospitalization compared with either azithromycin or periods of no clarithromycin use. Thus, the concurrent use of clarithromycin and DOACs poses a significant drug-drug interaction. Clinicians need to consider the risk of hemorrhage, the indication and microbial susceptibility of the infection being treated, and whether viable alternatives (either anticoagulant or antimicrobial) are readily available.

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REFERENCES

1. Canadian Institute for Health Information. *Adverse Drug Reaction–Related Hospitalizations Among Seniors, 2006 to 2011*. Canadian Institute for Health Information; 2013.

2. Weitz JI, Semchuk W, Turpie AGG, et al. Trends in prescribing oral anticoagulants in Canada, 2008-2014. *Clin Ther*. 2015;37(11):2506-2514. doi:10.1016/j.clinthera.2015.09.008

3. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151. doi:10.1056/NEJMoa0905561

4. Granger CB, Alexander JH, McMurray JJV, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992. doi:10.1056/NEJMoa1107039

5. Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011; 365(10):883-891. doi:10.1056/NEJMoa1009638

6. Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808. doi:10.1056/NEJMoa1302507

7. Bauersachs R, Berkowitz SD, Brenner B, et al; EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510. doi:10.1056/NEJMoa1007903

8. Büller HR, Prins MH, Lensin AW, et al; EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366(14):1287-1297. doi:10.1056/NEJMoa1113572

9. Büller HR, Décousus H, Grosso MA, et al; Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369(15):1406-1415. doi:10.1056/NEJMoa1306638

10. Schulman S, Kakkar AK, Goldhaber SZ, et al; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129(7):764-772. doi:10.1161/CIRCULATIONAHA.113.004450

11. Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361(24):2342-2352. doi:10.1056/NEJMoa0906598

12. Palacio AM, Kirolos I, Tamariz L. Patient values and preferences when choosing anticoagulants. *Patient Prefer Adherence*. 2015;9:133-138.

13. Skanes AC, Healey JS, Cairns JA, et al; Canadian Cardiovascular Society Atrial Fibrillation Guidelines Committee. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. *Can J Cardiol*. 2012;28(2):125-136. doi:10.1016/j.cjca.2012.01.021

14. Thrombosis Canada. Clinical guides. Accessed August 13, 2019. http://thrombosiscanada.ca/clinicalguides/#

15. Voukalis C, Lip GYH, Shantsila E. Drug-drug interactions of non–vitamin K oral anticoagulants. *Expert Opin Drug Metab Toxicol*. 2016;12(12):1445-1461. doi:10.1080/17425255.2016.1225037

16. Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics: clinical implications. *Clin Pharmacokinet*. 2003;42(1):59-98. doi:10.2165/00003088-200342010-00003

17. Lin JH, Lu AYH. Inhibition and induction of cytochrome P450 and the clinical implications. *Clin Pharmacokinet*. 1998;35(5):361-390. doi:10.2165/00003088-199835050-00003

18. Westphal JF. Macrolide-induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin. *Br J Clin Pharmacol*. 2000;50(4):285-295. doi:10.1046/j.1365-2125.2000.00261.x

19. Kanoh S, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. *Clin Microbiol Rev*. 2010;23(3):590-615. doi:10.1128/CMR.00078-09

20. Shulman ST, Bisno AL, Clegg HW, et al; Infectious Diseases Society of America. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2012;55(10):e86-e102. Published correction appears in *Clin Infect Dis*. 2014;58(10):1496. doi:10.1093/cid/cis629

21. Stevens DL, Bisno AL, Chambers HF, et al; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):e10-e52. Published correction appears in *Clin Infect Dis*. 2015;60(9):1448. doi:10.1093/cid/ciu296

22. Karlowsky JA, Lagacé-Wiens PRS, Low DE, Zhanel GG. Annual macrolide prescription rates and the emergence of macrolide resistance among *Streptococcus pneumoniae* in Canada from 1995 to 2005. *Int J Antimicrob Agents*. 2009;34(4):375-379. doi:10.1016/j.ijantimicag.2009.05.008

23. Fralick M, Juurlink DN, Marras T. Bleeding associated with coadministration of rivaroxaban and clarithromycin. *CMAJ*. 2016;188(9):669-672. doi:10.1503/cmaj.150580

24. Liesenfeld KH, Lehr T, Dansirikul C, et al. Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. *J Thromb Haemost*. 2011;9(11):2168-2175. doi:10.1111/j.1538-7836.2011.04498.x

25. Mueck W, Kubitza D, Becka M. Co-administration of rivaroxaban with drugs that share its elimination pathways: pharmacokinetic effects in healthy subjects. *Br J Clin Pharmacol*. 2013;76(3):455-466. doi:10.1111/bcp.12075

26. Delavenne X, Ollier E, Basset T, et al. A semi-mechanistic absorption model to evaluate drug-drug interaction with dabigatran: application with clarithromycin. *Br J Clin Pharmacol*. 2013;76(1):107-113. doi:10.1111/bcp.12055

27. Vranckx P, Valgimigli M, Heidbuchel H. The significance of drug-drug and drug-food interactions of oral anticoagulation. *Arrhythm Electrophysiol Rev*. 2018;7(1):55-61. doi:10.15420/aer.2017.50.1

28. Zhao Y, Hu Z-Y. Physiologically based pharmacokinetic modelling and *in vivo* $[I]/K_i$ accurately predict P-glycoprotein-mediated drug-drug interactions with dabigatran etexilate. *Br J Pharmacol*. 2014;171(4):1043-1053. doi:10.1111/bph.12533

29. Garonzik S, Byon W, Myers E, Li X, Marchisin D, Murthy B. The effects of clarithromycin on the pharmacokinetics of apixaban in healthy volunteers: a single-sequence crossover study. *Am J Cardiovasc Drugs*. 2019;19(6):561-567. doi:10.1007/s40256-019-00348-2

30. Gouin-Thibault I, Delavenne X, Blanchard A, et al. Interindividual variability in dabigatran and rivaroxaban exposure: contribution of *ABCB1* genetic polymorphisms and interaction with clarithromycin. *J Thromb Haemost*. 2017;15(2):273-283. doi:10.1111/jth.13577

31. Moj D, Maas H, Schaeftlein A, Hanke N, Gómez-Mantilla JD, Lehr T. A comprehensive whole-body physiologically based pharmacokinetic model of dabigatran etexilate, dabigatran and dabigatran glucuronide in healthy adults and renally impaired patients. *Clin Pharmacokinet*. 2019;58(12):1577-1593. doi:10.1007/s40262-019-00776-y

32. Stöllberger C, Finsterer J. Relevance of P-glycoprotein in stroke prevention with dabigatran, rivaroxaban, and apixaban. *Herz*. 2015;40(2)(suppl 2):140-145. doi:10.1007/s00059-014-4188-9

33. Xu R, Ge W, Jiang Q. Application of physiologically based pharmacokinetic modeling to the prediction of drug-drug and drug-disease interactions for rivaroxaban. *Eur J Clin Pharmacol*. 2018;74(6):755-765. doi:10.1007/s00228-018-2430-8

34. Fleet JL, Shariff SZ, Bailey DG, et al. Comparing two types of macrolide antibiotics for the purpose of assessing population-based drug interactions. *BMJ Open*. 2013;3(7):e002857. doi:10.1136/bmjopen-2013-002857

35. ELIQUIS (axpixaban). Product monograph. Accessed September 4, 2017. http://secure.healthlinks.net.au/content/bms/pi.cfm?product=bqpeliqu11112

36. Praxada (dabigatran etexilate). Product monograph. Accessed August 26, 2017. https://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000829/WC500041059.pdf

37. Xarelto (rivaroxaban). Product monograph. Accessed September 1, 2017. https://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944 /WC500057108.pdf

38. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv*. 2018;2(22):3257-3291. doi:10.1182/bloodadvances.2018024893

39. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315-352. doi:10.1016/j.chest.2015.11.026

40. Macle L, Cairns J, Leblanc K, et al; CCS Atrial Fibrillation Guidelines Committee. 2016 Focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. *Can J Cardiol*. 2016;32(10):1170-1185. doi:10.1016/j.cjca.2016.07.591

41. Statistics Canada. Population estimates on July 1st, by age and sex. Accessed May 1, 2018. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501

42. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Can J Clin Pharmacol*. 2003;10(2):67-71.

43. Benchimol EI, Smeeth L, Guttmann A, et al; RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med*. 2015;12(10):e1001885. doi:10.1371/journal.pmed.1001885

44. Wahl PM, Rodgers K, Schneeweiss S, et al. Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. *Pharmacoepidemiol Drug Saf*. 2010;19(6):596-603. doi:10.1002/pds.1924

45. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med*. 2006;25(10):1768-1797. doi:10.1002/sim.2302

46. Othman F, Crooks CJ, Card TR. Community acquired pneumonia incidence before and after proton pump inhibitor prescription: population based study. *BMJ*. 2016;355:i5813. doi:10.1136/bmj.i5813

47. Douglas IJ, Evans SJW, Hingorani AD, et al. Clopidogrel and interaction with proton pump inhibitors: comparison between cohort and within person study designs. *BMJ*. 2012;345:e4388. doi:10.1136/bmj.e4388

48. Masclee GMC, Valkhoff VE, Coloma PM, et al. Risk of upper gastrointestinal bleeding from different drug combinations. *Gastroenterology*. 2014;147(4):784-792.e9. doi:10.1053/j.gastro.2014.06.007

49. Suchard MA, Zorych I, Simpson SE, Schuemie MJ, Ryan PB, Madigan D. Empirical performance of the self-controlled case series design: lessons for developing a risk identification and analysis system. *Drug Saf*. 2013;36(1)(suppl 1):S83-S93. doi:10.1007/s40264-013-0100-4

50. Abraham NS, DeSilva R, Richardson P. Derivation and validation of an algorithm to identify *helicobacter pylori* infected patients using administrative data: 850. *Am J Gastroenterol*. 2007;102:S431. doi:10.14309/00000434-200709002-00850

51. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat*. 2009;38:1228-1234. doi:10.1080/03610910902859574

52. 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

53. Wang N, Giblin E, Rodgers JE. Drug interactions with non–vitamin K oral anticoagulants. *JAMA*. 2018;319(8):830. doi:10.1001/jama.2017.20850

54. Li Y, Dong S, Soria-Saucedo R. Drug interactions with non–vitamin K oral anticoagulants. *JAMA*. 2018;319(8):827-828. doi:10.1001/jama.2017.20830

55. Fralick M, Juurlink DN, Marras T. Bleeding associated with coadministration of rivaroxaban and clarithromycin. *CMAJ*. 2016;188(9):669-672. doi:10.1503/cmaj.150580

56. Gnoth MJ, Buetehorn U, Muenster U, Schwarz T, Sandmann S. In vitro and in vivo P-glycoprotein transport characteristics of rivaroxaban. *J Pharmacol Exp Ther*. 2011;338(1):372-380. doi:10.1124/jpet.111.180240

57. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest*. 2008;133(6)(suppl):257S-298S. doi:10.1378/chest.08-0674