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Potential interactions between antimicrobials and direct oral anticoagulants: Population-based cohort and case-crossover study

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ABSTRACT

BACKGROUND Although drug interactions between clarithromycin/erythromycin/fluconazole and direct oral anticoagulants (DOACs) are mechanistically plausible, it is uncertain whether they are clinically relevant.

OBJECTIVE This study aims to investigate the association among coprescribed DOACs and antimicrobials and bleeding, cardiovascular disease and mortality.

METHODS We identified DOAC users in the Clinical Practice Research Datalink Aurum from January 1, 2011 to March 29, 2021. We used a cohort design to estimate hazard ratios (HRs) for bleeding outcomes (intracranial bleeding, gastrointestinal bleeding, other bleeding), comparing DOACs + clarithromycin/erythromycin/fluconazole users with DOACs users not receiving these antimicrobials. Cardiovascular outcomes were ischaemic stroke, myocardial infarction, venous thromboembolism, cardiovascular mortality, and all-cause mortality. A 6-parameter case-crossover design comparing odds of exposure with different drug initiation patterns for all outcomes in hazard window vs referent window within an individual was also conducted.

RESULTS Of 483,815 DOAC users, we identified 21,701 coprescribed clarithromycin, 4532 coprescribed erythromycin, and 4840 coprescribed fluconazole. We observed an increased risk of gastrointestinal bleeding over 7 days following coprescription of DOAC + erythromycin vs DOAC alone (HR 3.66; 99% confidence interval [CI] 1.27–10.51), with wide CIs in case-crossover analysis. No evidence of increased risk of bleeding outcomes was seen for DOAC + clarithromycin/fluconazole in cohort and case-crossover analyses. For cardiovascular outcomes, compared with DOAC alone, an increased risk of cardiovascular mortality with DOAC + clarithromycin (HR 3.36; 99% CI 1.73–6.52) and increased risk of all-cause mortality with DOAC + clarithromycin/erythromycin/fluconazole were observed in cohort analysis. However, similar risks were found when initiating erythromycin/fluconazole with and without DOACs.

CONCLUSION We found no strong evidence of increased risks of bleeding and cardiovascular outcomes in DOACs + clarithromycin/fluconazole/erythromycin users except a possible short-term increased risk of gastrointestinal bleeding in DOACs + erythromycin users.

KEYWORDS Anticoagulants; Drug interactions; Macrolides; Fluconazole

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Introduction

Direct oral anticoagulants (DOACs) are commonly used in patients with atrial fibrillation (AF) and venous thromboembolism (VTE). They are substrates for the efflux transporter P-glycoprotein and are metabolised by the cytochrome P450 system (CYP3A4 enzymes).[1]

Macrolide antibiotics including clarithromycin, erythromycin, and an antifungal drug fluconazole are commonly used for treatment of respiratory bacterial infections and fungal infections respectively.[2,3] However, as they are CYP3A4 inhibitors or p-glycoprotein inhibitors,[4] their coprescription with DOACs could result in an increased risk of

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DOAC side effects. British National Formulary guidance recommends avoiding itraconazole and ketoconazole prescription among people receiving some DOACs, but there are no clear recommendations for fluconazole, despite hypothetical risks based on a biologically plausible mechanism.[5,6] Despite these drugs predicted to interact with DOACs based on biological mechanisms of action, the current evidence for clinically meaningful interactions between DOACs and antimicrobials is limited and conflicting,[7–13] leading to uncertainty when coprescribing these medications. There is also no clear recommendation about coprescription of these drugs on the drug labels.

Therefore, this population-based study aimed to investigate the risk of serious clinical outcomes associated with combined use of DOAC and clarithromycin, erythromycin, or fluconazole compared with DOAC therapy alone using routine clinical data in England in 2 study designs.

Method

Study design

We conducted both cohort and case-crossover studies (see Supplemental Figure S1 and Figure S2 for design illustrations).

Data Source

We used data from the Clinical Practice Research Datalink (CPRD) Aurum. It contains primary care records of >13 million currently registered patients from 1491 general practices in the United Kingdom. It is broadly representative in terms of age and sex of the general population.[14] We also used linked death data from the Office for National Statistics (ONS), hospital admissions data from Hospital Episode Statistics (HES), and individual-level and practice-level deprivation data from Index of Multiple Deprivation. As we used deidentified patient-level data, individual informed consent was not required. The UK study protocol was approved by the London School of Hygiene and Tropical Medicine ethics committee (29592) and the Independent Scientific Advisory Committee for the Medicines and Healthcare products Regulatory Agency (Number 23_002786).

Abbreviations

AF: atrial fibrillation

CI: confidence interval

CPRD: Clinical Practice Research Datalink

DOACs: direct oral anticoagulants

HES: Hospital Episode Statistics

HR: hazard ratio

MI: myocardial infarction

OR: odds ratio

ONS: Office for National Statistics

PS: propensity score

VTE: venous thromboembolism

Cohort study

Study population

We identified people aged ≥18 years receiving their first DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) in CPRD Aurum during the study period of January 1, 2011 to March 29, 2021 with linked HES/ONS data. To ensure that we have reliable measures of drug use and baseline covariates, all participants had ≥1-year continuous registration before the first recorded DOAC prescription. Clarithromycin, erythromycin, and fluconazole were defined as the precipitant drugs, respectively, that were hypothesized to alter the effects of DOACs.[4] We also investigated other antifungal treatments that are potential precipitant drugs but the cohorts were small (Supplemental Table S1).

Exposure

The exposed group was defined as the person-times when a DOAC was prescribed with a precipitant drug, whereas the comparison group was defined as person-time when a DOAC but not clarithromycin, erythromycin, or fluconazole, respectively, was prescribed. The duration of prescriptions for DOACs and precipitant drugs was used to determine the exposure groups (details in Supplemental Material S1).

Outcomes

Effectiveness outcomes included ischemic stroke, myocardial infarction (MI), VTE, cardiovascular mortality, and all-cause mortality during the follow-up. Safety outcomes were intracranial bleeding, gastrointestinal bleeding, and other bleeding.

We followed both groups until the earliest of discontinued treatment of either drug (DOAC/precipitant drug), drug switching to warfarin, outcome occurrence, death, transfer out of the practice, last data collection date for the practice, or end of the study.

Covariates

Potential confounders and predictor of outcomes[15] were selected as propensity score (PS) covariates using a directed acyclic graph (Supplemental Figure S3–Figure S5).

Statistical analyses

To reduce bias caused by heterogeneity among exposure groups, PSs were used. We derived PS from logistic regression, to represent the probability of exposure given the covariates measured on the first day of follow-up for each exposure group. Hazard ratios (HRs) were computed using inverse probability-of-treatment-weighted Cox regression models with robust standard errors and 99% confidence interval (CI) to handle multiple testing. We performed multiple imputation through chained equations to address missing data,[16] assuming the missingness is missing at random. We restricted the cohort to those individuals whose PS were within the overlapping region of the distributions of the DOAC + precipitant drug group and DOAC therapy-alone group.[17] We also assessed the duration of effect by using follow-up of 0 to 7 days, 0 to 30 days, and 0 to 90 days as secondary analyses.

Subgroup analyses

Analyses were stratified by age, sex, indications, level of DOAC dose in people with AF (using strength as proxy), individual

DOACs, degree of polypharmacy, body weight, and kidney function, using estimated glomerular filtration rate.

Modified case-crossover study

The case-crossover design only includes individuals who experienced the outcome and compares each individual's exposure in a time period before the outcome (hazard window) to the exposure during an earlier control period (referent window) to eliminate fixed confounding.[18,19]

In each case-crossover analysis, we identified people who experienced the specific outcome and were exposed to at least 1 of the 2 interacting drugs before the outcome during a valid follow up, which started from the latest of study start date (January 1, 2011) or at least 1-year continuous registration of general practices, reaching age of 18 until occurrence of outcome, death, transfer out of the practice, last data collection date for the practice, or end of the study (March 29, 2021) (Supplemental Figure S2). Only discordant pairs of exposure status between hazard and referent window contributed to the analyses. Outcomes were the same as cohort design (Supplemental Material S2).

The hazard window started from days 1 to 7 on or before the diagnosis date of outcome, and the referent window started from days 68 to 74. We added a 60-day washout period to avoid auto correlation in exposure between periods and carryover effects.

We used conditional logistic regression to compare the odds of exposure to the interacting drugs between the hazard and referent window, conditioned on individual, with 99% CI to handle multiple testing. We estimated the odds ratios (ORs) for all outcomes associated with different drug initiation patterns using the 6-parameter model. Figure 1 shows the considerations of interpretations.

Subgroup analyses

We investigated different doses of DOAC and different types of DOACs as subgroup analyses.

Sensitivity analyses

In cohort design, we also added those covariates that were imbalanced among groups after weighting to the regression model for adjustment. We have conducted post hoc analyses by analyzing combined effectiveness outcomes including ischemic stroke, venous thromboembolism, MI, and cardiovascular mortality and combined safety outcomes including any bleeding and stratified the analysis by types of DOACs. In case-crossover design, we repeated the analysis using 30-day and 90-day hazard and referent windows to investigate the sensitivity of results to the choice of risk period length. In both designs, we repeated the analysis by restricting the study period of January 1, 2011 to December 31, 2019. The research reported in this paper adhered to RECORD (Reporting of Studies Conducted Using Observational Routinely Collected Data) guideline.[20] STATA/MP 17,18 (STATA Corp, College Station, TX) and R Studio 2023.12.1+402 (R Studio for Statistical Computing, Vienna, Austria) were used for data processing and analyses.

Results

We identified 483,815 DOAC users during January 1, 2011 to March 29, 2021. Compared with DOAC therapy alone, concomitant drug users were more likely to be older, women, nondrinkers, have obesity and comorbidities, polypharmacy, and comedications except for the use of aspirin, antiplatelet in the past 3 months, as well as tended to have more general practice active consultation in the past year (Table 1, Supplemental Table S2, and Supplemental Figure S6).

In case-crossover analysis, we identified 147,433 ischemic stroke; 173,920 MI; 158,856 VTE; 50,091 intracranial bleeding; 331,331 gastrointestinal bleeding; 396,962 other bleeding; 212,744 cardiovascular deaths; and 960,576 people who died, respectively, who had valid follow-up during the study period (Supplemental Figure S7).

Clarithromycin

In the cohort analysis, we found no evidence of increased risk of all outcomes except cardiovascular and all-cause mortality, comparing DOAC + clarithromycin vs DOAC alone. HRs ranged from 0.66 for VTE to 1.66 for other bleeding with CIs crossing 1 (Figure 2, Supplemental Figure S8, and Supplemental Table S3). We observed an increased risk of cardiovascular mortality (HR 3.36; 99% CI 1.73–6.52) and all-cause mortality (HR 3.43; 99% CI 2.66–4.43) associated with DOAC + clarithromycin, compared with DOAC alone. Results were similar for all outcomes in all prespecified follow-up periods (Supplemental Figure S9).

In the case-crossover analysis (Figure 2), no evidence of increased odds was observed for all outcomes except all-cause mortality in parameters related to drug interactions. An increased odds of all-cause mortality was observed among people initiating clarithromycin while taking DOACs (OR 2.52; 99% CI 2.09-3.04), which was greater than that for commencing clarithromycin monotherapy (OR 1.87; 99% CI 1.79–1.94).

Erythromycin

In the cohort analysis, no evidence of increased risk of all outcomes except all-cause mortality, comparing DOAC + erythromycin vs DOAC alone. HRs ranged from 0.47 for MI to 2.89 for ischemic stroke with CIs crossing 1 (Figure 3, Supplemental Figure S10, and Supplemental Table S4). We observed an increased risk of all-cause mortality (HR 1.84; 99% CI 1.12–3.04) associated with DOAC + erythromycin, compared with DOAC therapy alone. In the secondary analysis, an increased risk of gastrointestinal bleeding was observed comparing DOAC + erythromycin vs DOAC therapy alone in the 7-day risk period only but not in any other follow-up periods (HR 3.66; 99% CI 1.27–10.51) (Supplemental Figure S11).

In the case-crossover analysis (Figure 3), we observed an increased odds of all-cause mortality associated with initiating

In the 6-parameter model, the first 3 parameters address situations where a drug interaction could not have occurred, namely 1) use of one drug in the hazard window and the other drug in the control window, 2) initiation of DOAC monotherapy, 3) initiation of antimicrobial monotherapy; the remaining 3 parameters address situations related to potential drug-interaction: 4) joint initiation, 5) initiation of DOAC while taking antimicrobial, 6) initiation of antimicrobial while taking DOAC.

The following combinations of parameters should be considered:

Combination	Parameter 1	Parameter 2
A	Initiation of precipitant drug in the presence of DOAC	Initiation of precipitant drug monotherapy
B	Joint initiation of precipitant drug and DOAC	Initiation of precipitant drug monotherapy OR Initiation of DOAC monotherapy
C	Initiation of DOAC in the presence of precipitant drug	Initiation of DOAC monotherapy

*DOAC, direct oral anticoagulant

To identify potential increased risk of an outcome due to drug-drug interaction:

In each of these combinations, if the odds ratio (OR) derived from Parameter 1 is greater than that obtained from Parameter 2 and if a Wald test suggests evidence that the OR for parameter 1 was greater than the OR for parameter 2, this was considered to signify a potential drug-drug interaction.

Of note, if this pattern of results is only observed for Combination A, the drug-drug interaction could be due to poorly dose-titrated DOAC, e.g. if a prescriber was unaware to reduce the dose of the DOAC when initiating the antimicrobial drug to avoid a drug-drug interaction. Similarly, if this pattern of results is only observed for Combination C, the drug-drug interaction could reflect the dose of the antimicrobial drug not being adjusted when initiating DOAC to avoid a drug-drug interaction. If the pattern of results is observed for at least 2 of the combinations, this would suggest a drug-drug interaction.

To identify potential confounding:

If combination B shows an increased OR for initiating both drugs together, compared with initiation of either DOAC monotherapy/antimicrobial drug monotherapy (tested using a Wald test) AND, this is not observed in Combinations A and C, this could suggest confounding by indication, as the joint initiation of the two therapies may imply that multiple medical conditions requiring separate treatments were present at this point in time, and this multimorbidity rather than the drugs themselves could have driven poorer outcomes.

Figure 1
Considerations for interpreting the 6-parameter case-crossover model to identify the potential increased risk of an outcome due to drug–drug interaction.

Table 1 Baseline characteristics in cohort study

	Clarithromycin		Erythromycin		Fluconazole	
	DOAC monotherapy	DOAC + clarithromycin	DOAC monotherapy	DOAC + erythromycin	DOAC monotherapy	DOAC + fluconazole
Total	272,661	21,701	274,039	4532	274,046	4840
Median age at index date (IQR)	74.0 (64.2–82.2)	77.7 (69.4–84.8)	74.0 (64.2–82.2)	77.6 (68.4–85.0)	74.0 (64.2–82.2)	75.3 (66.8–82.7)
Male sex	142,074 (52.1)	9738 (44.9)	142,695 (52.1)	1835 (40.5)	142,715 (52.1)	1645 (34.0)
Medical history						
COPD	40,508 (14.9)	6331 (29.2)	40,951 (14.9)	1135 (25.0)	40,949 (14.9)	1447 (29.9)
Heart failure	47,514 (17.4)	6265 (28.9)	47,743 (17.4)	1320 (29.1)	47,743 (17.4)	1360 (28.1)
Ischemic heart disease	75,884 (27.8)	8198 (37.8)	76,243 (27.8)	1700 (37.5)	76,252 (27.8)	1799 (37.2)
Peptic ulcer	21,792 (8.0)	2341 (10.8)	21,931 (8.0)	468 (10.3)	21,926 (8.0)	554 (11.4)
Diabetes						
Without insulin	55,541 (20.4)	5546 (25.6)	55,875 (20.4)	1106 (24.4)	55,863 (20.4)	1396 (28.8)
With insulin	8734 (3.2)	1105 (5.1)	8793 (3.2)	253 (5.6)	8787 (3.2)	359 (7.4)
Peripheral arterial disease	15,970 (5.9)	1,974 (9.1)	16,062 (5.9)	437 (9.6)	16,070 (5.9)	372 (7.7)
Atrial fibrillation	166,470 (61.1)	16,089 (74.1)	167,015 (60.9)	3371 (74.4)	167,031 (60.9)	3491 (72.1)
Venous thrombo-embolism	67,912 (24.9)	5446 (25.1)	68,245 (24.9)	1232 (27.2)	68,216 (24.9)	1424 (29.4)
Any bleeding	139,400 (51.1)	13,585 (62.6)	140,198 (51.2)	2818 (62.2)	140,162 (51.1)	3351 (69.2)
Stroke/TIA	36,129 (13.3)	3867 (17.8)	36,294 (13.2)	825 (18.2)	36,288 (13.2)	875 (18.1)
Chronic kidney disease						
Stage 3A	32,992 (12.1)	3,507 (16.2)	33,180 (12.1)	764 (16.9)	33,179 (12.1)	674 (13.9)
Stage 3B	15,097 (5.5)	1,847 (8.5)	15,184 (5.5)	410 (9.0)	15,191 (5.5)	371 (7.7)
Stage 4	3002 (1.1)	398 (1.8)	3025 (1.1)	103 (2.3)	3024 (1.1)	67 (1.4)
Stage 5	3001 (1.1)	337 (1.6)	3014 (1.1)	68 (1.5)	3011 (1.1)	71 (1.5)
Missing	60,552 (22.2)	2915 (13.4)	60786 (22.2)	643 (14.2)	60,777 (22.2)	626 (12.9)
Medication use in the past 3 months						
PPIs	107,328 (39.4)	11,035 (50.9)	107,960 (39.4)	2198 (48.5)	107,918 (39.4)	2952 (61.0)
Valproate/ valproic acid/ ethosuximide	1854 (0.7)	213 (1.0)	1876 (0.7)	41 (0.9)	1874 (0.7)	46 (1.0)
Diazepam	5536 (2.0)	601 (2.8)	5575 (2.0)	131 (2.9)	5563 (2.0)	201 (4.2)
Aspirin	64,844 (23.8)	2079 (9.6)	65,147 (23.8)	413 (9.1)	65,162 (23.8)	368 (7.6)
Antiplatelet	29,786 (10.9)	1092 (5.0)	29,932 (10.9)	220 (4.9)	29,942 (10.9)	206 (4.3)
SSRI/SNRI	28,773 (10.6)	3119 (14.4)	28,973 (10.6)	562 (12.4)	28,933 (10.6)	921 (19.0)
ACEI	78,364 (28.7)	6233 (28.7)	78,750 (28.7)	1316 (29.0)	78,774 (28.7)	1236 (25.5)
ARB	36,293 (13.3)	3409 (15.7)	36,482 (13.3)	720 (15.9)	36,485 (13.3)	761 (15.7)
CCBs	76,964 (28.2)	5541 (25.5)	77,328 (28.2)	1090 (24.1)	77,336 (28.2)	1221 (25.2)
Beta blockers	126,595 (46.4)	11,251 (51.8)	127,022 (46.4)	2334 (51.5)	127,029 (46.4)	2511 (51.9)
NSAIDs	35,259 (12.9)	2931 (13.5)	35,518 (13.0)	611 (13.5)	35,518 (13.0)	738 (15.2)
Oral corticosteroids	24,306 (8.9)	5167 (23.8)	24,687 (9.0)	762 (16.8)	24,639 (9.0)	1094 (22.6)
Statins	120,539 (44.2)	10,369 (47.8)	121,105 (44.2)	2101 (46.4)	121,109 (44.2)	2300 (47.5)
Estrogen/ estrogen-like drugs	3506 (1.3)	228 (1.1)	3525 (1.3)	45 (1.0)	3520 (1.3)	106 (2.2)

ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; DOAC = direct oral anticoagulant; IQR = interquartile range; NSAIDs = nonsteroidal anti-inflammatory drugs; PPIs = proton pump inhibitors; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitor; TIA = transient ischemic attack.

erythromycin while taking DOACs (OR 1.97; 99% CI 1.17–3.32) with wide CIs but the estimate was similar to that of initiating erythromycin monotherapy (OR 1.42; 99% CI 1.31–1.53). Similarly, wide CIs were observed in parameters related to drug interactions for any outcomes.

Fluconazole

In the cohort analysis, no evidence of increased risk of any outcomes except all-cause mortality, comparing DOAC + fluconazole vs DOAC alone. HRs ranged from 0.48 for ischemic stroke to 2.76 for intracranial bleeding with CIs crossing 1

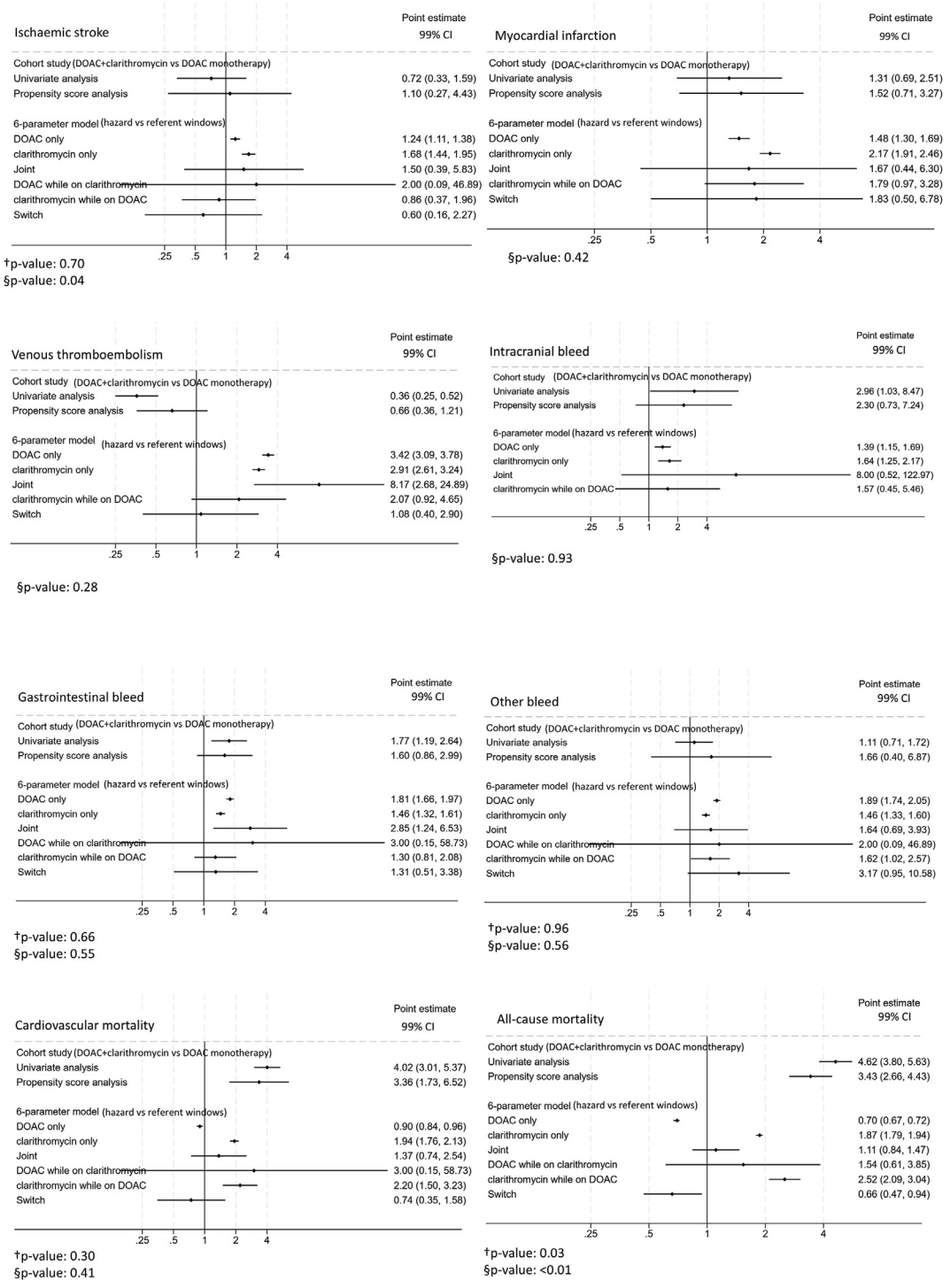
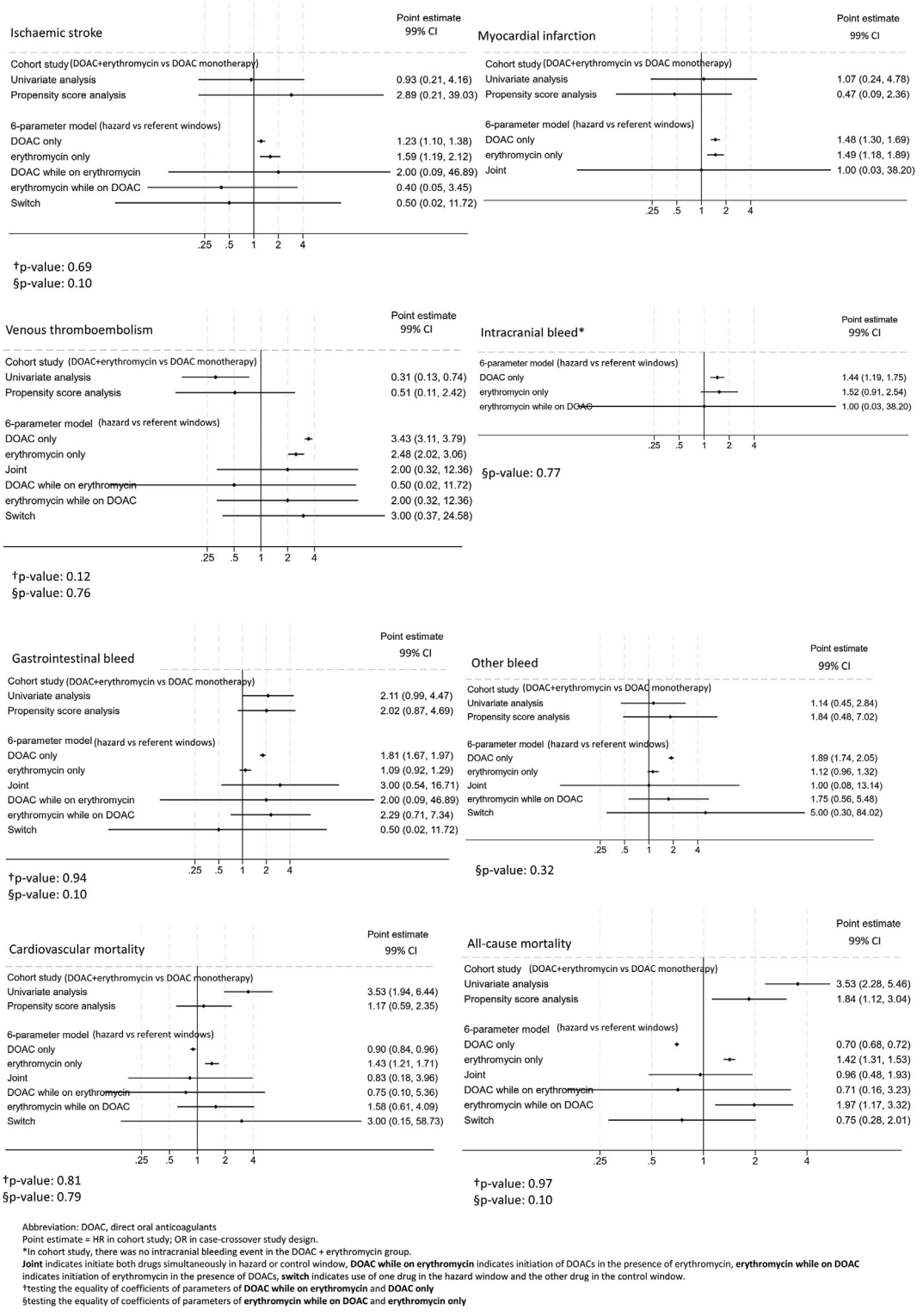


Figure 2
Results for DOACs + clarithromycin using cohort study design and case-crossover study design. DOACs = direct-acting anticoagulants.

(Figure 4, Supplemental Figure S12, and Supplemental Table S5). An increased risk of all-cause mortality associated with DOAC + fluconazole was observed, compared with DOAC alone (HR 2.90; 99% CI 1.74–4.83). A lower risk of VTE was observed comparing DOAC + fluconazole vs DOAC alone (HR 0.25; 99% CI 0.08–0.74). Results were similar for all outcomes in all prespecified follow-up periods (Supplemental Figure S13).

In the case-crossover analysis (Figure 4), we observed an increased odds of all-cause mortality associated with initiating



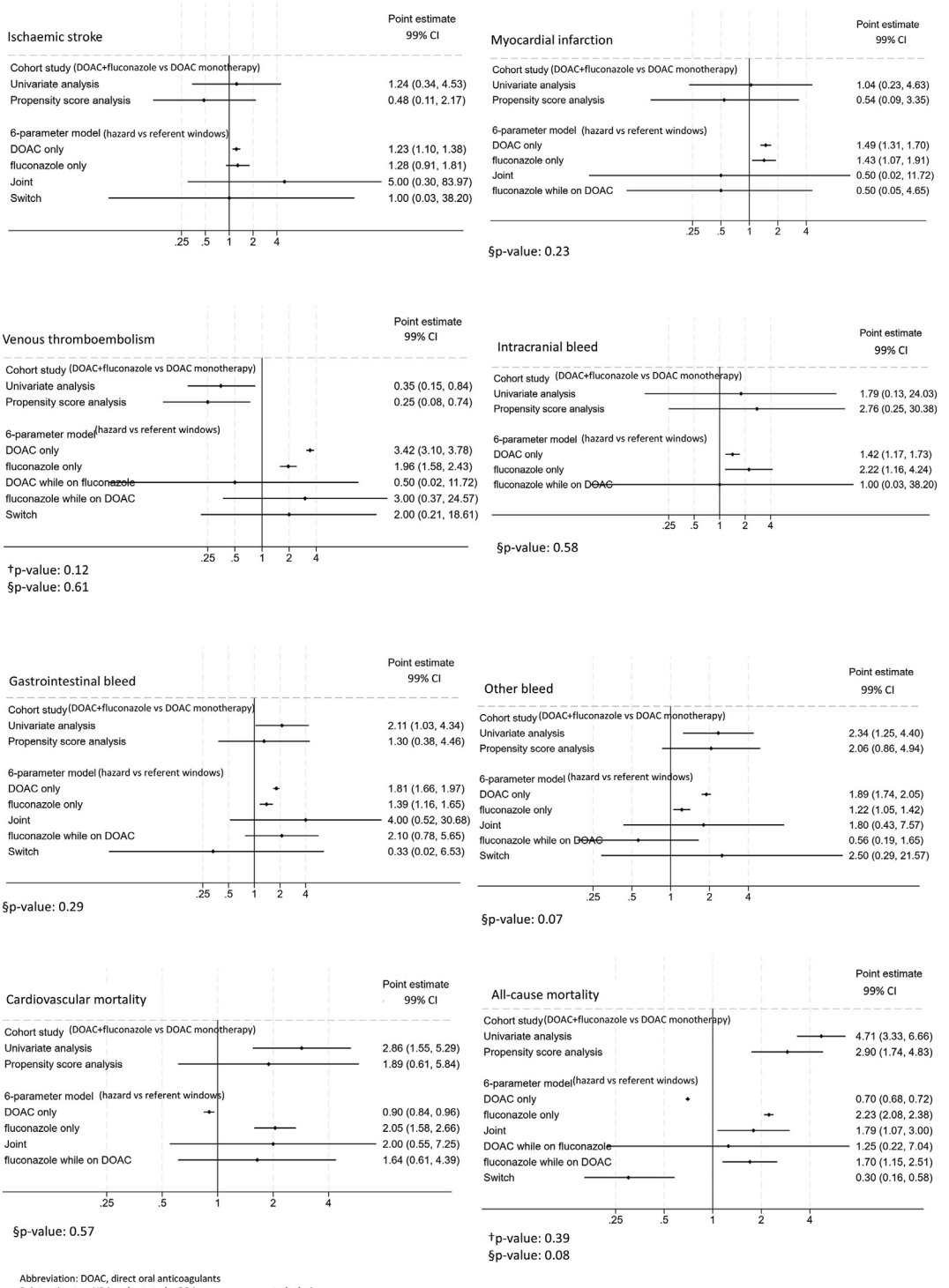
Abbreviation: DOAC, direct oral anticoagulants
Point estimate = HR in cohort study; OR in case-crossover study design.
*In cohort study, there was no intracranial bleeding event in the DOAC + erythromycin group.
Joint indicates initiate both drugs simultaneously in hazard or control window, **DOAC while on erythromycin** indicates initiation of DOACs in the presence of erythromycin, **erythromycin while on DOAC** indicates initiation of erythromycin in the presence of DOACs, **switch** indicates use of one drug in the hazard window and the other drug in the control window.
†testing the equality of coefficients of parameters of **DOAC while on erythromycin** and **DOAC only**
§testing the equality of coefficients of parameters of **erythromycin while on DOAC** and **erythromycin only**

Figure 3
Results for DOACs + erythromycin using cohort study design and case-crossover study design. Abbreviation as in Figure 2.

fluconazole while taking DOACs (OR 1.70; 99% CI 1.15–2.51) with wide CIs, but the estimate was smaller than that of initiating fluconazole monotherapy (OR 2.23; 99% CI 2.08–2.38). Similarly, wide CIs were observed in parameters related to drug interactions for all outcomes.

Subgroup analyses

In the cohort analysis, an increased risk of cardiovascular mortality was observed in high dose DOAC + clarithromycin (HR 8.89; 99% CI 2.50–31.61) but not in low-dose DOAC + clarithromycin (HR 1.80; 99% CI 0.86–3.76) vs DOAC alone



Abbreviation: DOAC, direct oral anticoagulants
Point estimate = HR in cohort study; OR in case-crossover study design.
Joint indicates initiate both drugs simultaneously in hazard or control window, **DOAC while on fluconazole** indicates initiation of DOACs in the presence of fluconazole, **fluconazole while on DOAC** indicates initiation of fluconazole in the presence of DOACs, **switch** indicates use of one drug in the hazard window and the other drug in the control window.
†testing the equality of coefficients of parameters of **DOAC while on fluconazole** and **DOAC only**
§testing the equality of coefficients of parameters of **fluconazole while on DOAC** and **fluconazole only**

Figure 4
Results for DOACs + fluconazole using cohort study design and case-crossover study design. Abbreviation as in Figure 2.

(interaction *P* value .001) (Supplemental Table S6). An increased risk of all-cause mortality was observed in people with body weight ≤120 kg but not in those >120 kg, comparing DOAC + clarithromycin with DOAC alone (interaction *P* value .03) (Supplemental Table S7). An increased risk of all-cause mortality was observed in high dose DOAC + erythromycin (HR 3.23; 99% CI 1.59–6.56) but not in low-dose DOAC + erythromycin (HR 1.36; 99% CI 0.61–3.05) vs DOAC alone (interaction *P* value .03). Comparing DOAC + fluconazole with DOAC alone, the HRs for all-cause mortality

ranged between 2.93 (99% CI 0.93–9.23) and 10.28 (99% CI 2.00–52.74) for all chronic kidney disease stages except stage 3B (HR 0.69; 99% CI 0.15–3.18) (interaction *P* value .02).

In case-crossover analysis, the odds for mortality did not differ with DOAC dose in people with AF or type of DOACs for clarithromycin (Supplemental Figure S14 and Figure S15). Power was limited to conduct subgroup analyses for erythromycin and fluconazole.

Sensitivity analyses

In the cohort study, we found an increased hazard of any bleeding associated with dabigatran + clarithromycin compared with dabigatran therapy alone (HR 6.46; 99% CI 1.56–26.66) but not for other DOACs with wide CIs. However, there was no evidence that the association differed across types of DOACs with an interaction *P* value of .22. Results were similar when varying the hazard and referent window duration in case-crossover analysis except the odds for all-cause mortality associated with clarithromycin while taking DOACs in 30-day and 90-day, which were smaller than those for initiating clarithromycin monotherapy (Supplemental Figure S16–Figure S18). All other sensitivity analyses also showed similar results to the main analyses.

Discussion

Summary

We found a short-term 7-day increased risk of gastrointestinal bleeding associated with erythromycin vs nonuse in DOAC users in cohort analysis, although this could not be confirmed in the case crossover design because of limited power. Notably, we found no evidence of increased risks of DOAC safety outcomes indicating potential drug interactions with clarithromycin and fluconazole with consistent results from both cohort and case-crossover analyses.

Erythromycin is a moderate CYP3A4 and P-glycoprotein inhibitor that could theoretically increase the risk of DOAC level,[21] thus leading to higher risk of gastrointestinal bleeding. However, we could not confirm or refute this in case-crossover analysis because of wide CIs. More studies of larger sample sizes are required to confirm the association. Although we observed an increased risk of mortality outcomes in cohort analysis comparing the use of clarithromycin/ erythromycin/ fluconazole, with nonuse in DOAC users, the observed risk could be caused by confounding by indication (ie, infections). Our case-crossover study design that should eliminate time-invariant confounding strongly suggests that the elevated risk of mortality observed in cohort analysis was driven by indications (ie, infections) when initiating the antimicrobials rather than drug–drug interactions. Supporting this interpretation, none of the case-crossover ORs for mortality associated with an initiation of antimicrobials while taking DOACs were larger than those for initiating antimicrobials only (except clarithromycin in 7-day hazard and referent windows only). The estimates between these parameters were generally very similar despite wide CIs in some cases.

We also observed a lower risk of VTE associated with fluconazole vs nonuse in DOAC users in the cohort analysis. As DOAC + fluconazole users were more likely to have history of VTE and other comorbidities than DOAC therapy-alone users, we may have expected to observe an increased risk of VTE associated with fluconazole vs nonuse in DOAC users before controlling for confounding, and the estimate would have been shifted toward null using the PS model. However, as we observed that the effect was shifted away from null (ie, much lower risk of VTE comparing fluconazole vs nonuse in DOACs) after confounder adjustment, it appears that confounding was unlikely to explain the observed results. As fluconazole could potentially increase DOAC levels,[21] it might partly explain the lower risk of VTE observed in DOAC + fluconazole vs DOAC therapy alone. In our case-crossover analysis, power was too limited to further explore this association. Power was also limited to assess the risk of bleeding associated with DOAC + fluconazole.

Strengths and limitations

This is the first population-based study investigating drug interactions between DOACs and clarithromycin, erythromycin, and fluconazole using 2 complementary study designs in England. We can use both designs to minimize confounding. We also showed the coprescribing patterns of antimicrobial medications in DOAC users and their characteristics in England.

This study has some limitations. First, drug adherence and persistence were unknown, leading to potential misclassification bias of drug exposure. However, assuming a nondifferential misclassification of exposure, estimates would be biased toward null. Second, we did not have large cohorts for some drug-outcome pairs: specifically, for intracranial bleeding and some rare cardiovascular outcomes with erythromycin and fluconazole. Third, bias could arise if our data are not missing at random. Further, our study population is predominantly White, so results may not be generalizable to other ethnic groups. Fourth, data on anticoagulant use during admissions to hospital, including low molecular weight heparin or unfractionated heparin, are not available, which likely led to an underestimation of any effect of drug interactions because of misclassification bias of DOAC exposure. Fifth, data on DOAC levels or Anti-FXa activity are not available for further investigation. Finally, we could not eliminate residual confounding, but we attempted to minimize confounding by using a PS method and self-controlled design.

Comparison with existing literature

A Canadian study[9] showed a 71% increased risk of major bleeding comparing clarithromycin with azithromycin in DOAC users. Another Belgian study[11] showed a 55% increased risk of major bleeding: specifically, gastrointestinal bleeding associated with DOACs + clarithromycin among people with AF in a subgroup analysis. No increased risk of stroke or all-cause mortality associated with DOACs + clarithromycin vs DOAC therapy alone was observed. Case-only studies conducted as empirical examples to compare study

designs using US data showed no increased risk of bleeding associated with dabigatran and clarithromycin, but other DOACs were not investigated.[13] In contrast, a Taiwanese study[8] showed a lower risk of bleeding associated with concomitant use of DOACs and erythromycin/clarithromycin. Another Swedish study[12] showed no evidence of bleeding associated with DOACs + macrolides, but the sample size was small (n = 764). A cohort study of small sample size showed no evidence of increased risk of bleeding associated with DOACs + fluconazole vs DOAC therapy alone.[10] A Danish study[7] showed a 3.6 times odds of bleeding associated with systematic fluconazole in apixaban users comparing 30-day hazard with referent periods, but not in rivaroxaban and dabigatran users, using a case-crossover study design. A 2-fold increase in risk of bleeding associated with concomitant use of DOACs and fluconazole was found in a Taiwanese cohort study.[8]

Implications for research and practice

Existing clinical guidance concluded an interaction between rivaroxaban and erythromycin that could increase the risk of bleeding.[22] However, they did not specify the bleeding sites or provide any information on potential interaction between erythromycin and other DOACs. Our result showed a short-term increased risk of gastrointestinal bleeding associated with concomitant use of DOACs and erythromycin but not clarithromycin or fluconazole. Erythromycin and DOACs should be used concomitantly with caution.[23]

Conclusion

Our study suggests no clinically relevant drug interactions between DOACs and clarithromycin, erythromycin, or fluconazole. However, there is a suggestion of a short-term increased risk of gastrointestinal bleeding with erythromycin, which warrants further investigation to determine whether it is causal or explained by underlying infection.

Data Availability

Computing code and study protocol are available from the corresponding author upon request for the purposes of reproducing the results. The study data cannot be made available to other researchers because of the terms specified in Data Use Agreements.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2025.01.007.

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