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ORIGINAL RESEARCH

Potential interactions between digoxin and direct oral anticoagulants: application of cohort & novel case-crossover designs

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Abstract

Objectives: Direct oral anticoagulants (DOACs) are commonly co-prescribed with digoxin, but whether there is a drug interaction between them is unclear. We aimed to investigate potential drug interactions between DOACs and digoxin.

Study Design and Setting: We identified DOAC users during January 1, 2011−December 31, 2019 using data from Clinical Practice Research Datalink Aurum in cohort design with propensity score to compare the hazards of effectiveness cardiovascular and mortality outcomes and safety bleeding outcomes, respectively, in DOAC + digoxin users versus DOAC + beta-blocker users. A case-crossover design was conducted to compare odds of exposure to different drug initiation patterns in hazard period versus referent period.

Results: Of 397,459 DOAC users, we identified 25,251 co-prescribed digoxin and 109,779 co-prescribed beta-blockers in cohort study. A lower proportion of DOAC + digoxin users were men (46%) in contrast with that of DOAC + beta-blocker users (53%). Mean age of DOAC + digoxin users (77.1 years) were higher than DOAC + beta-blocker users (74.5 years). No increased risk of pharmacologically predictable DOAC safety outcomes or specific effectiveness outcomes was seen with DOAC + digoxin. A higher risk of all-cause mortality (hazard ratio: 1.35; 99% confidence interval [CI]: 1.14−1.61) was observed with DOAC + digoxin versus DOAC + beta-blockers. In the case-crossover study, a 24% higher odds of all-cause mortality was seen with initiating digoxin while taking DOAC (odds ratio: 1.24; 99% CI: 1.06−1.45); and a 63% higher odds was also seen with initiating DOAC while taking digoxin (odds ratio: 1.63; 99% CI: 1.41−1.88).

Conclusion: We found no increased risk of bleeding when DOACs are used with digoxin, suggesting combined use does not lead to drug-drug interaction. Future work is recommended to investigate the underlying mechanism of association with all-cause mortality.

Keywords: Digoxin; Direct-acting oral anticoagulant; Drug interactions; Cohort studies; Epidemiologic research design; Propensity score

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Plain Language Summary

This study aimed to examine potential drug interactions between direct oral anticoagulants (DOACs) (a drug class to prevent blood clots) and digoxin (treatment of abnormal heart rhythms). We compared a range of clinical outcomes in people prescribed DOAC and digoxin with people prescribed DOAC and beta-blockers (a treatment alternative to digoxin). We also used a new study design (case-crossover design) to compare the risk of clinical outcomes between different periods within a person as a validation. In both study designs, we found no increased risk of bleeding when DOACs are used with digoxin, suggesting combined use does not lead to drug-drug interaction. However, we found an increased risk of all-cause death associated with digoxin in DOAC users which requires further investigation.

1. Introduction

Direct oral anticoagulants (DOACs) are commonly used for the prevention of arterial embolism among patients with atrial fibrillation and acute coronary syndromes, and the treatment and prevention of venous thromboembolism (VTE).

A recent clinical guideline recommended with moderate evidence that digoxin may be considered for acute rate control in people with atrial fibrillation with rapid ventricular response [1]. DOACs and digoxin are p-glycoprotein substrates so they may compete for the p-glycoprotein transporter, theoretically increasing either the plasma concentrations of DOAC and/or digoxin [2]. Therefore, any clinically relevant interaction with digoxin would be expected to increase the risk of DOAC side effects, in particular, bleeding. Since the hypothesized mechanism of interaction would not reduce DOAC levels, we would not anticipate any major impact on DOAC effectiveness outcomes. However, whether these biologically plausible drug interactions ultimately lead to clinical effects is still unclear due to conflicting and limited clinical evidence [3−6]. Routine clinical datasets can be used to systematically investigate potential effects of drug interactions with robust methodologies. Combining results from different study designs with different strengths and weaknesses help to triangulate findings.

Therefore, this population-based study aimed to investigate the risk of serious clinical outcomes associated with combined use of DOAC and digoxin versus DOAC with an active comparator (beta-blocker) or DOAC alone using routine clinical data in England in 2 study designs.

2. Materials and methods

2.1. Study design

We conducted cohort (details in Material S1) and case-crossover studies (Material S2) to investigate potential drug interactions between DOACs and digoxin (Fig S1 and 2 & Fig 1) as cohort study can estimate both relative risk and risk difference, while case-crossover study is a case-only design to eliminate between-person confounding.

2.2. Data source

We used data from the Clinical Practice Research Datalink Aurum. It contains primary care records of >13 million currently registered patients from 1491 general practices (GPs) in the United Kingdom, which is broadly representative in terms of age and sex of the general population [7]. We 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.

2.3. Cohort study

2.3.1. Exposure

We identified people aged ≥18 years receiving their first DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) in Clinical Practice Research Datalink Aurum during January 1, 2011−December 31, 2019. To ensure reliable measures of drug use and baseline covariates, all participants had ≥1 year continuous registration before the first DOAC prescription with records of acceptable research quality. Digoxin is a p-glycoprotein substrate [2] (defined as the precipitant drug) that was hypothesized to alter the effects of DOACs.

To reduce confounding by indication, the exposure was defined as receipt of a DOAC (defined as the object drug) with digoxin (DOAC + digoxin) vs. receipt of a DOAC with an active comparator drug (DOAC + active comparator). Beta-blockers were active comparator as they share similar indications with digoxin and are not anticipated to interact with DOACs. People with any warfarin before cohort entry were excluded to remove a carry-over effect of warfarin. The duration of prescriptions for DOACs and digoxin was calculated and used to determine the exposure groups. The exposure groups were defined as person-time

What is new?

Key findings

- In both cohort and novel case-crossover designs, we found no increased risk of bleeding when direct oral anticoagulants (DOACs) are used with digoxin, suggesting combined use does not lead to drug-drug interaction.
- We observed an increased risk of all-cause mortality associated with concomitant use of DOACs and digoxin.

What this adds to what is known?

- This study used both cohort and novel 6-parameter model case-crossover designs to investigate drug-drug interactions. The novel case-crossover study design has recently been developed to study drug-drug interactions taking different drug-initiation patterns into account and eliminate time-invariant confounding. This study additionally recommends considerations to interpret results of the novel case-crossover design.

What is the implication and what should change now?

- Our study suggests the combined use of DOAC with digoxin is likely to be a safe combination with respect to known DOAC side effects.
- The finding of an increased risk of all-cause mortality associated with digoxin in DOAC users shows these patients are clinically vulnerable and likely require close monitoring.

when a DOAC and digoxin or beta-blockers were prescribed concurrently (Fig S1).

2.3.2. Outcomes

Effectiveness outcomes included ischemic stroke, myocardial infarction, VTE, cardiovascular mortality, and all-cause mortality. Safety outcomes were intracranial bleeding, gastrointestinal bleeding, and other bleeding. We identified the first recorded event using HES and/or ONS data only to capture incident events in a cohort of people with a possible history of the outcome.

We followed both groups until the earliest of discontinued treatment of either drug (DOAC/digoxin), drug switching to warfarin, switching between digoxin and beta-blocker, outcome occurrence, death, transfer out of the practice, last data collection date for the practice, or end of the study (December 31, 2019).

2.3.3. Covariates

Potential confounders and predictors of outcomes [8] were selected as covariates in the propensity score (PS) model using a directed acyclic graph (Supplementary Figs S3−5).

2.3.4. Statistical analyses

To reduce bias due to heterogeneity between exposure groups, PSs were used which are the probability of a patient receiving a certain treatment, based on their individual characteristics [9]. We derived PS from logistic regression, predicting the probability of exposure given the covariates measured on the first day of follow-up. Weights were calculated as the inverse of the PS for the exposed group and the inverse of 1-PS for the comparison group for the estimation of the average treatment effects. The balance of covariate distributions was assessed after weighting using standardized mean difference. We computed the hazard ratios (HRs) of the association using inverse probability of treatment-weighted Cox regressions and 99% confidence interval (CI) to handle multiple testing.

Multiple imputations through chained equations with 10 imputed datasets were used to address the missingness in blood pressure measurements, body mass index, smoking status, alcohol consumption, and region in the PS method. The imputation model contained all covariates, exposure, and outcome. We estimated the individual PSs and the treatment effect from each imputed dataset, followed by combining the treatment effect estimates for an overall estimate using Rubin's rules [10]. We restricted the cohort to those individuals whose PS were within the overlapping region of the distributions of the DOAC + digoxin group and the comparison group [9].

2.3.5. Subgroup analyses

The analyses were stratified by age, sex, indications (diagnoses of atrial fibrillation and VTE), level of DOAC dose (using the strength as proxy) in people with atrial fibrillation, individual DOACs, degree of polypharmacy, bodyweight, order of drug initiation, and kidney function using estimated glomerular filtration rate (calculated using chronic kidney disease epidemiology collaboration formula).

2.3.6. Sensitivity analyses

First, we included DOAC alone group as the comparison group. The DOAC alone group was defined as person-time when a DOAC but not digoxin was prescribed. Second, as some individuals could contribute person-times both in the concomitant group and DOAC alone group which might have led to overconfidence in our estimates, we computed the 99% CI using bias-corrected bootstrapping method with 100 iterations when the evidence of the associations was moderate. Third, for those covariates that were imbalanced when standardized mean difference $\geq$0.1 between groups

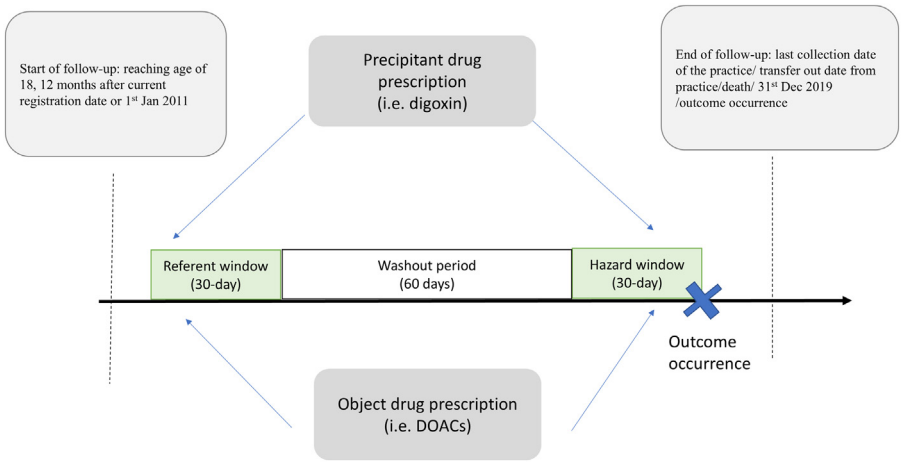


Figure 1. Illustration of the modified case-crossover study design.

after weighting, we additionally added them to the regression model for adjustment.

2.4. Novel 6-parameter case-crossover study

The case-crossover design eliminates time-invariant confounding as risks are compared within the individual [11]. It only includes individuals who experienced the outcome (cases) and compares each individual's exposure in a time period prior to the outcome (hazard window) to the exposure during an earlier control period (referent window) [12]. This study design has recently been developed to specifically investigate drug-drug interactions, by fitting 6-parameter models, which allow for the investigation of 6 different drug initiation patterns [12].

In each case-crossover analysis, we identified people with records of acceptable research quality who experienced the specific outcome and were exposed to at least one of the two interacting drugs (ie, DOACs/digoxin) prior to 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 GPs, reaching age of 18 until outcome occurrence, death, transfer out of the practice, last data collection date for the practice, or end of the study (December 31, 2019) (Fig 1). Only the first event was included. Only discordant pairs of exposure status between hazard and referent window contributed to the analyses.

The hazard window started from days 1-30 on/before the diagnosis date of outcome, and the control window started from days 91-120 before the diagnosis date in the main analysis. We added a 60-day washout period to avoid autocorrelation in exposure between periods and carryover effects.

We used conditional logistic regression to compare the odds of exposure to the interacting drugs during the hazard window to the odds of exposure in the 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 six-parameter model. The first three 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 precipitant drug monotherapy; the remaining 3 parameters address situations related to potential drug interaction; (4) joint initiation; (5) initiation of DOAC while taking precipitant drug; and (6) initiation of precipitant drug while taking DOAC. We illustrated the 6-parameter model in Material S2. Figure 2 shows the considerations of interpretations for 6-parameter model.

We conducted subgroup analyses according to different doses of DOAC and types of DOACs. We repeated the analysis using 7-day and 90-day hazard and referent windows to investigate the sensitivity of results to the choice of risk period length.

3. Results

3.1. Main analysis

Among those with linkage to HES/ONS between January 1, 2011 and December 31, 2019, 397,459 people were prescribed DOAC prescriptions.

Of the study population, ≥95% of the study population was of White ethnicity (Table 1). DOAC + digoxin users (n = 25,251) were more likely to be older, have higher levels of deprivation, higher level of alcohol consumption, have heart failure, peripheral artery disease, atrial fibrillation, have at least one prescription of oral corticosteroids, and macrolides in the past 3 months, and polypharmacy than DOAC + beta-blocker group (n = 109,779). They also tended to have more GP active consultation in the past year.

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 digoxin monotherapy; the remaining 3 parameters address situations related to potential drug-interaction: 4) joint initiation, 5) initiation of DOAC while taking digoxin, 6) initiation of digoxin 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 precipitant 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 precipitant 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/precipitant 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 2. Considerations for interpreting the 6-parameter case-crossover model to identify the potential increased risk of an outcome due to drug-drug interaction.

Standardized differences for each outcome were shown in Table S1−3.

There was no or little evidence of increased risk of most outcomes except all-cause mortality associated with DOAC + digoxin versus DOAC + beta-blockers in cohort design (Fig 3 & Fig S6 & Table S4). In case-crossover design, we observed increased odds of all outcomes for some concomitant drug initiation patterns (ie, initiation of a DOAC while taking digoxin and vice versa, and joint initiation of both drugs). However, the relative effect estimates were similar to those seen for DOAC monotherapy and digoxin monotherapy initiation patterns with overlapping CIs (except for all-cause mortality), indicating little evidence of synergistic increased risks due to a drug interaction (Fig 3).

With a median follow-up time of 30 days (interquartile range: 28−61), a higher risk of all-cause mortality (unadjusted HR: 2.01; 99% CI: 1.77−2.27; PS weighted HR:

Table 1. Baseline characteristics of the DOAC + digoxin group and DOAC + beta-blocker group before restricting people with overlapping propensity score distributions between groups

Baseline characteristics	DOAC + beta-blocker	DOAC + digoxin
Total	109,779	25,251
Age at index date		
Mean (SD)	74.5 (11.5)	77.1 (11.0)
Median (IQR)	75.7 (67.9-82.9)	78.5 (70.4-85.2)
Minimum, maximum	18.5, 104.7	18.8, 105.9
Age group		
18 to <40	890 (0.8)	73 (0.3)
40 to <50	2478 (2.3)	388 (1.5)
50 to <60	8460 (7.7)	1464 (5.8)
60 to <70	22,163 (20.2)	4123 (16.3)
70 to <80	37,273 (34.0)	7977 (31.6)
80+	38,515 (35.1)	11,226 (44.5)
Male sex	58,617 (53.4)	11,582 (45.9)
Calendar year at cohort entry		
2011	83 (0.1)	16 (0.1)
2012	815 (0.7)	338 (1.3)
2013	2843 (2.6)	922 (3.7)
2014	6336 (5.8)	1804 (7.1)
2015	12,717 (11.6)	3206 (12.7)
2016	18,002 (16.4)	4080 (16.2)
2017	21,413 (19.5)	4733 (18.7)
2018	23,305 (21.2)	4953 (19.6)
2019	24,265 (22.1)	5199 (20.6)
Body mass index		
Underweight	1924 (1.8)	871 (3.4)
Normal	28,325 (25.8)	7461 (29.5)
Overweight	38,917 (35.5)	7952 (31.5)
Obese	39,000 (35.5)	8428 (33.4)
Missing	1613 (1.5)	539 (2.1)
Smoking status		
Nonsmoker	25,337 (23.1)	5557 (22.0)
Current smoker	22,723 (20.7)	5621 (22.3)
Ex-smoker	61,586 (56.1)	14,041 (55.6)
Missing	133 (0.1)	32 (0.1)
Ethnicity		
White	104,465 (95.2)	24,306 (96.3)
South Asian	2194 (2.0)	386 (1.5)
Black	1329 (1.2)	224 (0.9)
Other	613 (0.6)	102 (0.4)
Mixed	340 (0.3)	68 (0.3)
Not stated	479 (0.4)	107 (0.4)
Missing	359 (0.3)	58 (0.2)
Index of multiple deprivation		
1 (least deprived)	26,414 (24.1)	5603 (22.2)
2	24,906 (22.7)	5642 (22.3)
3	21,643 (19.7)	5033 (19.9)
4	19,475 (17.7)	4612 (18.3)
5 (most deprived)	17,341 (15.8)	4361 (17.3)
Nondrinker	9540 (8.7)	2627 (10.4)

(*Continued*)

Table 1. Continued

Baseline characteristics	DOAC + beta-blocker	DOAC + digoxin
Current low level	47,938 (43.7)	10,251 (40.6)
Current medium level	12,096 (11.0)	2271 (9.0)
Current high level	5962 (5.4)	1573 (6.2)
Ex-drinker	22,326 (20.3)	5621 (22.3)
Current drinker with missing data on consumption level	8545 (7.8)	1979 (7.8)
Missing	3372 (3.1)	929 (3.7)
Systolic blood pressure *(in quartile)*		
Q1 (50–120 mmHg)	28,950 (26.4)	9425 (37.3)
Q2 (121–130 mmHg)	23,624 (21.5)	5294 (21.0)
Q3 (130.2–140 mmHg)	27,000 (24.6)	5169 (20.5)
Q4 (141–238 mmHg)	23,691 (21.6)	4073 (16.1)
Missing	6514 (5.9)	1290 (5.1)
Diastolic blood pressure (in quartiles)		
Q1 (30–70 mmHg)	35,699 (32.5)	9183 (36.4)
Q2 (71–76 mmHg)	16,495 (15.0)	3525 (14.0)
Q3 (77–82 mmHg)	27,353 (24.9)	5914 (23.4)
Q4 (83–165 mmHg)	23,650 (21.5)	5301 (21.0)
Missing	6582 (6.0)	1328 (5.3)
Region[b]		
North East	4395 (4.0)	940 (3.7)
North West	20,720 (18.9)	4175 (16.5)
Yorkshire & The Humber	4200 (3.8)	990 (3.9)
East Midlands	2365 (2.2)	495 (2.0)
West Midlands	17,970 (16.4)	5025 (19.9)
East of England	5570 (5.1)	1110 (4.4)
London	11,635 (10.6)	2600 (10.3)
South East	24,885 (22.7)	5835 (23.1)
South West	18,045 (16.4)	4085 (16.2)
Missing	<5	<5
Polypharmacy (≥5 drugs)	90,667 (82.6)	23,660 (93.7)
Polypharmacy degree		
1–4 drugs	19,112 (17.4)	1591 (6.3)
5–9 drugs	54,586 (49.7)	10,828 (42.9)
≥10 drugs	36,081 (32.9)	12,832 (50.8)
Medical history		
COPD	15,549 (14.2)	6282 (24.9)
Heart failure	26,128 (23.8)	11,814 (46.8)
Ischemic heart disease	41,684 (38.0)	9530 (37.7)
Peptic ulcer	9530 (8.7)	2486 (9.8)
Diabetes		
without insulin	24,798 (22.6)	5947 (23.6)
with insulin	3909 (3.6)	967 (3.8)
Peripheral arterial disease	7113 (6.5)	2063 (8.2)
Atrial fibrillation	93,782 (85.4)	24,780 (98.1)
Venous thromboembolism	12,125 (11.0)	1984 (7.9)
Any bleeding	56,684 (51.6)	13,746 (54.4)
Stroke/TIA	16,572 (15.1)	4019 (15.9)

(*Continued*)

Table 1. Continued

Baseline characteristics	DOAC + beta-blocker	DOAC + digoxin
Chronic kidney disease		
Stage 3a	15,947 (14.5)	4629 (18.3)
Stage 3b	7639 (7.0)	2293 (9.1)
Stage 4	1581 (1.4)	453 (1.8)
Stage 5	1291 (1.2)	325 (1.3)
Missing	17,117 (15.6)	3479 (13.8)
Medication use in the past 3 mo		
PPIs	45,579 (41.5)	11,279 (44.7)
Amiodarone	3066 (2.8)	835 (3.3)
Aspirin	34,157 (31.1)	6349 (25.1)
Antiplatelet	13,902 (12.7)	2329 (9.2)
SSRIs/SNRIs	10,142 (9.2)	2841 (11.3)
Anticonvulsant[a]	647 (0.6)	208 (0.8)
ACEIs	40,901 (37.3)	9787 (38.8)
ARBs	18,050 (16.4)	4105 (16.3)
CCBs	33,786 (30.8)	7336 (29.1)
NSAIDs	13,017 (11.9)	2781 (11.0)
Oral corticosteroids	8817 (8.0)	3789 (15.0)
Statins	60,203 (54.8)	12,278 (48.6)
Macrolides	3800 (3.5)	1444 (5.7)
Estrogen/estrogen-like drugs	788 (0.7)	166 (0.7)
No. of GP active consultation in the past year		
Median (IQR)	13 (8–20)	16 (10–24)
Minimum, maximum	0, 311	0, 221
≥12 visits	60,653 (55.3)	16,988 (67.3)
<12 visits	48,517 (44.2)	8166 (32.3)
None	609 (0.6)	97 (0.4)

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; GP, general practice; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-noradrenaline reuptake inhibitors; TIA, transient ischemic attack.

[a] Anticonvulsant with side effect of bleeding.

[b] Round to nearest five due to data redaction.

1.35; 99% CI: 1.14−1.61) was associated with DOAC + digoxin (rate: 173.3/1000 person-year) versus DOAC + beta-blockers (rate: 85.8/1000 person-year) in the cohort study (Fig 3 & Table S4). Results for cardiovascular mortality were similar to all-cause mortality but the evidence was weaker (HR: 1.24; 99% CI: 0.98−1.57). The case-crossover study showed higher odds of all-cause mortality associated with an initiation of digoxin while taking DOACs (OR: 1.24; 99% CI: 1.06−1.45), in contrast to the OR of 0.87 (99% CI: 0.83−0.91) associated with digoxin monotherapy. Higher odds of all-cause mortality was also associated with the initiation of a DOAC while taking digoxin (OR: 1.63; 99% CI: 1.41−1.88), in contrast to the OR of 1.31 (99% CI: 1.25-1.37) associated with DOAC monotherapy.

We observed a lower risk of VTE associated with DOAC + digoxin versus DOAC + beta-blockers in cohort study (HR: 0.59; 99% CI: 0.36−0.96) but digoxin users had a lower baseline prevalence of VTE and the standardized difference for VTE was 0.1 indicating potential imbalance between groups. Power was also low for specific drug initiation patterns in case-crossover studies for both VTE and intracranial bleeding.

3.2. Subgroup analyses

Results for subgroup analyses were largely similar to the main analysis in the cohort study (Table S5−7). Notably, some evidence showed the increased risk of all-cause mortality associated with DOAC + digoxin versus DOAC +

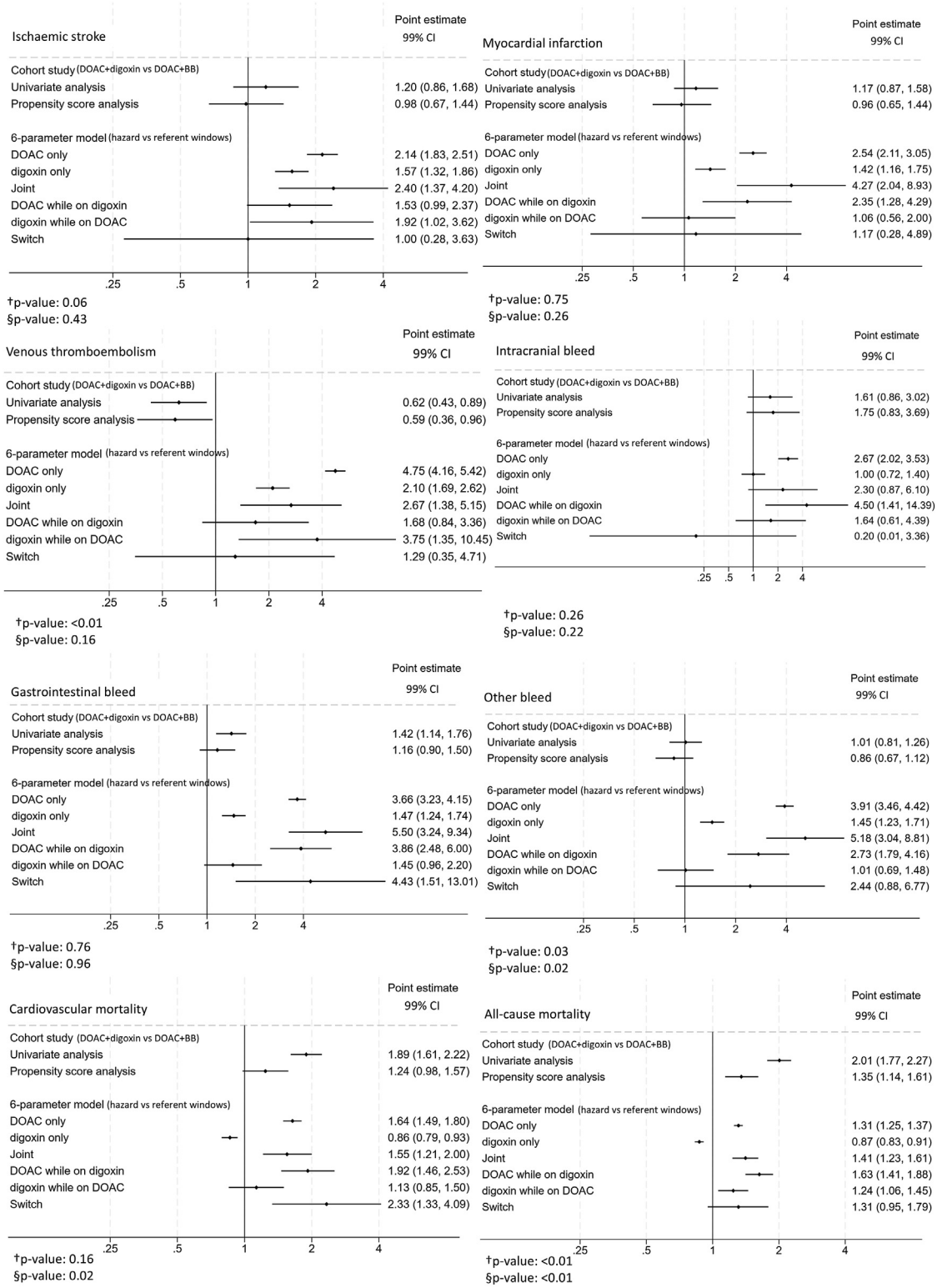


Figure 3. Results for DOACs + digoxin using cohort study design and case-crossover study design. DOACs, direct oral anticoagulants.

Table 2. Subgroup analysis for the association between concomitant use of DOAC and digoxin and all-cause mortality, compared with DOAC and beta-blockers in cohort study

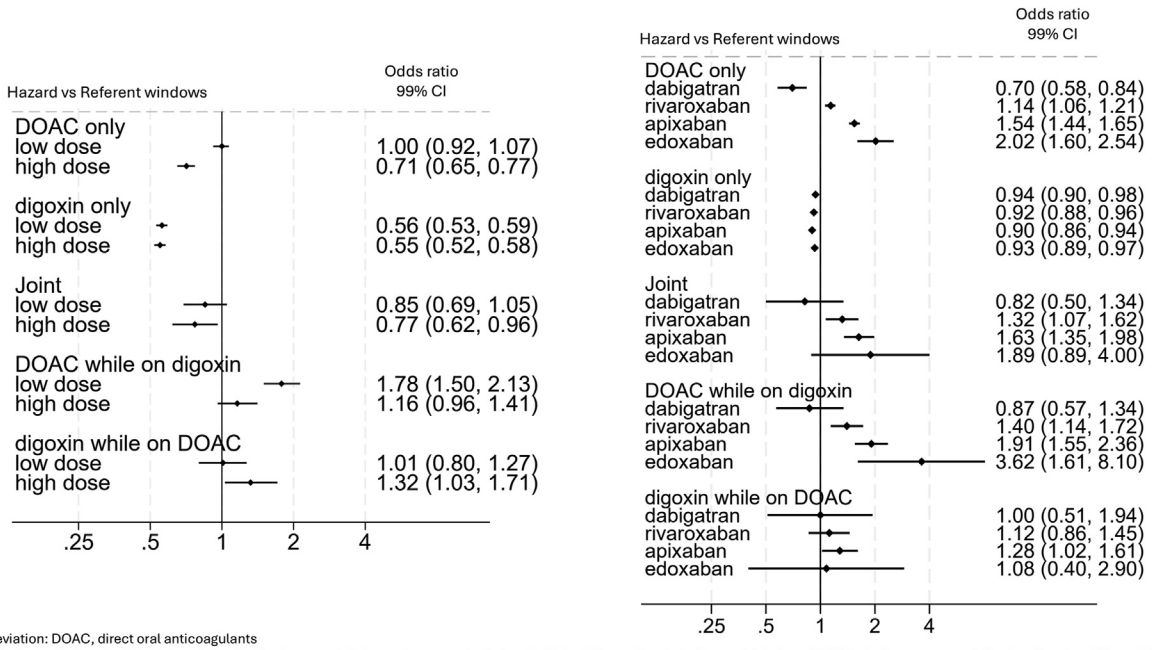
	All-cause mortality			
Subgroup	**HR**	**99% CI**		**Interaction *P* value**
Age at cohort entry				
≥18 to <65	1.58	0.86	2.89	.72
≥65 to <75	1.33	0.83	2.13	
≥75	1.29	1.07	1.56	
Bodyweight				
≤60 kg	1.14	0.88	1.47	.06
>60 to ≤120 kg	1.47	1.18	1.84	
>120 kg	0.87	0.31	2.49	
Potential indication				
Atrial fibrillation	1.37	1.18	1.57	.77
Venous thromboembolism	1.51	0.92	2.49	.59
Polypharmacy				
No. of drugs <5	0.92	0.33	2.53	.31
No. of drugs ≥5	1.37	1.16	1.63	
Renal function				
No CKD	1.63	1.30	2.04	.003
Stage 3a	1.01	0.71	1.44	
Stage 3b	0.91	0.63	1.31	
Stage 4	1.17	0.56	2.45	
Stage 5	1.09	0.37	3.25	
Sex				
Female	1.19	0.98	1.43	.03
Male	1.59	1.19	2.11	
Individual DOAC				
Dabigatran	1.01	0.57	1.78	.46
Rivaroxaban	1.43	1.09	1.87	
Apixaban	1.37	1.07	1.74	
Edoxaban	1.10	0.52	2.29	
Level of dose of DOAC[a]				
Low dose	1.23	1.01	1.50	.14
High dose	1.45	1.18	1.78	
Order of initiation				
Initiation of DOAC	1.24	0.92	1.68	.53
Initiation of digoxin	1.16	0.85	1.58	
Both drugs initiate together	1.38	1.06	1.78	

CI, confidence interval; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; HR, hazard ratio.

[a] Only restricted the cohort to people with atrial fibrillation in this analysis. High dose of DOAC for atrial fibrillation was defined when drug strength was 150 mg for dabigatran, 20 mg for rivaroxaban, 5 mg for apixaban, and 60 mg for edoxaban, respectively, while low dose was defined as 110 mg for dabigatran, 15 mg for rivaroxaban, 2.5 mg for apixaban, and 30 mg for edoxaban.

beta-blockers in men (HR: 1.59; 99% CI: 1.19−2.11) but not in women (HR: 1.19; 99% CI: 0.98−1.43) (interaction *P* value: .03) (Table 2 & S7). We also noted potential interaction for renal function (interaction *P* value: .003). Increased risks were only seen for those without chronic kidney disease (HR: 1.63; 99% CI: 1.30−2.04).

In the case-crossover study, among people with atrial fibrillation we observed increased odds of all-cause mortality associated with an initiation of low-dose DOAC while taking digoxin (OR: 1.78; 99% CI: 1.50−2.13) in contrast to low-dose DOAC monotherapy (OR: 1.00; 99% CI: 0.92−1.07) (Fig 4 & S7). We also observed increased odds of all-cause mortality associated with digoxin while taking high dose of DOAC (OR: 1.32; 99% CI: 1.03−1.71) in contrast to digoxin monotherapy (OR: 0.71; 99% CI: 0.65−0.77). For individual types of DOACs, we observed increased odds of all-cause mortality associated with initiation of digoxin while taking



Abbreviation: DOAC, direct oral anticoagulants
joint indicates initiate both DOAC and digoxin simultaneously in hazard or control window, **DOAC while on digoxin** indicates initiation of DOACs in the presence of digoxin, **digoxin while on DOAC** indicates initiation of digoxin in the presence of DOACs.
High dose of DOAC for atrial fibrillation was defined when drug strength was 150mg for dabigatran, 20mg for rivaroxaban, 5mg for apixaban, 60mg for edoxaban respectively while low dose was defined as 110mg for dabigatran, 15mg for rivaroxaban, 2.5mg for apixaban, 30mg for edoxaban.

Figure 4. Results of subgroup analysis in case-crossover study design.

apixaban (OR: 1.28; 99% CI: 1.02−1.61) in contrast to the OR of 0.90 (99% CI: 0.86−0.94) associated with digoxin monotherapy with *P* value of <.01, but not in other DOACs (Fig 4 & S8). We also observed increased odds of all-cause mortality associated with initiation of rivaroxaban/apixaban while taking digoxin, larger than the ORs associated with rivaroxaban/apixaban monotherapy with *P* value of .01.

3.3. Sensitivity analyses

Sensitivity analysis additionally adjusted for history of VTE due to its imbalance of standardized differences were similar to the primary analysis suggesting a lower risk of VTE comparing DOAC + digoxin with DOAC + beta-blockers, although the effect estimate was weaker and CIs crossed null (HR: 0.69; 99% CI: 0.42−1.13). For 7-day and 90-day risk windows, the association with all-cause mortality was no longer observed, in contrast to a 30-day risk window (Fig S9). We observed one new association using a 7-day risk window which was DOAC + digoxin with gastrointestinal bleeding.

All other sensitivity analyses showed similar results to the main analyses.

4. Discussion

4.1. Summary of findings

This study aimed to investigate whether there is a pharmacological and clinically relevant interaction between DOACs and digoxin. Our expectation was that any such interaction would involve potential p-glycoprotein competition, leading to increased DOAC levels which could increase the risk of DOAC side effects. Reassuringly, among 397,459 DOAC users in routine care in England, we found no evidence of an increased risk of bleeding outcomes in either cohort or case-crossover analysis.

4.2. Interpretation of the findings

All-cause mortality is related to DOAC effectiveness outcomes, and we would not anticipate an increased risk of an effectiveness outcome due to the potential mechanism of a drug-drug interaction between DOAC and digoxin. We surprisingly observed an increased risk of all-cause mortality associated with concomitant use of DOACs and digoxin. Notably, all-cause mortality is a composite outcome which requires further investigation of the specific causes involved to understand the mechanism behind. As we did not have data on all causes of death, we are unable to determine what causes were behind the observed increased risk. Future studies are required to evaluate the causes of death associated with DOACs + digoxin. A previous cohort study also found an increased risk of death associated with digoxin use among anticoagulant users. However, both warfarin and DOAC users were combined in this analysis [4]. Other studies also showed increased risk of all-cause mortality associated with digoxin in people with atrial fibrillation regardless of anticoagulant use [13,14]. Similar to our study, an interaction between sex and digoxin use was found where the higher risk

was found in men but not in women [4]. This might suggest that our findings of an elevated risk of all-cause mortality could be associated with digoxin instead of a drug interaction between digoxin and DOACs. As this is an observational study, we also cannot rule out the possibility of hard to measure time-varying confounding around the time of commencing a new medication.

An increased risk of gastrointestinal bleeding was associated with baseline digoxin use in dabigatran users but they did not take concomitant exposure to digoxin and DOAC into account [15]. In contract, the lack of evidence we found for an increased bleeding risk has also been reported by others [3]. Regarding VTE, DOAC + beta-blocker users were more likely to have a history of VTE than DOAC + digoxin users as an imbalanced covariate, leading to a spurious protective effect of DOAC + digoxin against VTE. However, after adding VTE as an adjusted variable in addition to PS, we noted that the estimate shifted toward null, demonstrating that history of VTE was a confounder that could not be fully accounted for using PS alone.

4.3. Clinical implications and recommendations

Current clinical guidelines for the management of atrial fibrillation stated that current clinical data directly comparing rate-control agents that could slow a rapid ventricular response were too limited to provide further recommendation [1]. Our study suggests the combined use of DOAC with digoxin is likely to be a safe combination with respect to known DOAC side effects. The finding of an increased risk of all-cause mortality associated with digoxin in DOAC users shows these patients are clinically vulnerable and likely require close monitoring. Our findings also suggest further investigation of potential effect modification by sex and renal function is warranted.

4.4. Potential advantages and challenges of using two study designs for drug-drug interaction studies

To investigate possible causal associations in drug-drug interaction research, conventional observational study designs including cohort studies have long been used. However, these designs are susceptible to between-person confounding because the risk of the outcomes of interest is compared between exposed group (those receiving the drug of interest) and comparison group (those not receiving the drug of interest). As a within-person study design, the case-crossover study can eliminate between-person confounding but cannot provide estimates of absolute risk. Notably, a cohort design is needed for estimating absolute risks which can then be used to quantify drug-drug interactions for evaluating public health impact. Therefore, cohort study and case-crossover study designs are an optimal combination of study designs by obtaining both robust relative and absolute measures of effect. Like our study, such an approach works well when the results from both designs align.

However, it is challenging to interpret the findings when results are conflicting. In situations when health characteristics are considerably different between exposed and comparison groups in cohort design, finding from case-crossover design is preferred to support the interpretation of cohort study design. However, the case-crossover study design is susceptible to time trend bias as observed changes in exposure between hazard and referent periods could be simply due to a population-level upward or downward trend in prescribing of the interacting drugs over time. In that case, findings from the cohort study design may be preferred as it is not prone to time-trend bias. As different study designs have their inherent strengths and limitations, the approach of using both designs can complement each other, thus could be applied in other contexts as triangulation for drug-drug interaction research.

4.5. Strengths and limitations

To date, this is the first population-based study investigating possible drug interactions between DOACs and digoxin using two study designs in England. With two study designs and robust methods, we can capture signals, estimate the absolute risk for public health implications, and reduce confounding. Notably, the six-parameter case-crossover design allows us to study potential drug interactions across a range of drug initiation patterns to help better understand possible clinical implications.

This study has some limitations. First, drug adherence and persistence were unknown, leading to potential misclassification bias of exposure. However, assuming a nondifferential misclassification of exposure, estimates would only be biased toward null. We also do not have data on plasma dosage of DOACs in our database, which could be explored in future studies. Whether the plasma concentrations of digoxin would be increased when concomitantly used with DOACs could also be investigated in future studies. Second, we did not have large cohorts for some drug-drug pairs. Notably, we conducted several subgroup analyses to further identify high-risk group, but they may be prone to type I error. Cautious interpretation is needed in particular when the size of subgroups varied substantially, leading to statistical significance. Third, our study population is predominantly Caucasians so results may not be generalizable to other ethnic groups. Fourth, there were also missing data for lifestyle factors and region but we used multiple imputation approach in PS which is shown to be unbiased [10]. Fifth, we were not able to determine potentially withheld DOAC treatment after any bleeding events, which might consequently lead to a temporary increased risk of

ischemic events. In our data, only a small proportion (7.7%) of first ischemic stroke occurs after any bleeding. Finally, we could not eliminate residual confounding, particularly in cohort design where DOAC + digoxin users appear to be frailer than DOAC + beta-blocker users. However, we attempted to minimize confounding by using a PS method. Our self-controlled design that can eliminate between-people confounders showed similar results, suggesting our results were robust.

5. Conclusion

We found no increased risk of DOAC-related side effects when DOACs are used with digoxin, suggesting combined use does not lead to drug-drug interactions. Future work is recommended to better understand the association with all-cause mortality and possible effect modification by underlying characteristics.

Submission declaration and verification

This work described has not been published previously (except in the form of an abstract, a published lecture or academic thesis, see Multiple, redundant or concurrent publication for more information), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright holder.

Ethics statement

We only used deidentified patient-level data; therefore, 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 (No. 23_002786). Stata/MP 17 and RStudio 2021.09.0 were used for data processing and analyses.

Data statement

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.

CRediT authorship contribution statement

Angel Y.S. Wong: Writing − review & editing, Writing − original draft, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Charlotte Warren-Gash:** Writing − review & editing, Methodology, Investigation. **Krishnan Bhaskaran:** Writing − review & editing, Methodology, Investigation. **Clémence Leyrat:** Writing − review & editing, Methodology, Investigation. **Amitava Banerjee:** Writing − review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Liam Smeeth:** Writing − review & editing, Supervision, Methodology, Investigation, Funding acquisition. **Ian J. Douglas:** Writing − review & editing, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Transparency declaration

This manuscript's guarantors (A. W. and I. D.) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Declaration of competing interest

I. J. D. has received research grants from GlaxoSmithKline (GSK) and AstraZeneca and holds shares in GSK. C. W. G. participated in a Data Safety Monitoring Board for an investigator-led trial of the effect of influenza vaccination after heart attack on future cardiovascular prognosis (NCT02831608) from January 2019 to April 2020. A. Y. S. W. received honoraria from the 6th Annual Meeting of the Society for Clinical Epidemiology in Tokyo and 28th Annual Meeting of the Japanese Society for Pharmacoepidemiology in Kyoto in November 2023, outside the submitted work. All other co-authors declare no conflict of interest.

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support. The interpretation and conclusions contained in this study are those of the authors alone.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2025.111709.

Data availability

The authors do not have permission to share data.

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