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Potential interactions between medications for rate control and direct oral anticoagulants: Population-based cohort and case-crossover study

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ABSTRACT

BACKGROUND Direct oral anticoagulants (DOACs) are commonly co-prescribed with amiodarone/diltiazem/verapamil, but whether there is a drug interaction between these drugs is unclear.

OBJECTIVE The purpose of this study was to investigate the risk of clinical outcomes associated with concomitant use of DOACs and amiodarone/diltiazem/verapamil.

METHODS We identified DOAC users in the Clinical Practice Research Datalink Aurum from January 1, 2011, to December 31, 2019. We used a cohort design to estimate hazard ratios for ischemic stroke, myocardial infarction, venous thromboembolism, intracranial bleeding, gastrointestinal bleeding, other bleeding, cardiovascular mortality, and all-cause mortality, comparing DOACs + amiodarone/diltiazem/verapamil users and DOACs + beta-blocker users. A case-crossover design comparing odds of exposure to different drug initiation patterns for all outcomes in hazard window vs referent window within an individual also was conducted.

RESULTS Of 397,459 DOAC users, we included 9075 co-prescribed amiodarone, 9612 co-prescribed diltiazem, and 2907 co-prescribed verapamil. There was no difference in risk of any outcomes between DOACs + amiodarone/diltiazem/verapamil users vs DOACs + beta-blocker users in the cohort design. However, in the case-crossover design, we observed an odds ratio (OR) of 2.09 (99% confidence interval [CI] 1.37–3.18) for all-cause mortality associated with initiation of a DOAC while taking amiodarone, which was greater than that observed for DOAC monotherapy (OR 1.30; 99% CI 1.25–1.35). Similar findings were observed for cardiovascular mortality and all-cause mortality respectively with diltiazem.

CONCLUSION Our study showed no evidence of higher bleeding or cardiovascular risk associated with co-prescribed DOACs and amiodarone, diltiazem, or verapamil. Elevated risks of cardiovascular and all-cause mortality were only observed during DOAC initiation when diltiazem/amiodarone were being taken.

KEYWORDS Direct oral anticoagulant; Amiodarone; Diltiazem; Verapamil; Drug–drug interactions

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Introduction

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

Beta-blockers or nondihydropyridine calcium channel blockers (diltiazem/verapamil) are recommended for acute rate control in people having AF with rapid ventricular response.[1,2] Amiodarone is a treatment of arrhythmias including AF, particularly when other drugs are ineffective; it also could be used for acute rate control.[2] Therefore, these cardiovascular drugs are commonly prescribed for people with AF. Because amiodarone, diltiazem, and verapamil are P-glycoprotein competitors and cytochrome P450 3A4 inhibitors, their co-prescription with a DOAC could result in an

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increased risk of drug–drug interactions, leading to thromboembolic or bleeding complications.[3,4] They are anticipated to potentially increase the risk of bleeding, which can be a side effect of anticoagulation, by increasing DOAC levels. However, the current clinical evidence of their potential drug–drug interactions is conflicting.[5–19] Routinely collected clinical datasets with robust methodologies using both cohort and within-person designs can be used to systematically investigate the potential effects of interactions and minimize the effect of confounding.

This population-based study aimed to investigate the risk of serious clinical outcomes associated with combined use of DOAC and amiodarone, diltiazem, and verapamil compared with DOAC with an active comparator (beta-blocker) using routine clinical data in England in 2 study designs.

Methods

Study designs

We conducted cohort (details in Supplemental Material S1) and case-crossover (details in Supplemental Material S2) studies to investigate potential drug interactions between DOACs and amiodarone, diltiazem, and verapamil (see Supplemental Figures S1 and S2 for design illustrations). The research reported in this paper adhered to RECORD guidelines.[20]

Data source

We used data from the Clinical Practice Research Datalink Aurum, which 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.[21] We also used linked death data from the Office for National Statistics, hospital admission data from Hospital Episode Statistics, and individual-level and practice-level deprivation data from the Index of Multiple Deprivation. Because we used de-identified patient-level data, individual informed consent was not required. The U.K. 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).

Abbreviations

AF: atrial fibrillation

CI: confidence interval

DOAC: direct oral anticoagulant

HR: hazard ratio

MI: myocardial infarction

OR: odds ratio

PS: propensity score

VTE: venous thromboembolism

Cohort study

Exposure

We identified people aged ≥18 years receiving their first DOAC (dabigatran, rivaroxaban, apixaban, edoxaban) in the Clinical Practice Research Datalink Aurum with acceptable research quality records during the period January 1, 2011, to December 31, 2019. To ensure that we had reliable measures of drug use and baseline covariates, all participants had ≥1-year continuous registration before the first recorded DOAC prescription. Amiodarone, diltiazem, and verapamil were defined as the precipitant drugs that were hypothesized to alter the effects of DOACs.[3,4]

To reduce confounding by indication, exposure was defined as receipt of a DOAC (ie, object drug) with a precipitant drug and was compared with receipt of a DOAC with an active comparator drug. Beta-blockers was chosen as the active comparator because they share similar indications of these cardiovascular drugs of interest and are not anticipated to interact with DOACs. People with any warfarin prescription before cohort entry were excluded to remove a carryover effect of warfarin. The overlapped duration of prescriptions for DOACs and precipitant drugs was used to determine the exposure groups. The exposure groups were defined as person-time when a DOAC and precipitant drugs or beta-blockers were prescribed concurrently (Supplemental Figure S1).

Outcomes

Effectiveness outcomes included ischemic stroke, myocardial infarction (MI), VTE, cardiovascular mortality, and all-cause mortality during follow-up. Safety outcomes were intracranial bleeding, gastrointestinal bleeding, and other bleeding (details in Supplemental Material S1).

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

Covariates

Potential confounders and predictor of outcomes[22] were selected as propensity score (PS) covariates using a directed acyclic graph (Supplemental Figures S3 to S5).

Statistical analyses

To reduce bias due to heterogeneity between exposure groups, PS values 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. Weights were calculated as the inverse of the PS of the treatment actually received for estimating average treatment effects. Covariate balance was assessed after weighting using standardized differences for each covariate. Hazard ratios (HRs) were computed using inverse probability-of-treatment-weighted Cox regressions with robust standard errors and 99% confidence interval (CI) to handle multiple testing.

We performed multiple imputation through chained equations with 10 imputed datasets[23] to address the missingness in blood pressure measurements, body mass index, smoking status, alcohol consumption, and region. We estimated the treatment effect from each imputed dataset and combined them using Rubin rules. We restricted the cohort to those

individuals whose PS values were within the overlapping region of the distributions of the DOAC + precipitant drug group and the comparison group.[24]

Subgroup analyses

To evaluate potential effect modification, analyses were stratified by age, sex, indications, level of DOAC dose (using strength as proxy) in people with AF, individual DOACs, degree of polypharmacy, bodyweight, drug initiation pattern, and kidney function using estimated glomerular filtration rate.

Sensitivity analyses

First, we included the DOAC alone group as the comparison group. The DOAC alone group was defined as person-time when a DOAC but not amiodarone/diltiazem/verapamil was prescribed. For those covariates that were imbalanced between groups after weighting, we also added them to the regression model for adjustment.

Modified case-crossover study

The case-crossover design eliminates time-invariant confounding as all comparisons are within the individual.[25] It only includes individuals who experienced the outcome (cases) 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).[26]

In each case-crossover analysis, we identified people who experienced the specific outcome with acceptable research quality records 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 the study start date (January 1, 2011) or at least 1-year continuous registration of general practitioner practices, reaching age 18 years until outcome occurrence, death, transfer out of the practice, last data collection date for the practice, or end of the study (December 31, 2019) (Supplemental Figure S2). Only discordant pairs of exposure status between hazard and referent windows contributed to the analyses. Outcomes were the same as for the cohort design.

The hazard window started from days 1–30 on/before the diagnosis date of outcome, and the control window started from days 91–120. 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 6-parameter model. The first 3 parameters address situations in which a drug interaction could not have occurred: (1) use of one drug in the hazard window and the other drug in the control window; (2) initiation of DOAC monotherapy; and (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. Figure 1 shows the considerations of interpretations for the 6-parameter model.

Subgroup analyses

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

Sensitivity analyses

First, 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. Stata/MP 17 (StataCorp LLC, College Station, TX) and RStudio 2023.12.1+402 (PBC, Boston, MA) were used for data processing and analyses.

Results

From January 1, 2011, to December 31, 2019, 397,459 people were prescribed a DOAC. Supplemental Table S1 lists the baseline characteristics of the exposure groups.

Compared with DOAC + beta-blocker users, DOAC + amiodarone users were more likely to be older, obese, have chronic obstructive pulmonary disease, heart failure, ischemic heart disease, AF, polypharmacy, and have ≥1 prescription for angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and oral corticosteroids but less likely to have VTE, a prescription for aspirin, antiplatelets, nonsteroidal anti-inflammatory drugs, or calcium channel blockers in the past 3 months.

Compared with DOAC + beta-blocker users, DOAC + diltiazem/verapamil users were more likely to be older, obese, have chronic obstructive pulmonary disease, peripheral artery disease, AF, polypharmacy, and have ≥1 prescription for oral corticosteroids, macrolides, and estrogen/estrogen-like drugs but less likely to have aspirin or antiplatelets in the past 3 months.

Compared with DOAC + beta-blocker users, DOAC + amiodarone/diltiazem/verapamil users also tended to have more general practitioner active consultation in the past year. Apixaban was the most commonly used of the DOACs, followed by rivaroxaban, dabigatran, and edoxaban. Standardized differences of all the covariates were <0.1, indicating balance between exposed groups after PS weighting (Supplemental Tables S2 to S8).

In case-crossover design, we identified 130,674 ischemic stroke, 154,598 MI, 135,808 VTE, 44,124 intracranial bleeding, 297,041 gastrointestinal bleeding, 359,857 other bleeding, 191,682 cardiovascular deaths, and 832,373 people who died and had valid follow-up during the study period.

Amiodarone

In the cohort design, we observed no difference in risk of all-cause mortality associated with DOAC + amiodarone vs DOAC + beta-blockers (HR 0.96; 99% CI 0.71–1.31) (Figure 2, Supplemental Figure S6, and Supplemental Table

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, with non-overlapping confidence intervals, this could 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, without overlapping confidence intervals 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 interactions.

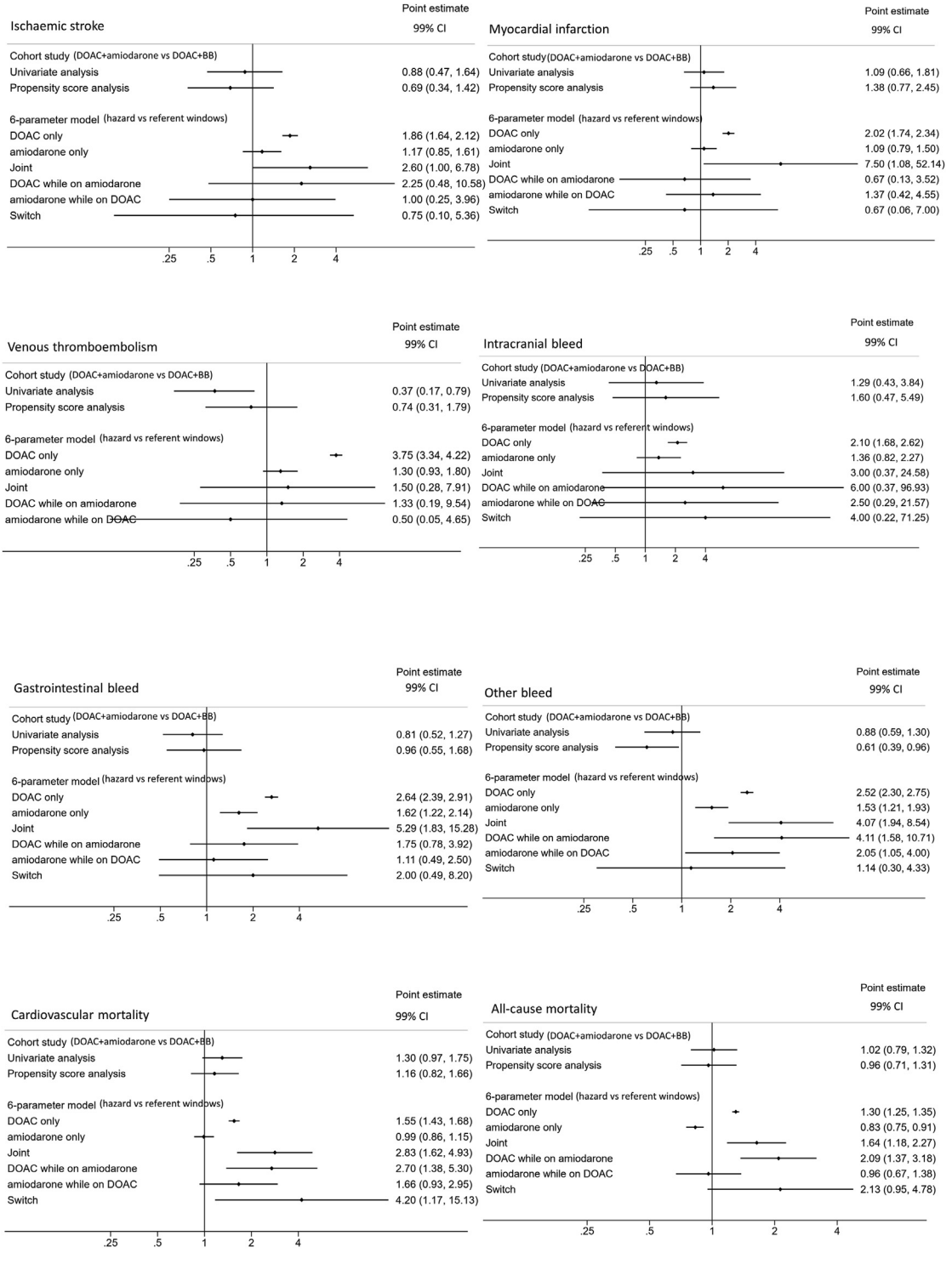
S9). In the case-crossover design, we observed OR of 2.09 (99% CI 1.37–3.18) for all-cause mortality associated with initiating DOAC while taking amiodarone, with nonoverlapping CIs with DOAC monotherapy (OR 1.30; 99% CI 1.25–1.35). An increased odds of all-cause mortality was also observed for joint initiation of DOAC and amiodarone (OR 1.64; 99% CI 1.18–2.27), but their CIs overlapped with DOAC monotherapy. No difference in odds was associated with initiating amiodarone while taking DOAC (OR 0.96; 99% CI 0.67–1.38).

We observed a lower risk of other bleeding associated with DOAC + amiodarone compared with DOAC + beta-blockers in the cohort design (HR 0.61; 99% CI: 0.39–0.96). Similar patterns were not found in the case-crossover design.

There was no difference in the risk of other outcomes associated with DOAC + amiodarone vs DOAC + beta-blockers in the cohort design, with HRs ranging from 0.69 for ischemic stroke to 1.60 for intracranial bleeding, and all CIs crossed 1 (Figure 2). In the case-crossover design, we observed an increased odds of MI only associated with joint initiation of DOAC and amiodarone, and its CI overlapped with that of DOAC/amiodarone monotherapy. We also observed an increased odds of other bleeding and cardiovascular mortality associated with both joint initiation of DOAC and amiodarone, and initiating DOAC while taking amiodarone, but their CIs overlapped with DOAC monotherapy.

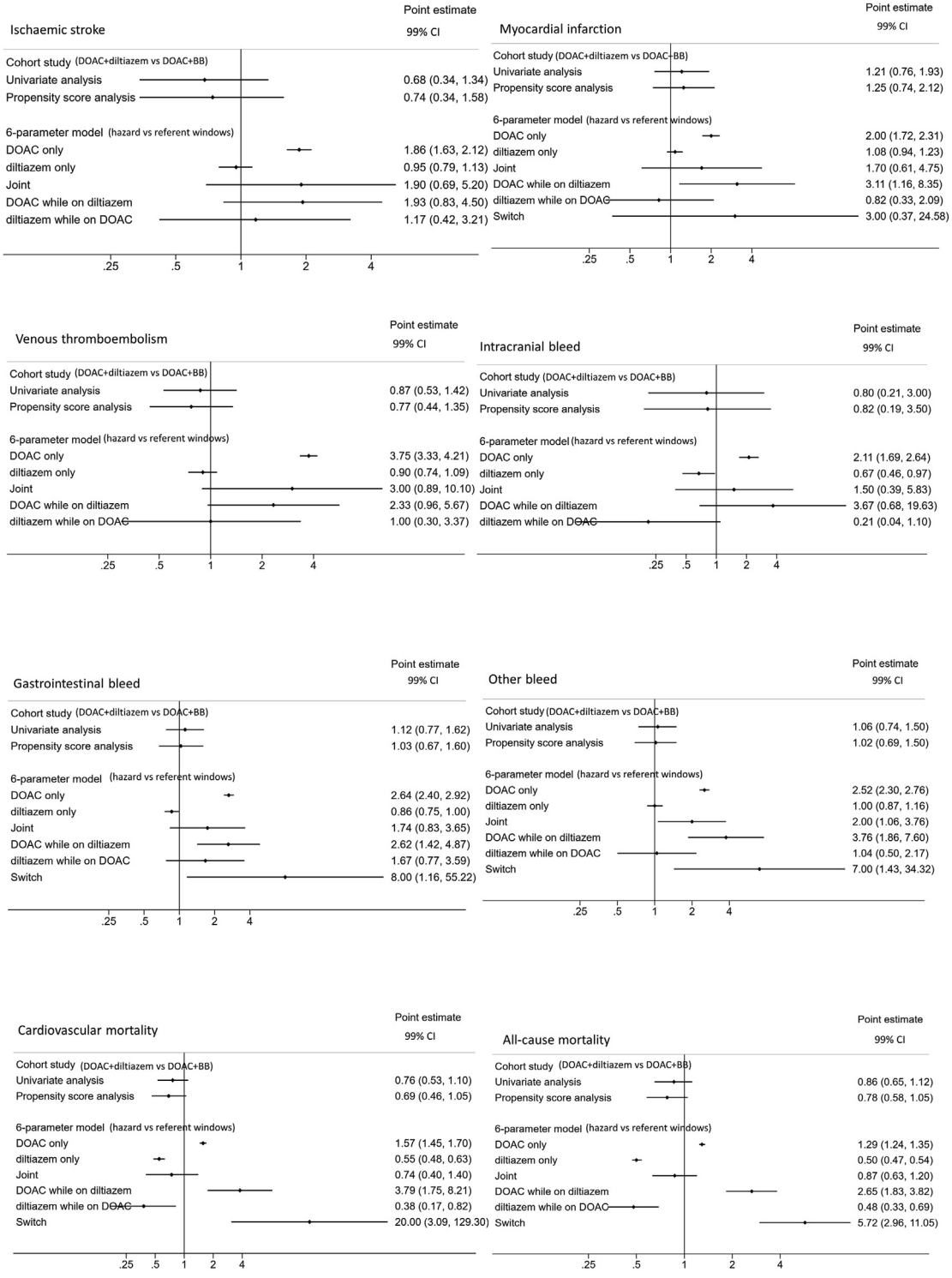
Diltiazem and verapamil

We observed no difference in risk of cardiovascular mortality associated with DOAC + diltiazem compared with DOAC + beta-blockers in the cohort design (HR 0.69; 99% CI 0.46–1.05) (Figure 3, Supplemental Figure S7, and Supplemental Table S10). However, in the case-crossover design, we observed an OR of 3.79 (99% CI 1.75–8.21) for cardiovascular mortality associated with initiating DOAC while taking diltiazem, with nonoverlapping CIs with DOAC monotherapy (OR 1.57; 99% CI 1.45–1.70). No difference in odds of cardiovascular mortality was observed for joint initiation of DOAC



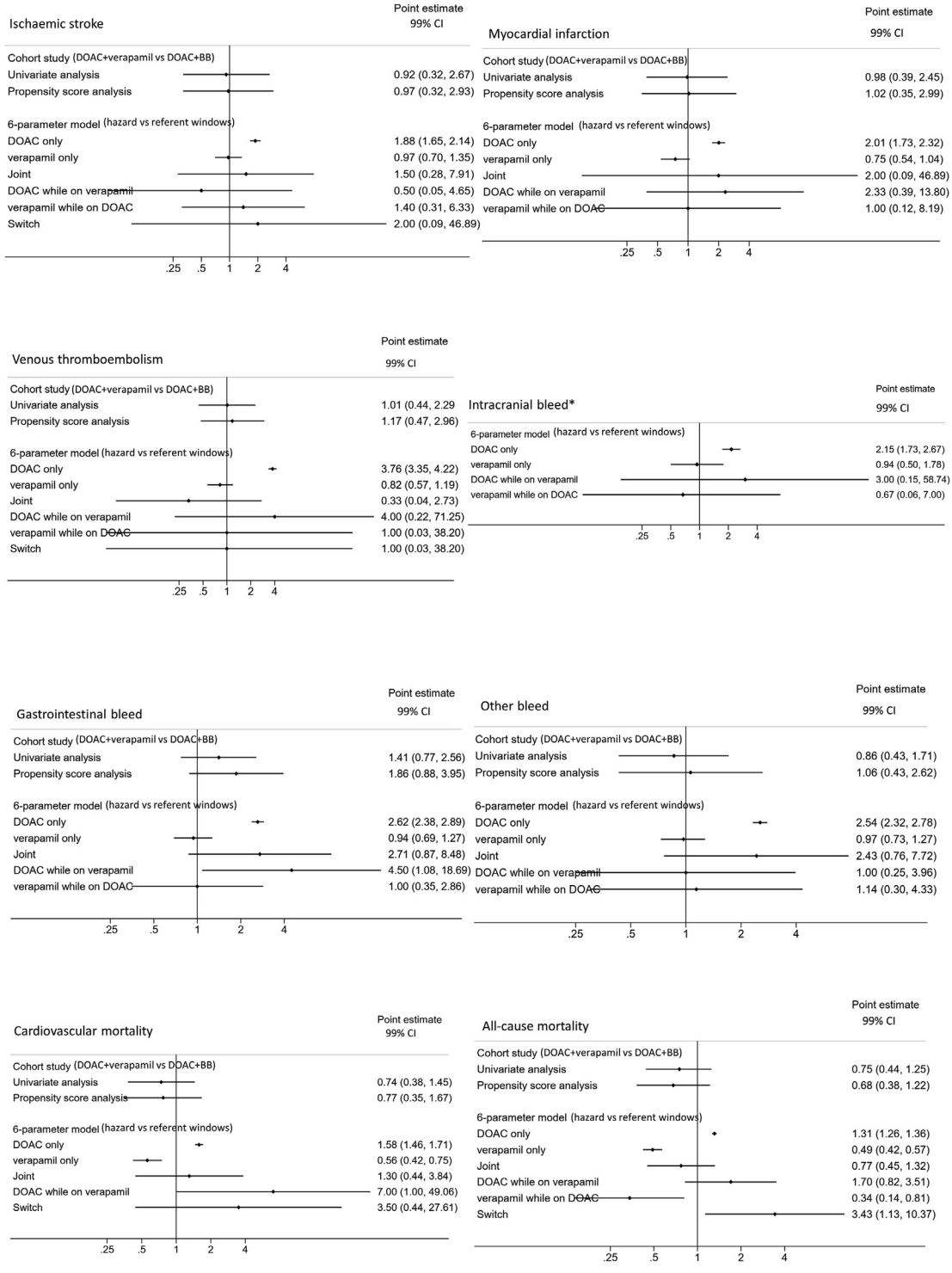
Abbreviation: DOAC, direct oral anticoagulants; BB, beta-blockers
Point estimate = HR in cohort study; OR in case-crossover study design.
Joint indicates initiate both drugs simultaneously in hazard or control window, **DOAC while on amiodarone** indicates initiation of DOACs in the presence of amiodarone, **amiodarone while on DOAC** indicates initiation of amiodarone in the presence of DOACs, **switch** indicates use of one drug in the hazard window and the other drug in the control window.

Figure 2
Results for direct oral anticoagulants (DOACs) + amiodarone using cohort study and case-crossover study designs. BB = beta-blocker; CI = confidence interval.



Abbreviation: DOAC, direct oral anticoagulants; BB, beta-blockers
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 diltiazem** indicates initiation of DOACs in the presence of diltiazem, **diltiazem while on DOAC** indicates initiation of diltiazem in the presence of DOACs, **switch** indicates use of one drug in the hazard window and the other drug in the control window.

Figure 3
Results for DOACs + diltiazem using cohort study and case-crossover study designs. Abbreviations as in Figure 2.



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

Figure 4
Results for DOACs + verapamil using cohort study and case-crossover study designs. Abbreviations as in Figure 2.

and diltiazem (OR 0.74; 99% CI 0.40–1.40), and initiating diltiazem while taking DOAC (OR 0.38; 99% CI 0.17–0.82). Similar patterns were were observed for all-cause mortality in both the cohort and case-crossover designs.

There was no difference in risk of other outcomes associated with DOAC + diltiazem vs DOAC + beta-blockers in the cohort design, with HRs ranging from 0.74 for ischemic stroke to 1.25 for MI, and all CIs crossed 1 (Figure 3). In the case-crossover design, we observed increased odds of MI and gastrointestinal bleeding only associated with initiating DOAC while taking diltiazem, and their CIs overlapped with that of diltiazem monotherapy. We also observed an increased odds of other bleeding associated with both joint initiation of DOAC and diltiazem, and initiating DOAC while taking diltiazem, but their CIs overlapped with DOAC monotherapy.

The cohort study showed no difference in risk of all outcomes associated with DOAC + verapamil compared with DOAC + beta-blockers, but the CIs were wide (Figure 4, Supplemental Figure S8, and Supplemental Table S11) as in the case-crossover analysis.

Subgroup analyses

Supplemental Tables S12 to S18 list the results of subgroup analyses in the cohort design. We observed an increased risk of MI associated with DOAC + amiodarone vs DOAC + beta-blockers in women (HR 2.33; 99% CI 1.10–4.96) but not in men (HR 0.77; 99% CI 0.31–1.90; interaction $P = .02$) (Supplemental Table S13). We also observed weak evidence of an increased risk of other bleeding when DOAC and diltiazem were initiated together vs DOAC and beta-blockers initiated together (HR 1.83; 99% CI 1.00–3.34) but not in other drug initiation patterns (interaction $P = .008$) (Supplemental Table S18). No other potential effect modifiers were found, aligning with our main analysis. Power was inadequate for conducting subgroup analyses for verapamil. In the case-crossover design, the increased odds of all-cause mortality associated with initiating DOAC while taking amiodarone/diltiazem was limited to low-dose DOAC monotherapy (Supplemental Figures S9 and S10). The odds did not differ by type of DOAC for DOACs + amiodarone (Supplemental Figure S11). We also observed an increased odds of all-cause mortality associated with initiating rivaroxaban/apixaban while taking diltiazem greater than rivaroxaban/apixaban monotherapy (Supplemental Figure S12).

Sensitivity analyses

Supplemental Figures S13 and S14 show the impact of varying the risk and referent window duration in the case-crossover design. For a 7-day risk window, the associations of DOAC + amiodarone with all-cause mortality, DOAC + diltiazem with cardiovascular mortality, and DOAC + diltiazem with all-cause mortality were no longer observed. For a 90-day risk window, the association of DOAC + diltiazem with cardiovascular mortality was no longer observed. All other sensitivity analyses showed results similar to the main analyses.

Discussion

Summary of findings

Among 397,459 DOAC users in cohort analyses of routine health care data in England, we found no difference in risk of DOAC effectiveness or safety outcomes indicating potential drug interactions with amiodarone, diltiazem, or verapamil. Case-crossover analysis showed similar findings except for evidence of a possible increased odds of all-cause mortality and cardiovascular mortality within 30 days after initiation of DOACs during ongoing diltiazem/amiodarone therapy.

Amiodarone, diltiazem, and verapamil are P-glycoprotein competitors and moderate cytochrome P450 3A4 inhibitors, so theoretically they could increase the risk of bleeding with DOACs. Both our cohort and case-crossover studies showed no evidence of a higher risk of bleeding associated with coprescribed DOAC with these drugs. The pharmacological profile of amiodarone, diltiazem, and verapamil would not indicate an increased risk of DOAC effectiveness outcomes. Therefore, the increased risk of all-cause and cardiovascular mortality associated with initiation of DOACs when taking diltiazem/amiodarone detected in the case-crossover analysis is surprising. However, the elevated risk was not observed in other relevant drug interaction initiation patterns. Understanding the mechanism underlying this elevated risk of mortality should be investigated in future studies. Unexpectedly, we observed a 39% lower risk of other bleeding associated with DOAC + amiodarone vs DOAC + beta-blockers in the cohort analysis. However, we did not observe a similar pattern in the case-crossover design, suggesting the results of the cohort analysis may have been due to time-invariant between person confounding. Notably, we also conducted large number of analyses, which may be prone to type I error.

Amiodarone

Previous observational studies showed a higher risk of bleeding associated with amiodarone vs nonuse in DOAC users (Supplemental Table S19).[5,10,11,13,18,27] A further study showed no difference in risk of bleeding associated with any DOAC + amiodarone vs nonuse but an increased risk of bleeding associated with amiodarone vs nonuse in rivaroxaban users only.[19] A study showed increased risk of bleeding associated with amiodarone in rivaroxaban/apixaban users vs other antiarrhythmic drugs, but they did not have data on aspirin/body mass index to account for confounding.[14] Similar to our findings, a systematic review using data from 4 randomized controlled trials showed no difference in risk of stroke and bleeding comparing people taking DOAC and amiodarone vs DOAC monotherapy, although the numbers of patients involved were low.[16] One study similarly showed no difference in risk of stroke but an increased risk of all-cause mortality associated with amiodarone in DOAC users vs nonuse.[10] Given that the health characteristics of people prescribed DOACs with amiodarone were systematically different from those prescribed DOAC monotherapy, studies with nonuse of precipitant drugs as the comparison group could be prone to a higher degree of confounding.

Diltiazem and verapamil

Consistent with our results, 2 studies reported no difference in risk of bleeding associated with diltiazem/verapamil compared with nonuse of diltiazem/verapamil in DOAC users (Supplemental Table S19).[5,15] Two other cohort studies with concomitant use of DOACs and beta-blockers as the comparison group to reduce confounding by indication showed similar results.[6,7] However, a cohort study showed increased risk of serious bleeding comparing diltiazem with metoprolol in apixaban/rivaroxaban users, but the type of bleeding was not thoroughly investigated.[28] A cohort study showed dabigatran users had an increased risk of bleeding when co-prescribed diltiazem/verapamil but not rivaroxaban/apixaban users.[7] However, our subgroup analysis according to different types of DOAC did not show similar results. Studies have shown an increased risk of bleeding associated with diltiazem/verapamil compared with nonuse in DOAC users.[8,10–12,27,29] One study showed an increased risk of bleeding associated with diltiazem/verapamil but DOAC and warfarin users were combined, with no evidence available restricted to DOACs.[29] One study showed an increased risk of bleeding associated with verapamil but not diltiazem in DOAC users vs nonuse.[19] For cardiovascular outcomes, 2 studies similarly showed no difference in risk of stroke associated with diltiazem/verapamil vs nonuse among DOAC users.[10,29]

Study strengths and limitations

This is the first population-based study to investigate possible drug interactions between DOACs and amiodarone, diltiazem, and verapamil using 2 complementary study designs in England. With both designs, we can compare the risk of outcome between rate control agents and minimize confounding. We also showed the co-prescribing patterns of rate control medications in DOAC users and their characteristics in England.

This study has some limitations. First, as in all observational research on drug interactions, 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 verapamil. Furthermore, our study population was predominantly Caucasian, so results may not be generalizable to other ethnic groups. We were not able to determine whether DOAC treatment was withheld after any bleeding events, which consequently might lead to a temporary increased risk of ischemic events. In our study, only a small proportion (8%–9%) of ischemic stroke occurring after any bleeding. Lastly, we could not eliminate residual confounding and lack data on ejection fraction to determine the baseline heart condition, but we attempted to minimize confounding by using a PS method and self-controlled design.

Clinical implications and recommendations

Rate control and stroke prevention are the 2 management priorities in individuals with AF both acutely and chronically, yet drug interactions have not been comprehensively studied. Current clinical data directly comparing rate-control agents that could slow a rapid ventricular response were limited,[1] so our study adds important evidence that the risks of these clinical outcomes in DOAC + amiodarone/diltiazem/verapamil users were comparable to those of DOAC + beta-blocker users. We showed a synergistically increased risk of mortality, specifically when initiating a DOAC in amiodarone/diltiazem users vs initiating a DOAC monotherapy, suggesting the need for close clinical monitoring in these patients. Our study showed that drug–drug interactions between these drugs were unlikely, especially with regard to bleeding risk, which should help with prescribing decisions for people with AF/VTE. However, given the lack of power for some outcomes, larger studies are required to confirm the findings.

Conclusion

We found no strong evidence of increased risk of bleeding and cardiovascular disease outcomes when DOACs were used with amiodarone, diltiazem, and verapamil. We found a higher risk of mortality outcomes associated with initiating DOACs when taking diltiazem/amiodarone, which might require close clinical monitoring in these patients.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2024.06.033.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

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.

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