Accepted Manuscript

British Journal of General Practice

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DOI: https://doi.org/10.3399/BJGP.2024.0349

To access the most recent version of this article, please click the DOI URL in the line above.

Received 18 June 2024
Revised 06 November 2024
Accepted 11 November 2024

Potential interactions between direct oral anticoagulants and atorvastatin/simvastatin: cohort and case-crossover study

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Word count (<2500): 2638

Abstract (<250 words)

Background: Direct oral anticoagulants (DOACs) are commonly co-prescribed with statins. Although biologically plausible, whether there is a drug interaction between DOACs and atorvastatin/simvastatin is unclear.

Aim: To investigate the association between co-prescribed DOACs and atorvastatin/simvastatin and bleeding, cardiovascular disease and mortality.

Design and Setting: Clinical Practice Research Datalink Aurum(1/1/2011-31/12/2019).

Method: We used a cohort design to estimate hazard ratios for clinically relevant pharmacological interaction safety outcomes (intracranial bleeding, gastrointestinal bleeding, other bleeding) comparing DOACs+atorvastatin/simvastatin with DOACs+other statins (fluvastatin, pravastatin and rosuvastatin which are not anticipated to interact with DOACs). Effectiveness outcomes (ischaemic stroke, myocardial infarction, venous thromboembolism, cardiovascular mortality, and all-cause mortality) were also included. A case-crossover design comparing odds of exposure to different drug initiation patterns in hazard window versus referent window within an individual was also conducted.

Results: Of 397,459 DOAC users, we selected 70,318 people co-prescribed atorvastatin, and 38,724 co-prescribed simvastatin. The cohort analysis showed no difference in risk of all outcomes comparing DOACs+atorvastatin/simvastatin versus DOACs+other statins. In case-crossover analysis, ORs for other bleeding (OR:5.06; 99%CI:3.79–6.76) amongst those initiating DOACs while taking atorvastatin, and the ORs for gastrointestinal bleeding (OR:6.05; 99%CI:4.28–8.54) and other bleeding (OR:6.81; 99%CI:4.74–9.78) amongst those initiating DOACs while taking simvastatin were greater than those initiating DOAC monotherapy. Similar patterns were also observed for cardiovascular mortality and all-cause mortality.

Conclusion: This study shows no evidence of interaction between DOACs and atorvastatin/simvastatin. However, people starting a DOAC whilst taking atorvastatin/simvastatin, were at high risk of bleeding and mortality, likely due to temporal clinical vulnerability.

Keywords:Hydroxymethylglutaryl-CoA Reductase Inhibitors;Anticoagulants;Drug Interactions

Word count: 250

How this fit in

Direct oral anticoagulants (DOACs) are commonly co-prescribed with statins. Although biologically plausible, whether there is a drug interaction between DOACs and atorvastatin/simvastatin is unclear. Our study analysed data on 70,318 DOAC users co-prescribed atorvastatin, and 38,724 co-prescribed simvastatin in England. Our results suggest that the use of different statins is unlikely to influence the risk of bleeding, cardiovascular disease, and mortality in DOAC users. However, healthcare providers and patients need to be alert to the elevated risks of bleeding and mortality which were only observed in specific situation of starting a DOAC whilst taking statin.

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).

Patients requiring anticoagulation are usually older and often have chronic diseases, including coronary artery disease, resulting in polypharmacy[1-3]. Statins including atorvastatin and simvastatin are also commonly used as a primary and secondary prevention of cardiovascular disease.[4,5] Notably, DOACs are substrates for the efflux transporter P-glycoprotein and are metabolised by the cytochrome P450 system (CYP3A4 enzymes).[6] As atorvastatin and simvastatin are p-glycoprotein competitors and CYP3A4 inhibitors[7,8], their co-prescription with DOAC might lead to an increased risk of drug-drug interactions. Therefore, any clinically relevant interaction with atorvastatin/simvastatin would be expected to increase the risk of DOAC side effects, particularly bleeding. As the hypothesised 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.[9-12]

Therefore, this study aimed to investigate the risk of serious clinical outcomes associated with combined use of DOAC and atorvastatin/simvastatin using routine clinical data in England in two study designs.

Methods

Study design

We conducted cohort and case-crossover studies (design illustration in Figure S1-S2). Material S3 summarises the reporting of our study was in accordance with REporting of studies Conducted using Observational Routinely-collected Data reporting (RECORD) guidelines (Material S3)[13].

Data Source

We used data from the Clinical Practice Research Datalink (CPRD) Aurum. It contains primary care records of more than 13 million currently registered patients from 1491 general practices in the UK using EMIS software systems. 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, hospital admissions data from Hospital Episode Statistics, and individual-level and practice-level deprivation data from Index of Multiple Deprivation.

Cohort study

Exposure

We selected people aged ≥18 years receiving their first DOACs (dabigatran, rivaroxaban, apixaban and edoxaban) with acceptable research quality records in CPRD Aurum during 1/1/2011-31/12/2019. To ensure reliable measures of drug use and baseline covariates, all participants had ≥1-year continuous registration before the first recorded DOAC prescription. Atorvastatin and simvastatin were defined as the precipitant drug that was hypothesised to alter the effects of DOACs as they are p-glycoprotein competitors and cytochrome P450 3A4 inhibitors.[7,8]

The exposure was defined as concurrent prescription of DOAC with atorvastatin or simvastatin respectively (e.g. DOAC+atorvastatin) and was compared with concurrent prescription of DOAC with

other statins (fluvastatin, pravastatin and rosuvastatin). We selected other statins as comparison group as they share similar indications with atorvastatin/simvastatin and are not anticipated to interact with DOACs.[7,8] People with any warfarin prescription before cohort entry were excluded to remove a carry-over effect of warfarin. The duration of drug prescriptions was calculated (Material S1) and used to determine the exposure groups (Figure S1).

Outcomes

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

We followed both groups until the earliest of discontinued treatment of either drug (DOAC/atorvastatin/simvastatin), drug switching to warfarin, switching between atorvastatin/simvastatin and active comparators, outcome occurrence, death, transfer out of the practice, last data collection date for the practice or end of the study (31/12/2019).

Covariates

Potential confounders and predictors of outcomes[15] were selected as propensity score (PS) covariates using a directed acyclic graph (Supplementary Figures S3-S5).

Statistical analyses

To reduce bias due to heterogeneity between exposure groups, PS 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 received for estimating average treatment effects. Covariate balance was assessed after weighting using standardised 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 to address the data missingness. We estimated the treatment effect from each imputed dataset and combined them using Rubin's rules. We restricted the cohort to those individuals whose PS were within the overlapping region of the distributions of the DOAC+precipitant drug group and the comparison group.[16]

Subgroup analyses

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.

Sensitivity analyses

We included DOAC alone group as the comparison group, defined as person-time when a DOAC but not atorvastatin/simvastatin was prescribed.

Modified case-crossover study

The case-crossover design eliminates time-invariant confounding as all comparisons are within the individual.[17] It only includes individuals who experienced the outcome and compares each

individual's exposure in a period before the outcome (hazard window) to the exposure during an earlier control period (referent window).[18]

We selected people who experienced the specific outcome with acceptable research quality records and were exposed to DOACs and/or atorvastatin/simvastatin prior to the outcome during a valid follow up, which started from the latest of study start date (1/1/2011) or at least 1-year continuous registration of GP practices, 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 (31/12/2019) (Figure S2). Only the first event was included (Material S2).

The hazard window started from days 1-30 on/before the outcome occurrence, and the control window started from days 91-120 before the outcome occurrence. We added a 60-day washout period to avoid auto correlation in exposure between periods and carryover effects.

We used conditional logistic regression to estimate the odds ratios (ORs) for all outcomes associated with different drug initiation patterns using the 6-parameter model, conditioned on individual with 99% CI to handle multiple testing. Figure 1 shows the considerations of interpretations.

Subgroup analyses

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

Sensitivity analyses

We used 7-day and 90-day hazard and referent windows to investigate the sensitivity of results to risk period length. We conducted a *post-hoc* sensitivity analysis by repeating the analyses for concomitant use of DOACs and other statins.

Stata/MP17,18 and RStudio2021.09.0 was used for data processing and analyses.

Results

A total of 397,459 people were prescribed a DOAC. Compared with other statins (n=8577), DOAC+atorvastatin users (n=70,318) were more likely to be younger, have higher levels of deprivation, higher level of alcohol consumption, but with similar proportions of comorbidities and medications used in the past 3 months (Figure S6, Table S1).

Compared with other statins(n=8922), DOAC+simvastatin users(n=38,724) were more likely to be older, have higher levels of deprivation, but with similar proportions of comorbidities and medications used in the past 3 months (Figure S6, Table S2). DOAC+atorvastatin/simvastatin users tended to have fewer GP active consultation in the past year than DOAC+other statins users. Standardised differences for each outcome were shown in Table S3-7.

In case-crossover studies (Figure S7), we selected 130,674 ischaemic stroke, 154,598 MI, 135,808 VTE, 44,124 intracranial bleeding, 297,041 gastrointestinal bleeding, 359,857 other bleeding, 191,682 cardiovascular death, and 832,373 people who died.

Atorvastatin

In the cohort analysis, no evidence of an increased risk of either safety or effectiveness outcomes was observed. HRs ranged from 0.60 for intracranial bleeding to 1.35 for ischaemic stroke or other bleeding, with CIs all including 1 (Figure 2 & S8, Table S8).

In the case-crossover analysis, the ORs for other bleeding and mortality outcomes amongst those initiating a DOAC while taking atorvastatin (ORs ranging from 2.28 for all-cause mortality to 5.06 for other bleeding) were greater than those observed with DOAC monotherapy. However, no increased odds of these outcomes were observed for people initiating atorvastatin while taking a DOAC.

Simvastatin

In the cohort analysis, no evidence of increased risk of all outcomes except all-cause mortality, comparing DOAC+simvastatin versus DOAC+other statins. HRs ranged from 0.48 for intracranial bleeding to 1.44 for ischaemic stroke with CIs crossing 1 (Figure 3 & S9, Table S9). Although an increased risk of all-cause mortality associated with DOAC+simvastatin was observed, compared with DOAC+other statins (HR:1.49; 99%CI:1.02–2.18), finer adjustment for age (categorised as 18-40, 40-50, 50-60, 60-70, 70-80, 80+ years) weakened this association (HR:1.44; 99%CI:0.98–2.10).

In the case-crossover analysis, we observed that the odds of bleeding and mortality outcomes (except intracranial bleeding) amongst those initiating a DOAC while taking simvastatin (ORs ranging from 3.18 for all-cause mortality to 6.81 for other bleeding) were greater than those for DOAC monotherapy. However, no similar pattern was seen amongst people initiating simvastatin whilst receiving a DOAC.

Subgroup analyses

Results in the cohort analysis were similar to the main analysis (Tables S10-16).

In case-crossover analysis, the odds for all outcomes did not increase with higher DOAC dose in people with atrial fibrillation (Figure S10-S11). We observed that an increased odds of mortality associated with an initiation of DOACs while taking atorvastatin, greater than those for DOAC monotherapy, differed by type of DOAC, including cardiovascular mortality (apixaban:2.94) and all-cause mortality (rivaroxaban:1.57;apixaban:2.90) (Figure S12). Similarly, the odds of some outcomes associated with initiating DOACs while taking simvastatin were greater than the odds for DOAC monotherapy; that also differed by types of DOACs including gastrointestinal bleeding (apixaban:6.86), other bleeding (rivaroxaban:5.86), cardiovascular mortality (rivaroxaban:3.03;apixaban:5.41), and all-cause mortality (dabigatran:1.58; rivaroxaban:2.50;apixaban:3.87;edoxaban:6.10) (Figure S13).

Sensitivity analyses

In the cohort analysis, using DOAC alone group as comparison group produced similar results to the main analysis using active comparator as the comparison group (Tables S8-9). Notably, no increased risk of all-cause mortality was observed in DOAC+simvastatin, versus DOAC alone.

In the case-crossover analysis, we observed some evidence of greater ORs for other bleeding (OR: 7.91; 99%CI:3.47–18.03), cardiovascular mortality (OR: 2.83; 99%CI:1.54–5.22), and strong evidence of greater odds of all-cause mortality (OR: 2.29; 99%CI:1.61–3.25) amongst those initiating a DOAC while taking other statins compared with the ORs observed with DOAC monotherapy(Figure S14). For duration of effect (Figure S15), the association with initiating DOACs while taking atorvastatin and synergistic risks were no longer seen for other bleeding in other risk windows. For a 7-day and 90-day risk window, the association with initiating DOACs while taking simvastatin and synergistic risk of myocardial infarction was observed (Figure S16). New associations seen were a synergistic increased risk of ischaemic stroke using a 90-day risk window and increased risk of myocardial infarction using a 7-day risk window when initiating DOAC while taking atorvastatin (Figure S15). An

increased risk of intracranial bleeding using a 7-day risk window when initiating DOAC while taking simvastatin was observed (Figure S16).

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

Discussion

Summary

Using two complementary study designs, we observed no evidence of a clinically relevant pharmacological interaction between DOACs and statins. Although atorvastatin and simvastatin are p-glycoprotein competitors and moderate cytochrome P450 3A4 inhibitors and could theoretically increase the risk of bleeding, our cohort analysis found no evidence of a higher risk of bleeding associated with co-prescribed DOAC with these statins.

In the case-crossover design only, for atorvastatin and simvastatin we observed an increased risk of bleeding and mortality for people initiating a DOAC while taking statins. No increased risk of these outcomes was seen in people initiating either statin whilst receiving a DOAC. Whilst the case-crossover is an effective design for dealing with between person differences, it remains vulnerable to confounding by time-varying characteristics. This suggests these adverse outcomes are unlikely to be the result of a pharmacological interaction but are a marker of poor health around the time of DOAC initiation amongst statin users. We anticipated that risks of effectiveness outcomes would not be increased through the mechanism due to drug-drug interaction and showed no difference in risk of effectiveness outcomes except all-cause mortality with DOAC+simvastatin, versus DOAC+other statins in cohort analysis. Given that DOAC+simvastatin users were older than DOAC+other statins users, it might explain the spurious harmful effect of DOAC+simvastatin initially observed against all-cause mortality. After finer age adjustment in addition to PS, we noted that the estimate shifted towards null, supporting that age could not be fully accounted for using PS alone. Moreover, there was no evidence of an elevated risk of all-cause mortality when comparing DOAC+simvastatin versus DOAC alone in our sensitivity analysis. However, we observed a similar pattern for other bleeding, cardiovascular mortality and all-cause mortality that; the increased odds when initiating DOACs while taking other statins was greater than the increased odds associated with initiating DOAC monotherapy. It supports the interpretation that the increased odds of other bleeding, cardiovascular mortality and all-cause mortality were not specific to atorvastatin/simvastatin, and therefore unlikely due to a drug-drug interaction but possibly time-varying confounding.

Strengths and limitations

To-date, this is the first population-based study investigating drug interactions between DOACs and atorvastatin/simvastatin using two study designs in England. With active comparator, propensity scores, and self-controlled designs, we can robustly evaluate the relative risk of clinical outcomes, estimate the absolute risk for public health implications and reduce confounding.

This study has some limitations. First, drug adherence and persistence were unknown, leading to potential misclassification bias of exposure. Assuming a non-differential misclassification of exposure, estimates would be biased towards null. Second, we did not have large cohorts for some drug-outcome pairs, specifically for intracranial bleeding. We conducted several subgroup analyses, but they may be prone to type I error that requires cautious interpretation. Further, our study population is predominantly White so results may not be generalisable to other ethnicities. There

were also missing data but we used multiple imputation approach in propensity score. The data on discontinuing DOAC treatment due to bleeding was not available to investigate if the risk of thromboembolic events elevated after bleeding. However, only ~10% of our cohort had their first ischaemic stroke after bleeding during follow-up. Lastly, we could not eliminate residual confounding but we attempted to minimise confounding by using a PS method and self-controlled design.

Comparison with existing literature

A case-control study showed higher risk of major bleeding associated with simvastatin or lovastatin compared with other statins in dabigatran users.[10] However, they similarly showed no difference in risk of stroke. Notably, atorvastatin was included in the comparison group, which is a CYP3A4 inhibitor, leading to difficulty in result interpretation. Aligning to our findings, a cohort study reported no evidence of an increased risk of VTE and major bleeding comparing any statins with non-use in rivaroxaban users but they did not specifically investigate different types of statins.[11] Two cohort studies showed a lower risk of major bleeding associated with DOAC+atorvastatin or any statins compared with DOAC alone.[9,12] In contrast, we showed no difference in risk of bleeding in cohort analysis with and without active comparators. No previous studies evaluated the impact of drug initiation patterns and mortality outcomes for the concomitant use of DOACs and statins.

Implications for research and/or practice

Atorvastatin and simvastatin are the most widely prescribed statins accounting for 63 million and 14 million prescriptions respectively across all GP practices in England in 2023.[19] The safety of prescribing these statins in DOAC users is important information which reassures prescribers and patients. Our study directly compared atorvastatin and simvastatin with other statins and found no difference in risk of all important clinical outcomes. This suggests that the use of different statins is unlikely to influence the risk of bleeding, cardiovascular disease, and mortality in DOAC users. However, healthcare providers and patients need to be alert when atorvastatin/simvastatin users initiate a DOAC as these patients were at high risk of developing bleeding and mortality shown in our study.

Conclusions

Our study found no evidence of a clinically relevant pharmacological interaction between atorvastatin/simvastatin and DOACs. However, people starting a DOAC while taking atorvastatin/simvastatin were at high risk of developing bleeding and mortality, likely due to temporal clinical vulnerability.

Authors' contributions

Contributions are as follows:

Conceptualization ID AYSW;

Data curation AYSW;

Formal Analysis AYSW;

Funding acquisition AYSW;

Methodology ID AYSW LS CL KB AB CWG;

Writing (original draft) AYSW ID;

All authors were involved in design and conceptual development and reviewed and approved the final manuscript.

Acknowledgements

We would like to thank people living with cardiovascular conditions who reviewed the lay summary of the protocol and comment on their perceptions towards the clinical importance of outcome. We also thank Dr Adrian Root for research inspiration. This study is based on data from the CPRD, obtained under licence from the UK Medicines and Healthcare Products Regulatory Agency. The data are provided by patients and collected by the National Health Service as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone.

Funding

This work was supported by the British Heart Foundation (FS/19/19/34175). LS reports grants from Wellcome, MRC, NIHR, UKRI, British Council, GSK, British Heart Foundation, and Diabetes UK outside this work. ID holds grants from NIHR, GSK and AIR@InnoHK administered by Innovation and Technology Commission. CL is supported by the UK Medical Research Council (Skills Development Fellowship MR/T032448/1). CWG is funded by a Wellcome Career Development Award (225868/Z/22/Z). KB is funded by a Wellcome Senior Research Fellowship (220283/Z/20/Z)

This research was funded in part by Wellcome, For the purpose of Open Access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript (AAM) version arising from this submission.

Funders had no role in the study design, collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Competing interests

IJD has received research grants GlaxoSmithKline (GSK) and AstraZeneca and holds shares in GSK. All other co-authors declare no conflict of interest. CWG 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. AYSW received honorarium from 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.

Ethical approval

This study used only de-identified patient-level data, and 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).

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. The codelists identifying the outcomes and covariates are available in LSHTM Data Compass: https://doi.org/10.17037/DATA.00004214

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Figure legend

Figure 1. Description of interpretations for case-crossover design

Figure 2. Results for DOACs + atorvastatin using cohort study design and 6-parameter case-crossover study design

Figure 3. Results for DOACs + simvastatin using cohort study design and 6-parameter case-crossover study design

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 statins monotherapy; the remaining 3 parameters address situations related to potential drug-interaction: 4) joint initiation, 5) initiation of DOAC while taking statins, 6) initiation of statins 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 1. Description of interpretations for case-crossover design

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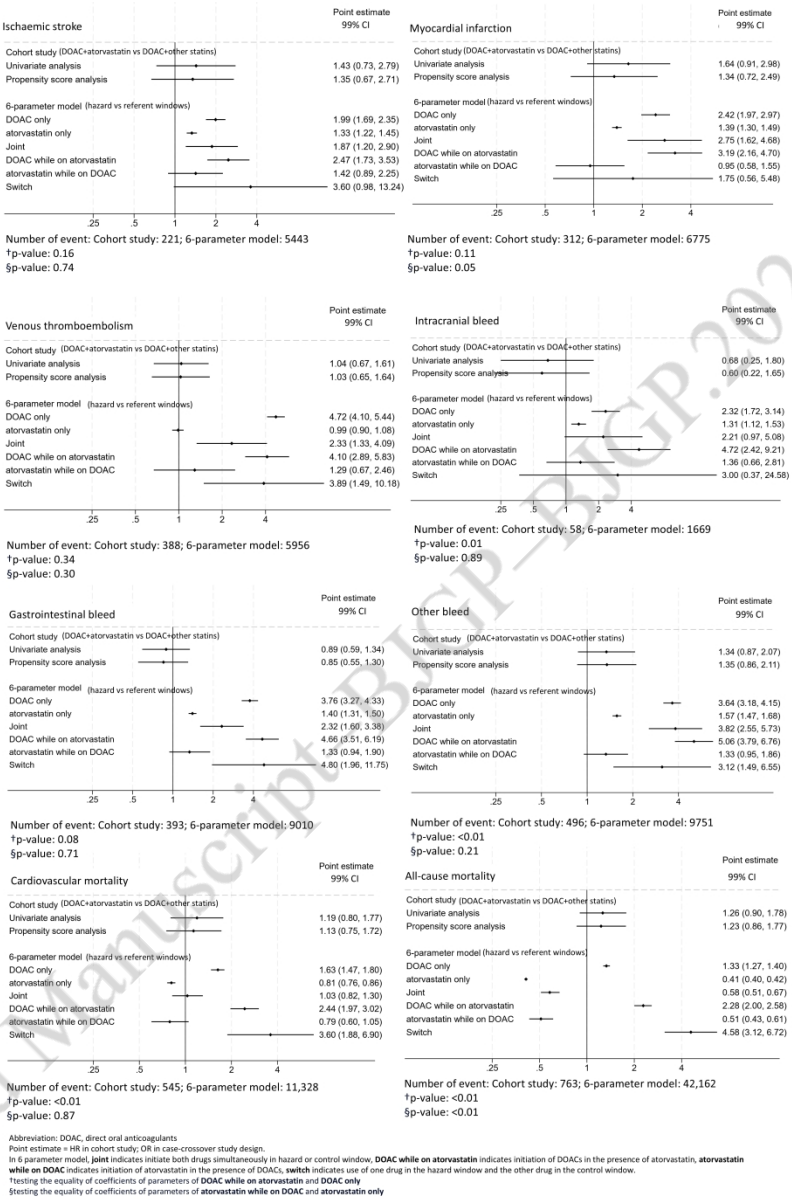

Figure 2. Results for DOACs + atorvastatin using cohort study design and 6-parameter case-crossover study design

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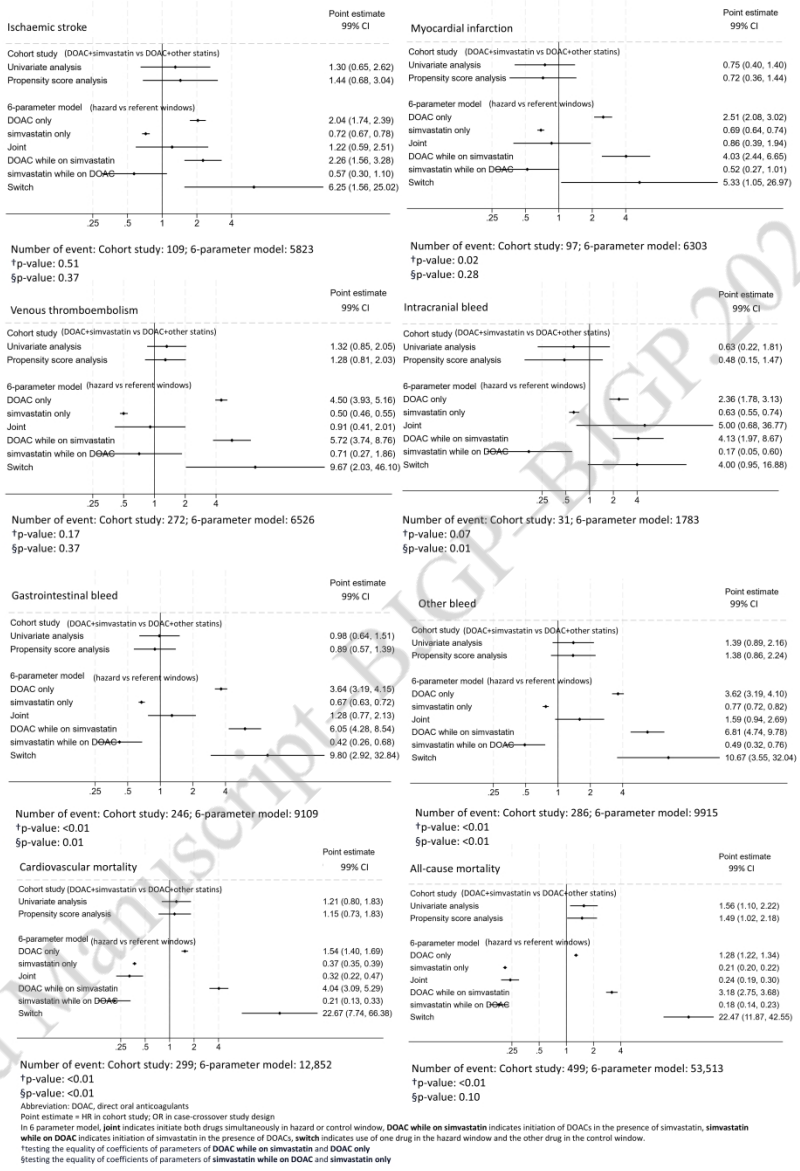

Figure 3. Results for DOACs + simvastatin using cohort study design and 6-parameter case-crossover study design

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