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Drug–drug interaction between dexamethasone and direct-acting oral anticoagulants: a nested case–control study in the National COVID Cohort Collaborative (N3C)

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ABSTRACT

Objective The goal of this work is to evaluate if there is an increase in the risk of thromboembolic events (TEEs) due to concomitant exposure to dexamethasone and apixaban or rivaroxaban. Direct oral anticoagulants (DOACs), as well as corticosteroid dexamethasone, are commonly used to treat individuals hospitalised with COVID-19. Dexamethasone induces cytochrome P450-3A4 enzyme that also metabolises DOACs apixaban and rivaroxaban. This raises a concern about possible interaction between dexamethasone and DOACs that may reduce the efficacy of the DOACs and result in an increased risk of TEE.

Design We used nested case–control study design.

Setting This study was conducted in the National COVID Cohort Collaborative (N3C), the largest electronic health records repository for COVID-19 in the USA.

Participants Study participants were adults over 18 years who were exposed to a DOAC for 10 or more consecutive days. Exposure to dexamethasone was at least 5 or more consecutive days.

Primary and secondary outcome measures Our primary exposure variable was concomitant exposure to dexamethasone for 5 or more days after exposure to either rivaroxaban or apixaban for 5 or more consecutive days. We used McNemar's X^2 test and adjusted logistic regression to evaluate association between concomitant use of dexamethasone with either apixaban or rivaroxaban.

Results McNemar's X^2 test did not find a discernible association of TEE in patients concomitantly exposed to dexamethasone and a DOAC (χ^2=0.5, df=1, p=0.48). In addition, a conditional logistic regression model did not find an increase in the risk of TEE (adjusted OR 1.15, 95% CI 0.32 to 4.18).

Conclusion This nested case–control study did not find evidence of an association between concomitant exposure to dexamethasone and a DOAC with an increase in risk of TEE. Due to small sample size, an association cannot be completely ruled out.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is reproducible within the National COVID Cohort Collaborative (N3C) Enclave with the workflow available to researchers with approved access.
⇒ The study is conducted by a multidisciplinary team of scientists who contributed their expertise and unique perspective of their field to develop an appropriate study design and statistical analysis that account for bias such as confounding by indication.
⇒ End of drug exposure dates has not always been provided by contributing data partners and, when missing, it was inferred by the N3C according to a set of rules and extrapolations.
⇒ Dosing data are rather sparse, thus we could not include these into our analysis.
⇒ Due to patient-level date shifting used by some data partners to protect patients' privacy, we had to greatly reduce the size of our cohort by dropping data partners who did not report date shifting details.

INTRODUCTION

Approximately a decade ago, direct oral anticoagulants (DOACs) introduced a new pharmacological mechanism in the prophylaxis and treatment of thromboembolic events.[1] Until that time, patients with thromboembolic disorders or atrial fibrillation (AF) were prescribed the vitamin K antagonist warfarin in the USA and acenocoumarol in Europe. The narrow therapeutic index for warfarin and acenocoumarol required patients to have a laboratory test to measure the international normalised ratio (INR) at least once monthly to assure the INR is in therapeutic range.[2] Since 2012, many patients needing an anticoagulant were prescribed a DOAC because it does not require therapeutic dose

monitoring and has a well-understood efficacy and safety profile.[3–5] In addition, DOACs have less documented drug–drug interactions (DDIs) than warfarin.[1]

The use of DOACs for AF treatment is expected to rise to an estimated 6–12 million people in the USA and almost 18 million in Europe by 2050.[6] Two currently approved DOACs, apixaban and rivaroxaban, are primarily metabolised by the cytochrome P450-3A4 (CYP3A4) enzyme system.[7 8] Evidence of safety concerns from interactions with drugs that affect the function of CYP3A4 is mixed. The Food and Drug Administration Prescribing Information warns of concomitant use with CYP3A4 inducers because a decrease in plasma levels could lead to a potential decrease in its anticoagulant mechanism.[9 10] However, a post-hoc analysis of data from the ARISTOTLE trial did not find differences in the efficacy and safety of apixaban compared with warfarin while on medications that could either induce or inhibit CYP3A4.[11]

During the COVID-19 pandemic, serious infections were found to be associated with abnormal coagulation values that resulted in severe haemostatic disorders and higher risk of thromboembolic events in hospitalised patients even up to 6 weeks after discharge.[12–15] Clinical guidelines for COVID-19 evolved and addressed whether patients should be prophylactically treated with anticoagulant regimens even when not hospitalised.[16–18] The National Institutes of Health COVID-19 treatment guidelines from February 2022 did not recommend anticoagulants for non-hospitalised patients with COVID-19. If hospitalised, it was recommended to receive thromboembolic event prophylaxis as the standard of care, and to continue on anticoagulant treatment if the patient was already receiving it before the diagnosis of COVID-19.[19] The American Society for Hematology recommended prophylactic intensity over intermediate intensity for patients with COVID-19-related critical illness who do not have suspected or confirmed thromboembolic event.[20] Also, patients on vitamin K antagonist treatment during the pandemic who had difficulties to accurately control their INR values were recommended to be switched to DOAC to facilitate care.[21]

During this time period, it was demonstrated that corticosteroids were effective in improving respiratory distress among hypoxic patients with COVID-19. Dexamethasone, a glucocorticoid with a potent anti-inflammatory effect and long duration of action (36–72 hours), showed lower rates of mortality in patients on mechanical ventilation or receiving oxygen in the RECOVERY trial.[22 23] However, dexamethasone has been shown to induce CYP3A4 activity, though the clinical relevance of the induction when concomitantly administered with a CYP3A4 substrate is still uncertain.[24]

Given the potential pharmacokinetic interactions of dexamethasone and apixaban or rivaroxaban, our goal was to evaluate the odds of concomitant exposure to dexamethasone in apixaban and rivaroxaban users among persons with (cases) or without (controls) thromboembolic events in patients with COVID-19.

METHODS

Study design and identification of cases and controls

We performed a nested case–control study of adults exposed to either apixaban or rivaroxaban for 10 or more consecutive days (figure 1). This time period was chosen to allow for steady-state blood levels of the DOAC. Cases were patients who experienced a thromboembolic event on or after 10 days of exposure to either apixaban or rivaroxaban. Cases were divided into three groups: patients who have no history of a thromboembolic event, patients who had an event within 30 days prior to entering the cohort and those who had an event more than 30 days

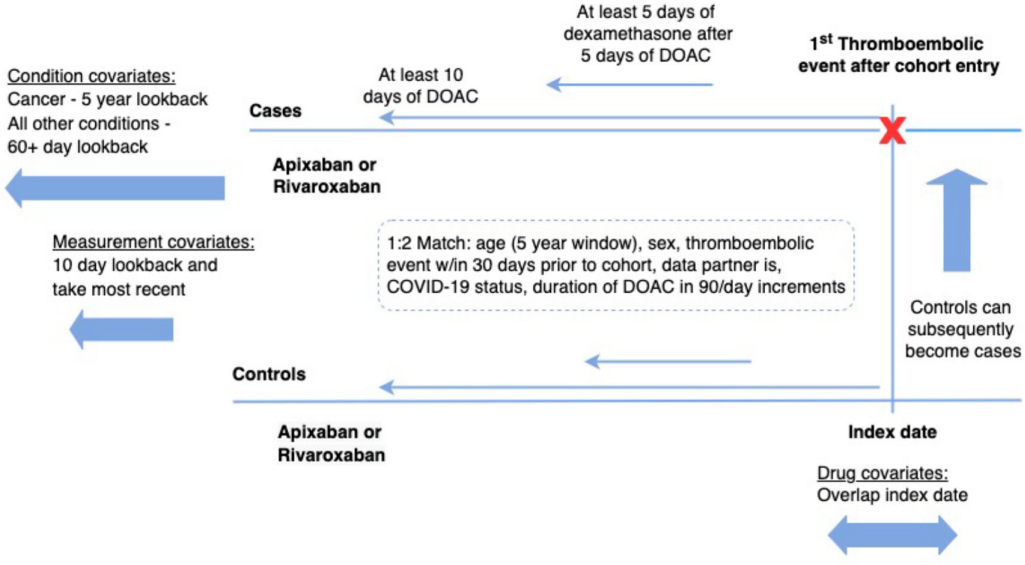

Figure 1 Schematic diagram representing retrospective observational nested case–control study design used in this study. DOAC, direct oral anticoagulant.

prior to entering the cohort. The reason for this stratification was to focus the study on individuals who had new thromboembolic events versus history of thromboembolic events (recent and long term). Controls were patients who were also exposed to either apixaban or rivaroxaban but did not experience a thromboembolic event during the same month and year, also matching on sex, age (±5 years), date of SARS-CoV-2 infection (up to 60 days) and prior thromboembolic event. The cohort entry date was defined by the apixaban/rivaroxaban prescription date for both cases and controls. Matching on the SARS-CoV-2 infection was done to reduce confounding.

We defined thromboembolic events as events that have SNOMED-CT (Systematized Nomenclature of Medicine – Clinical Terms) or ICD-10 (International Classification of Diseases 10th Revision) diagnostic code for deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischaemic stroke, disseminated intravascular coagulation or sepsis-induced coagulopathy. The complete listing of diagnostic identifiers is provided in online supplemental material.

Setting and study period

The data used in this study were from the National COVID Cohort Collaborative (N3C), the largest national repository of patients who meet a phenotype definition of COVID-19 diagnosis matched to non-infected individuals. The dataset includes harmonised de-identified data from the electronic health records of more than 72 sites from across the USA, and provides data about demographics, health conditions, laboratory test results, medications, procedures and encounters (medical appointments, inpatient visits, emergency visits and other visit types).[25] All data are transformed by contributing sites to the Observational Health Data Sciences and Informatics Common Data Model prior to its inclusion in the N3C.[26] Approved researchers conducted data analyses within the N3C 'Enclave', a secure cloud-based platform developed by Palantir Technologies and hosted by National Institutes of Health National Center for Advancing Translational Sciences that provides a set of tools for data transformation and analysis.

While the N3C was designed to study patterns in patients with COVID-19, it also includes longitudinal data since 2017 for some patients. We used data from the Limited Dataset present in the Enclave from prior to the start of the COVID-19 pandemic (1 March 2018) until 30 April 2021. Data prior to March 2018 were excluded from data analysis due to sparse data from that time period. Some contributing data partners use patient-level date shifting in the Limited Dataset as additional step to protect patients' privacy. In this study, we only included data from the Limited Dataset for which information about date shifting was provided. The flow of data for this study is shown in figure 2.

Variables

We defined our primary exposure variable as concomitant use of dexamethasone with apixaban or rivaroxaban for 5 or more days after exposure to either DOAC for at

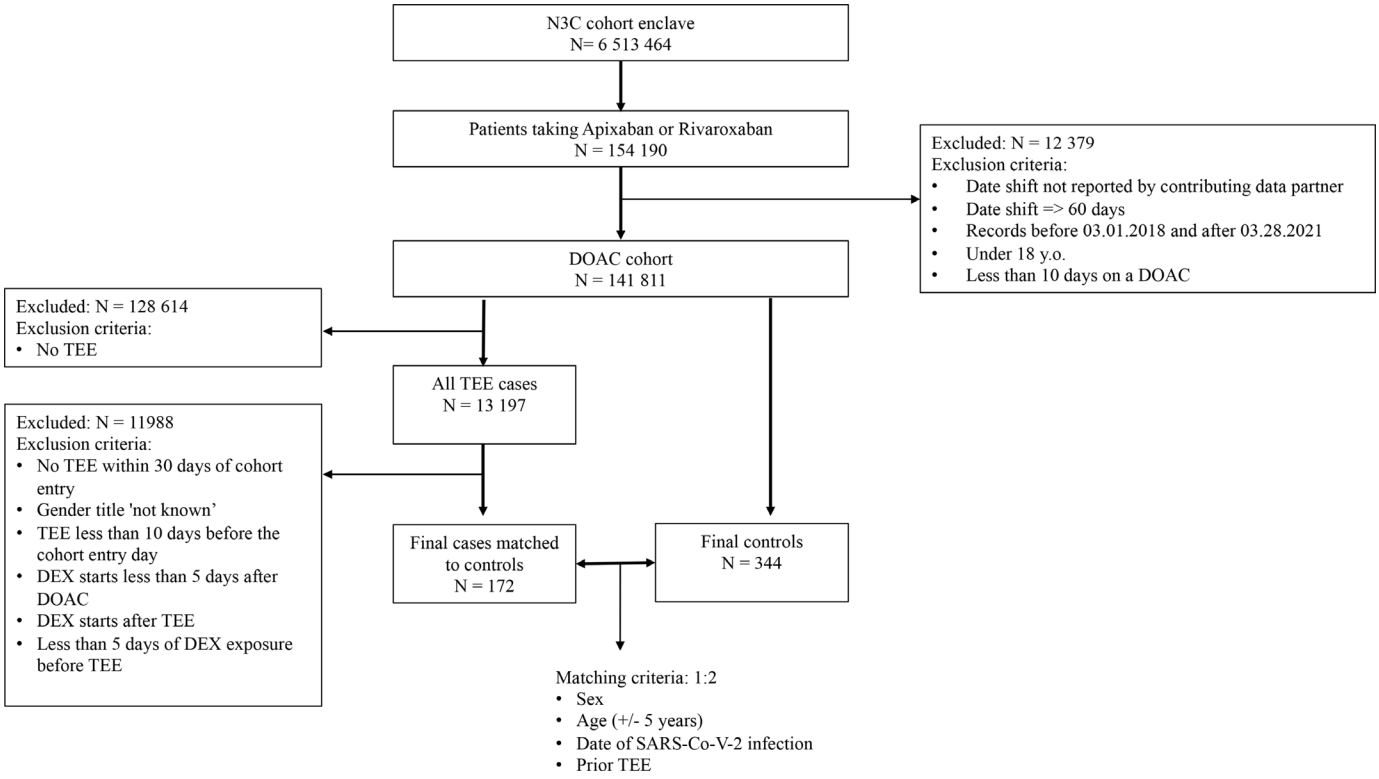

Figure 2 Schematic diagram representing the flow of data for cohort formation and selection of cases and controls. DEX, dexamethasone; DOAC direct oral anticoagulant; N3C, National COVID Cohort Collaborative; TEE, thromboembolic event.

least 5 consecutive days. The underlying mechanism of the potential pharmacokinetic interaction between dexamethasone (the putative precipitant drug) and apixaban or rivaroxaban (the putative object drug) is induction of CYP3A4. Because it could take up to a month after exposure to a medication that induces CYP3A4 metabolism to return to baseline, concomitant exposure was considered to continue up to 30 days past the stop of dexamethasone.[27] More details on the definition of these drug exposures are in the online supplemental material.

Use of other medications included aspirin, CYP3A4 inhibitors, CYP3A4 inducers, antiplatelets, unfractionated heparin and low molecular weight heparin (LMWH). We included the following comorbidities: diabetes, pulmonary diseases, heart failure, AF, hypertension, various cancers, history of smoking, obesity and Charlson Comorbidity Index. We imputed body mass index using the prevalence of obesity among US adults aged 60 years and over according to Centers for Disease Control and Prevention definitions.[28]

The primary analysis was repeated using prednisone that was prespecified as a comparator corticosteroid because it is widely used but not known to induce CYP3A4. We repeated the analysis using concomitant exposure of prednisone with apixaban or rivaroxaban for 5 or more days after exposure to either DOAC for at least 5 consecutive days as the primary independent variable.

Statistical methods

Descriptive statistics were used to describe the cohort and examine the prevalence of cases and controls. The crude marginal homogeneity of concomitant exposure to dexamethasone between cases and controls was calculated using McNemar's X^2 test for paired data. We used conditional logistic regression to estimate ORs and 95% CIs, while adjusting for all covariates listed in table 1. Since control patients were sampled at each point in time when a case occurred (ie, 'density' or 'risk set' sampling), and the risk of concomitant exposure was calculated at that point of time, the ORs for concomitant exposure (exposure OR) calculated in this study estimated the rate ratio from the cohort of patients with data present in the N3C.[29] However, because the N3C cohort was itself designed to have COVID-19 cases and controls, the actual interpretation of the rate ratio estimates is complex. Therefore, we refer to these simply as 'exposure OR'. All analyses were repeated using prednisone as the negative control precipitant drug.

We performed prespecified sensitivity analyses by (1) changing the age matching window from 5 years to 3 years and (2) removing the restriction on the data partner date shifting to include more data from more sites in the analysis. We also conducted three post-hoc sensitivity analyses: (1) removing the restriction for cohort entry order so that the dexamethasone exposure can occur anytime while on apixaban or rivaroxaban; (2) changing the criteria for concomitant dexamethasone/apixaban or rivaroxaban exposure from 5 to 2 days; and (3) adding race (black or African American) as a covariate to the original logistic regression model.

Patient and public involvement

Patients or members of the public were not involved in the study concept or design.

RESULTS

Study participants

A total of 141 811 patients were taking either apixaban or rivaroxaban between the second quarter of 2018 and 30 May 2021 (table 1). All patients are over 18 years of age. Of these, 172 patients were identified as cases matched to 344 controls. The mean age was 67.9 years for cases and 67.6 years for controls. For both cases and controls, 38.4% of patients were female and 61.6% were male. Of cases, 25.6% were identified as black or African American, 62.2% white, and 12.2% as other or unknown. The race identity of controls was 17.7% black or African American, 66.0% white, and 16.3% other or unknown. A greater proportion of cases were black or African American compared with controls (25.6% vs 17.7%, p<0.05).

The majority of both cases (81.98%) and controls (73.84%) were exposed to apixaban rather than rivaroxaban (p<0.05). Exposure to dexamethasone was slightly higher in the controls (50.29%) compared with cases (43.61%). The proportion of cases and controls receiving LMWH was 61.63% for cases and 66.28% for controls. Around half of the cases and controls (52.91%) were COVID-19 positive at the index date (equal due to matching). Both cases and controls had high proportion of hypertension (89% cases and 81% controls, p=0.01).

Study outcomes

McNemar's X^2 test did not find a difference between cases and controls in concomitant use of dexamethasone with either apixaban or rivaroxaban (X^2=0.5, df=1, p=0.48). After adjustment, we continued to find no discernible increase in thromboembolic events (adjusted relative risk 1.15, 95% CI 0.32 to 4.18) (table 2).

The logistic regression model identified several statistically significant associations: aspirin (OR=2.4, 95% CI: 1.4 to 4.0) and LMWH (OR=4.5, 95% CI: 1.9 to 10.7), as well as presence of the diagnoses of heart failure (OR=1.7, 95% CI: 1.1 to 2.8), hypertension (OR=2.0, 95% CI: 1.0 to 3.9) and obesity (OR=0.4, 95% CI: 0.2 to 0.7). These results were robust to the prespecified and post-hoc sensitivity analyses both for dexamethasone and for prednisone.

Analysis of prednisone showed a crude association using the McNemar test (X^2=10.562, df=1, p=0.001) but no discernible association in the conditional logistic model (online supplemental material). The full set of conditional logistic regression results is shown in the online supplemental material.

Table 3 summarises results of the four sensitivity analyses and compares the resulting ORs with the baseline analysis.

Table 1 Baseline characteristics of cases and controls

Baseline characteristic	Cases (n=172, 100%)	Controls (n=344, 100%)	P value*
Age, years			
Mean (SD)	67.92 (11.71)	67.63 (11.98)	0.40*
Median (range)	69.0 (25–90)	68.0 (28–95)	
Sex female	66 (38.37)	132 (38.37)	N/A
Race and ethnicity			
Black or African American	44 (25.58)	61 (17.73)	<0.05†
White	107 (62.21)	227 (65.99)	0.45
Other or unknown	21 (12.21)	56 (16.28)	0.28
Medications			
Apixaban	141 (81.98)	254 (73.84)	<0.05†
Rivaroxaban	60 (34.88)	118 (34.30)	0.97
Prednisone	58 (33.72)	103 (29.94)	0.44
LMWH	106 (61.63)	228 (66.28)	0.35
Unfractionated heparin	65 (37.79)	98 (28.49)	0.04†
Hormone replacement therapy	0	0	
Aspirin	102 (59.30)	185 (53.78)	0.27
Antiplatelets	34 (19.77)	50 (14.53)	0.16
CYP3A4 inducers	<20	<20	‡
CYP3A4 inhibitors	63 (36.63)	86 (25.00)	0.01†
Dexamethasone	75 (43.61)	173 (50.29)	0.18
Conditions			
Thrombotic event before cohort entry date	165 (95.93)	330 (95.93)	N/A
Over 30 days	<20	<20	
Up to 30 days	160	318	
Smoking	21 (13.37)	20 (6.40)	0.01†
COVID-19 positive	91 (52.91)	182 (52.91)	N/A
Cancer	57 (33.14)	119 (34.59)	0.82
Pulmonary disease	51 (29.65)	96 (27.91)	0.76
Hypertension	150 (87.21)	265 (77.03)	0.01†
Heart failure	76 (44.19)	102 (29.65)	0.01†
Diabetes mellitus	68 (39.53)	136 (39.53)	1
Atrial fibrillation	61 (35.47)	113 (32.85)	0.62

*Two-sample t-test was used for comparing age means and Pearson's X^2 test with Yates' continuity correction was used to compare all other non-outcome variables.
†Variables that show statistically significant difference between cases and controls (N/A represents matched covariates).
‡Low cell counts; the prevalence of thrombotic events is based on the number of thrombotic events prior to entering the study cohort.
CYP3A4, cytochrome P450-3A4; LMWH, low molecular weight heparin; N/A, not applicable.

None of the sensitivity analyses changed the overall finding of no association with concomitant exposure to dexamethasone and apixaban or rivaroxaban and a thromboembolic event (to see the complete results of the sensitivity analyses, please see online supplemental material).

DISCUSSION

Because DOACs apixaban and rivaroxaban are metabolised primarily by the P-glycoprotein and CYP3A4, there is a concern that dexamethasone, a CYP3A4 inducer, may lower concentration of a DOAC and result in a reduced anticoagulant effect that, in turn, may increase the risk of thromboembolic events for a patient. A limited number of studies have focused on this pharmacokinetic interaction. It is important to study this interaction because concomitant use of these drugs may be clinically necessary for certain patients, particularly for those who have medium to severe COVID-19. In this work, we approach

Table 2 Association between dexamethasone and thromboembolic events in the primary analysis

Characteristic	Adjusted OR (95% CI)
Medications	
Dexamethasone	1.2 (0.3 to 4.2)
Aspirin	2.4 (1.4 to 4.0)
CYP3A4 inhibitor	2.1 (0.9 to 5.1)
CYP3A4 inducer	2.2 (0.4 to 14)
Antiplatelet	1.0 (0.4 to 2.5)
Unfractionated heparin	1.7 (0.6 to 4.8)
Low molecular weight heparin	4.5 (1.9 to 10.7)
Conditions	
Diabetes	0.6 (0.4 to 1.0)
Pulmonary	0.8 (0.5 to 1.3)
Heart failure	1.7 (1.1 to 2.8)
Atrial fibrillation	0.9 (0.5 to 1.4)
Hypertension	2.0 (1.0 to 3.9)
Cancer	0.7 (0.5 to 1.2)
Smoker	1.9 (0.9 to 4.3)
Obese	0.4 (0.2 to 0.7)
Mild comorbidity	0.7 (0.4 to 1.3)

CYP3A4, cytochrome P450-3A4.

this question by analysing real-world data from the N3C Enclave and looking for evidence of an increased rate of thromboembolic events among patients who were exposed to dexamethasone while taking a DOAC, as compared with those who have not been exposed to dexamethasone while taking a DOAC.

The main outcome of this study is that we did not find evidence of an association between concomitant exposure to dexamethasone and a DOAC with a further increase in risk of thromboembolic events in the N3C population. Our findings were consistent across several sensitivity analyses in which we varied our definition for the age matching window, date shift restriction and cohort entry order, as well as shortened the required dexamethasone exposure time and added African American race as a covariate. Due to small sample size, however, the 95% CI for the non-significant exposure OR is rather wide (0.3 to 4.2). As such, it does not allow us to rule out a very protective association, or a very harmful one.

In a recent experimental study conducted in Italy, DOAC (apixaban, rivaroxaban and edoxaban) plasma levels were prospectively measured during and after exposure to dexamethasone in 26 patients who were hospitalised with COVID-19.[30] Patients in that study were treated with a 6 mg dose of dexamethasone once a day, which is also a recommended dose for treating patients with COVID-19 in the USA. It was reported that dexamethasone did not systematically affect DOAC plasma levels in study subjects, suggesting that a clinically relevant interaction is unlikely. This finding does not rule out the potential for an interaction at higher doses or longer exposure to dexamethasone. Our findings are qualitatively concordant with results of this study, though we were not able to obtain dosing information from the N3C Enclave to evaluate dose–response relationship.

Previously, N3C data have been used to address other pharmacoepidemiological questions relevant to COVID-19 outcomes.[31] While N3C is a very large and useful database of persons with COVID-19, it is not a complete account of all health information as many observations lacked laboratory markers useful for identifying and validating thromboembolic events. Several retrospective manuscripts on laboratory markers and COVID-19 severity and risk of complications have been published; however, to date, there are no clear results on the implications in clinical practice and even particular in the anticoagulation field for patients with COVID-19.[32 33]

The nested case–control study design was chosen for this study because it is an efficient approach to studying a suspected risk factor for thromboembolic events, which are relatively uncommon. This study design allows for smaller sample sizes to detect safety signals as compared with retrospective cohort studies or prospective randomised or observational studies. A main disadvantage of the nested case–control design is that the findings might not generalise to populations that are dissimilar to the cohort that the case–control is nested in, and there can be concerns about unbalanced data capture between cases and controls, such as lack of details about underlying severity of disease.

Confounding by indication is a common concern in pharmacoepidemiological studies using observational retrospective designs. Since our focus was on concomitant

Table 3 Association between dexamethasone and thromboembolic event in the sensitivity analyses

Sensitivity analysis	Base analysis OR (95% CI)	Relax age matching window OR (95% CI)	Allow data from sites that perform date shifts >35 days OR (95% CI)	Change cohort entry order (dexamethasone can start before DOAC) OR (95% CI)	Shorten dexamethasone drug era OR (95% CI)	Add race as a covariate in the logit model OR (95% CI)
Dexamethasone	1.2 (0.3 to 4.2)	2.8 (0.9 to 8.6)	0.8 (0.3 to 2.6)	1.3 (0.7 to 2.6)	1.4 (0.6 to 3.6)	1.3 (0.4 to 4.8)

DOAC, direct oral anticoagulant.

use of dexamethasone with the CYP3A4-metabolised apixaban or rivaroxaban, the specific concern would be if there were clinical indications associated with both the concomitant drug use of interest and thromboembolic events. We addressed this by matching cases and controls on history of thromboembolic events and by adjusting for the conditions shown in table 1 as well as other potential confounders. However, it is possible that there are other conditions that we did not adjust for because we were not aware of them as potential confounders.

This study has other limitations. First, a number of drug exposure records in the N3C do not provide end dates. We used the exposure dates that were inferred by the N3C according to a set of rules and extrapolations described in the online supplemental material. This may affect validity of our results given that our study design requires accurate estimates of the drug exposure. Second, we found that the drug dosing data in the N3C were too sparse to study the dosing effects on the outcome, in other words we have not been able to explore heterogeneity of the treatment effects. The data for various biomarkers such as platelet count, D-dimer, C reactive protein and estimated glomerular filtration rate were also too sparse to analyse. Moreover, we did not control for mechanical ventilator exposure and oxygen requirements as these data are known to be incomplete in the N3C Enclave and it is not likely that patients are exposed to apixaban or rivaroxaban while under ventilation. Third, for the sake of protecting patient data, some contributing sites perform patient-level date shifting in the Limited Dataset. We did not include data from those sites in the primary analysis because our study design requires exact knowledge of the exposure dates to evaluate the length of exposure to dexamethasone and apixaban or rivaroxaban.

The N3C Enclave is a new platform and the process of improving data collection and analysis tools is ongoing. Despite some limitations mentioned above, we found the N3C Enclave to be a unique source of healthcare data that can be used to generate evidence for important clinical research questions related to potential DDIs. For example, one could investigate whether rifampin results in a reduction in edoxaban bioavailability through induction of CYP3A4/P-glycoprotein, as suggested in the work conducted previously in healthy subjects.[34] In addition, the amount of data available in the N3C Enclave, and the fact that they are contributed by different sites from across the country, provide clinical heterogeneity. Also, all of the research artefacts created for studies, including ours, are saved in the Enclave in a way that makes them reproducible and therefore our results can be verified independently. We think that the workflow for this study could be used for other similar studies in the N3C Enclave.

CONCLUSION

While there is a theoretical concern of a pharmacokinetic DDI between dexamethasone and apixaban or rivaroxaban, this nested case–control study did not identify a discernible increase in the exposure OR of concomitant dexamethasone with CYP3A4-metabolised DOACs (apixaban and rivaroxaban) and thromboembolic events. Future studies with larger sample size or prospective clinical studies are needed to confirm our study findings.

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Contributors OVK is the guarantor of this manuscript and is responsible for the overall content. All authors critically evaluated each stage of the work and revised the manuscript. OVK participated in research design, data acquisition and analysis, preparation of results and drafted the manuscript. RDB participated in research design, data acquisition and analysis, and preparation of results. AG-L drafted study protocol, contributed to research design, data analysis, preparation of results and interpretation of the data. PTK contributed clinical expertise to study design and interpretation of data for the work. LVZ participated in developing study protocol, analysis and interpretation of data for the work. MT contributed to interpretation of data for the work and analysis. CEL participated in developing the study protocol, data analysis, interpretation of data for the work and interpretation of results. KMA contributed to data interpretation for the work and data analysis. HM contributed to data acquisition, data interpretation for the work and analysis. GCA contributed to data interpretation for the work and critical revision of the work. DCM supervised the study, revised study protocol and research design, guided the analysis of the data, reviewed and edited the manuscript.

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Competing interests After the completion of this work, KMA became a full-time employee of Pfizer. GCA is past Chair and a current member of Food and Drug Administration's(FDA) Peripheral and Central Nervous System Advisory Committee; is a co-founding Principal and equity holder in Monument Analytics, a healthcare consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a past member of OptumRx's National P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. CEL is an Executive Committee Member of the University of Pennsylvania's Center for Pharmacoepidemiology Research and Training. The centre receives funds from Pfizer and Sanofi to support pharmacoepidemiology education. CEL recently received honoraria from the American College of Clinical Pharmacy Foundation, the University of Florida, the University of Massachusetts, and the Scientific and Data Coordinating Center for the NIDDK-funded Chronic Renal Insufficiency Cohort Study. CEL is a Special Government Employee of the US FDA and consults for their Reagan-Udall Foundation. CEL receives travel support from John Wiley & Sons. CEL's spouse is an

employee of Merck. Neither CEL nor his spouse owns stock in the company. There are no other disclosures to report.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The following research has been approved by the University of Pittsburgh (STUDY20100069-N3C dexamethasone drug interaction) and the University of Utah (IRB_00139221) Institutional Review Board. N3C DUR ID is DUR-EBC6C0C. Since N3C data are anonymised, we did not obtain informed consent from the participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement To conduct this research, we have used the Limited Dataset (LDS) V.40, which is available in the N3C Enclave and can be accessed by researchers who have access approved by the N3C. Complete workflow that we produced, which includes SQL and python codes, along with all SQL and python codes that we have developed, along with data tables for each data transform, are also available in the N3C Enclave to researchers with approved access. Authors will be happy to provide additional clarifications upon request.

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