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Risk of bleeding amongst warfarin and direct oral anticoagulant users prescribed immediate antibiotics for respiratory tract infection: Cohort study

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Abstract

Purpose: Incidence of bleeding amongst warfarin and direct oral anticoagulant (DOAC) users is greater following a respiratory tract infection (RTI). It is unclear whether immediate antibiotics modify this association. We estimated the risk of bleeding amongst warfarin and DOAC users with RTI by antibiotic treatment.

Methods: This retrospective cohort study used data from the Clinical Practice Research Datalink (CPRD) GOLD for adults in England prescribed warfarin or a DOAC, who sought primary care for an RTI between 1st January 2011 and 31st December 2019. Outcomes were major bleeding (hospital admission for intracranial or gastrointestinal bleeding), and non-major bleeding (hospital admission or General Practice consult for epistaxis, haemoptysis, or haematuria). Cox models derived hazard ratios (HRs) and 95% confidence intervals (CIs) for each outcome, adjusting for confounders using inverse probability of treatment weighting.

Results: Of 14 817 warfarin and DOAC users consulting for an RTI, 8768 (59%) were prescribed immediate antibiotics and 6049 (41%) were not. Approximately 49% were female, and median age was 76 years. Antibiotics were associated with reduced risk of major bleeding (adjusted HR 0.38, 95% CI 0.25 to 0.58). This was consistent across several sensitivity analyses. Antibiotics were also associated with a reduced risk of non-major bleeding (adjusted HR 0.78, 95% CI 0.61 to 0.99).

Conclusions: Immediate antibiotics were associated with reduced risk of bleeding amongst warfarin and DOAC users with an RTI. Further work is needed to understand mechanisms and confirm whether a lower threshold for antibiotic use for RTI in this population may be beneficial.

Key Points

- The risk of bleeding amongst warfarin and Direct Oral Anticoagulant (DOAC) users is greater following a respiratory tract infection (RTI).
- It is unclear whether antibiotics modify this association.
- We found that immediate antibiotics for RTI were associated with a roughly 40% reduction in the risk of major bleeding, and 20% reduction in the risk of non-major bleeding.
- Further work is needed to understand why and how antibiotics may reduce the risk of bleeding and whether a lower threshold for antibiotic use for RTI in this population may be beneficial.

Plain Language Summary

Many people use blood thinning drugs such as warfarin and Direct Oral Anticoagulants (DOACs). The main harm from these drugs is that they can cause bleeding. Many other drugs can interact with warfarin and DOACs to cause bleeding. Previous research found that respiratory infections may also increase the risk of bleeding. However, it is not known whether antibiotics may affect this risk. We assessed anonymised data from 14 817 warfarin and DOAC users who saw their GP for a respiratory infection. 8768 (59%) were prescribed immediate antibiotics and 6049 (41%) were not. Approximately 49% were female, and the average age was 76 years. We found that those prescribed immediate antibiotics had a 40% lower risk of major bleeding and a 22% lower risk of non-major bleeding, compared to those not. Further work is needed to understand why and how antibiotics may reduce the risk of bleeding and whether a lower threshold for antibiotic use for respiratory infection in this population may be beneficial.

1 | INTRODUCTION

Warfarin and Direct Oral Anticoagulants (DOACs; apixaban, rivaroxaban, edoxaban, and dabigatran) effectively treat venous thromboembolism and prevent stroke but can cause major bleeding with associated morbidity and mortality.[1] A recent observational study found that the relative incidence of bleeding amongst warfarin and DOAC users was greater following the onset of a respiratory tract infection (RTI).[2] This potential relationship between mild community-acquired infections and bleeding amongst oral anticoagulant users is not well studied but is plausible given the well-recognised relationship between severe infection and coagulopathy.[3] RTIs may increase the risk of supra-therapeutic anticoagulation and subsequent bleeding due to (1) the effect of interactions with over-the-counter cough and cold treatments containing paracetamol,[4,5] and (2) increased vitamin-dependent clotting factor catabolism due to fever.[6] Antibiotic treatment for RTI may also contribute to bleeding. Summary of medicinal product characteristics,[7] the British National Formulary[8] and clinical guidelines[1] list several potential drug–drug interactions for warfarin and DOACs with antibiotics. Antibiotics may disrupt gut flora and reduce intestinal vitamin K_2 synthesis[9] or inhibit cytochrome P450 isozyme 2C9, potentiating the anticoagulant effect of warfarin.[10] Clarithromycin and erythromycin are potent inhibitors of CYP3A4 and P-glycoprotein and can increase serum levels of apixaban, rivaroxaban, and dabigatran.[11–13] Co-prescription of some antibiotic-anticoagulant combinations may increase the risk of a hospital admission for a major bleed.[14–17] However, it is unclear in these scenarios whether the bleeding risk is primarily driven by the infection or by the antibiotic treatment and potential drug–drug interaction.

An earlier retrospective cohort study estimated the risk of bleeding requiring an emergency department visit or hospital admission, irrespective of severity, amongst 5857 warfarin-users who were dispensed an antibiotic for a community-acquired infection. These were compared to 570 warfarin-users diagnosed with upper RTIs and not dispensed an antibiotic, and 5579 controls.[18] The proportions with bleeding were similar across the three groups (0.7%, 0.5% and 0.5%, respectively). However, the underlying site of infections in the antibiotic group were not known, the number in the upper RTI group may have been too small to detect a difference, DOAC users were not studied, and the chosen outcome did not differentiate between major and non-major bleeds.

Associations between community-acquired infections, antibiotic treatment, and major bleeding have implications for safe management of oral anticoagulant use during an infectious illness. There are also implications for antibiotic prescribing as the uncertainty around the main driver of bleeding risk (infection or antibiotic treatment) may influence antibiotic prescribing decisions. Therefore, the aim of this study was to estimate the risk of major and clinically relevant non-major bleeding amongst oral anticoagulant users with community-acquired RTIs with and without antibiotic prescription. We

hypothesised that underlying infection makes a substantial contribution to the risk of bleeding and thus, there would be no significant difference in the risk of bleeding irrespective of whether antibiotics were prescribed.

2 | METHODS

2.1 | Data source

We used anonymised longitudinal General Practice data from the GOLD version of the UK Clinical Practice Research Datalink (CPRD).[19] Most of the UK population are registered with a General Practice and core services include provision of urgent care (e.g., non-severe infection), management of long-term conditions, and prescriptions of acute (e.g., antibiotics) and long-term (e.g., anticoagulants) medication. Practices contributing data to CPRD GOLD are audited to assess the reliability and accuracy of data recording.[19] Patient-level data are also assessed, and considered 'acceptable' for inclusion in the CPRD if internally consistent in recording of age, sex, registration details, and clinical events.

As of May 2022, CPRD GOLD contained data for 3.1 million patients currently alive, with data deemed acceptable for research, registered at 401 Practices across the UK that use Vision® electronic health record software.[20] The CPRD GOLD sample represents 4.6% of the UK population and 4.9% of UK General Practices.[19] CPRD GOLD data were compared with the 2011 UK Census data and found to be broadly representative of the wider UK population in terms of age and sex distribution.[21] Practices "opt-in" to contribute data to CPRD and about 50% of Practices contributing to CPRD GOLD provide additional consent to allow linkage of patient-level data with other datasets, including hospital admission data.[22] Previous studies found that the characteristics of patients from practices with linked data were representative of the entire CPRD GOLD population in terms of age, sex, and deprivation.[23] Bleeding events assessed and diagnosed in hospital are poorly recorded in primary care records,[24] and therefore major bleeding outcomes in this study were ascertained from International Classification of Disease version 10 (ICD-10) codes recorded in linked hospital admission data.

2.2 | Study design, population, and follow-up

This was a retrospective cohort study of new users of warfarin and DOACs presenting to General Practice with an RTI. The source population were 4 553 515 people who contributed at least 1 day of data to CPRD GOLD between 1st January 2011 and 31st December 2019, whose data were deemed acceptable for research, and who were eligible for linkage to hospital admission data. From the source population, we identified people who had their first ever prescription of warfarin or a DOAC within the study period of 1st January 2011 to 31st December 2019. For inclusion, the date of the first prescription needed to be after the year of their 18th birthday, and after the date

their practice's data were regarded as "up-to-standard." From this cohort of warfarin and DOAC users, we identified those who had a General Practice consultation for an RTI during their period of anticoagulant treatment for inclusion in this study.

The observation period began on the date of the first RTI consultation during the period of treatment with warfarin or a DOAC. Relevant consultations were identified using a list of Read codes of symptoms and diagnoses attributable to an RTI (code list in e-Appendix 1 in Supporting Information). Use of Read codes varies amongst GPs and there is no validated list of Read codes for identifying RTIs. Therefore, we used a list of broad symptoms and diagnoses to capture as many potential episodes of RTI as possible. The observation period ended on the earliest of: 30 days after the date of the RTI consultation; end of warfarin or DOAC treatment period; death; end of CPRD data collection; or end of study period (31st March 2020). The end of warfarin or DOAC treatment period was defined as the earliest of 90 days after the date of the last prescription of the drug that was initiated, or the date of the first prescription for a different oral anticoagulant. The observation period only included the first ever oral anticoagulant treatment period akin to a new-user design.[25]

2.3 | Exposure

Individuals receiving an immediate antibiotic prescription on the same day as their RTI consultation were regarded as exposed (antibiotic group). Those with no record of a same-day antibiotic prescription were unexposed (no antibiotic group).

2.4 | Outcomes

The primary outcome was informed by the definition of major bleeding proposed by the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH): bleeds that result in death, are life-threatening, cause chronic sequelae or consume major health-care resources.[26] For this study, we defined major bleeding as a hospital admission for intra-cerebral or gastrointestinal bleeding. These are the commonly-encountered major bleeds and have been ascertained from UK health records by numerous previous studies, increasing confidence in the reliability and completeness of their recording in routine health data.[24,27,28] These bleeds reflected both a pragmatic approach to ascertainment of major bleeding and acknowledgement of the ISTH criteria for major bleeding. Major bleeding was ascertained from ICD-10 codes recorded in linked hospital admission data and included codes recorded at any point during a hospitalisation and in any position within the hierarchy of diagnoses for a hospitalisation. The secondary outcomes were events indicating a less severe bleed. The outcome definition was adapted from the ISTH SSC's criteria for clinically relevant non-major bleeding (hereafter known as non-major bleeding)[29] of a bleed that did not fit the criteria of major bleeding, but required medical intervention, hospitalisation,

or face-to-face evaluation. For this study, we defined non-major bleeds as a General Practice consultation or hospital admission for haemoptysis, epistaxis, or haematuria, which we ascertained from General Practice and hospital admission data using a combination of Read and ICD-10 codes. Code lists are available in the Supporting Information (e-Appendix 2).

2.5 | Statistical analysis

The cohort of warfarin and DOAC users consulting for their first RTI following initiation of oral anticoagulants were characterised using descriptive statistics stratified by prescription for antibiotics. We used a directed acyclic graph (DAG) to identify confounders of the relationship between prescription for antibiotics and bleeding (Figure e-1 in Supporting Information). Our DAG implied the following confounding variables required adjustment: age at date of RTI consultation, smoking status, presence, or absence of asthma, coronary heart disease, chronic obstructive pulmonary disease, cancer, heart failure, stroke, and use of non-steroidal anti-inflammatory drugs (NSAIDs). Confounding variables were determined prior to date of exposure. The absence of a record indicating a long-term condition or prescription drug use was taken as absence of the condition or drug. Absence of records related to smoking status ($n = 349$, 2.4%) or alcohol intake ($n = 4604$, 31%) were regarded as missing data and were imputed using multiple imputation with chained equations, implemented in the 'mice' package in R.[30] The imputation models included the confounding variables identified by the DAG, the General Practice, the outcome indicator, and the follow-up time. We used 10 imputations. This was considered sufficient as the fraction of missing information was small (<0.0002), and the imputation made little difference to the estimates, standard errors, and confidence intervals.[31,32]

Propensity scores for the probability of an immediate antibiotic prescription, given the confounding variables listed above, were calculated using logistic regression.[33] Propensity scores were calculated for each imputed dataset. We assessed the balance of measured covariates between groups graphically and using standardised mean or proportion differences.[34]

In the primary analysis, we used Cox models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of major and non-major bleeding between exposed and unexposed groups during 15 and 30 day periods from the date of the RTI consultation. The proportional hazards assumption was assessed graphically and with a formal score test for slope = 0, with no evidence that proportionality was violated.[35] Cox models were fitted to each of the 10 imputed datasets and estimates were combined using Rubin's rules.[36] Crude HRs and 95% CIs were estimated without inverse probability of treatment weighting (IPTW) or adjustment for any confounding variables. Adjusted HRs and 95% CIs were estimated after adjusting for confounders using IPTW and including the General Practice as a random effect to account for clustering.[37] Data management and analyses were carried out in R version 4.2.1.

2.6 | Sensitivity analyses

We pre-specified two sensitivity analyses: (1) a complete-case analysis excluding individuals with missing smoking status data; and (2) repeating the main analysis but censoring individuals in the no antibiotic group if and when an antibiotic was prescribed in the 30-day follow-up period.

We conducted several post-hoc analyses. First, we included an interaction term to assess whether risk of bleeding differed between warfarin and DOAC users. We report p-values for the interaction between anticoagulant type and antibiotic use. Second, we excluded individuals with potential for high-risk of bleeding, defined as those with a previous record of dyspepsia, gastrointestinal inflammation (e.g., gastritis), oesophageal varices, peptic ulcer disease, or bleeding disorder. Third, we excluded individuals whose RTI occurred within 30 days of oral anticoagulant initiation, given that this can be a period of high risk for bleeding in warfarin initiators whilst appropriate dosage is established. Fourth, we excluded individuals with COPD given such individuals may have home-held antibiotics for use during infectious exacerbations, which could lead to their misclassification as having received no antibiotic prescription. Fifth, we excluded individuals with a hospital admission on the same day as the RTI consultation as hospital antibiotic provision was not known. Sixth, we excluded individuals with an RTI-related hospital admission in the 14-days prior to the General Practice consultation in case the General Practice record was documentation of the hospital admission rather than a new incident RTI. Seventh, we explored whether bleeding was related to an acute cardiovascular event which itself may have been triggered by the RTI.[38] Finally, we repeated the main analysis but included the following additional potential confounders in the propensity score model: gender, dementia, depression, diabetes, hypertension, peripheral vascular disease, rheumatoid arthritis, alcohol status, use of statins, antiplatelets, proton-pump inhibitors, or H2 receptor antagonists.

3 | RESULTS

Of 61 790 eligible incident warfarin and DOAC users, 14 817 had a consultation for an RTI during their oral anticoagulant treatment period, of whom 8768 (59%) were prescribed immediate antibiotics and 6049 (41%) were not (Figure 1). Baseline characteristics were similar across the two groups with approximately 49% female, median age of 76 years, and similar proportions of use of the different anticoagulants (Table 1). People in the antibiotic group mostly received amoxicillin (5866, 67%), followed by doxycycline (1099, 13%), clarithromycin (717, 8%) and co-amoxiclav (346, 4%). After inverse probability of treatment weighting with propensity scores, confounding variables were adequately balanced with standardised mean differences of ≤0.01 (e-Table 1 in Supporting Information).

3.1 | Major bleeding

Of 8768 individuals prescribed immediate antibiotics, 18 (0.2%) had a major bleed during the 15-day risk period, and 35 (0.4%) during the
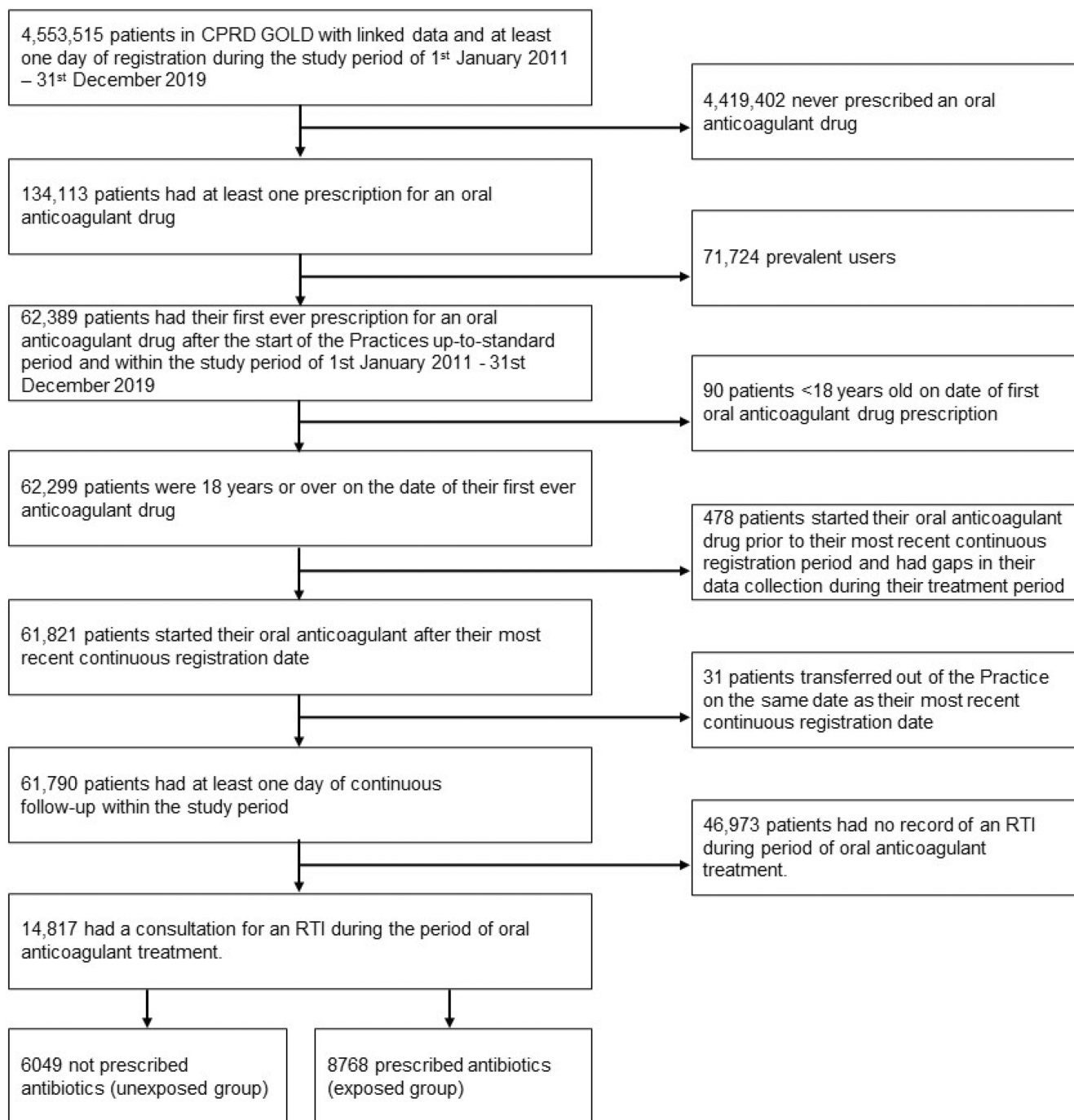
FIGURE 1 Flow of patients into the cohort.

30-day risk period (Table 2). Of the 6049 individuals not prescribed antibiotics, 34 (0.6%) had a major bleed during the 15-day risk period, and 39 (0.6%) during the 30-day risk period. 87% of major bleeds in the no antibiotic group occurred during the first 15 days following RTI consultation compared to 51% in the antibiotic group. The antibiotic group had reduced risk of major bleeding (15 days; adjusted HR 0.38, 95% CI 0.25 to 0.58, 30 days; adjusted HR 0.65, 95% CI 0.46 to 0.90). The reduced risk was observed for intracranial and gastrointestinal bleeds (e-Table 2 in Supporting Information).

3.2 | Non-major bleeding

Of 8768 individuals prescribed immediate antibiotics, 70 (0.8%) had a non-major bleed during the 15-day risk period, and 103 (1.2%) during the 30-day risk period (Table 3). Of the 6049 individuals not prescribed antibiotics, 64 (0.7%) had a non-major bleed during the 15-day risk period, and 88 (1.0%) during the 30-day risk period. In contrast to major bleeding, the proportion of non-major bleeds occurring in the first 15 days following RTI consultation were similar across

Characteristic	No antibiotic	Antibiotic	SMD
Number	6049	8768	
Female	2944 (48.7)	4268 (48.7)	<0.001
Anticoagulant			0.047
Apixaban	808 (13.4)	1132 (12.9)	
Dabigatran	171 (2.8)	268 (3.1)	
Edoxaban	59 (1.0)	66 (0.8)	
Rivaroxaban	1145 (18.9)	1549 (17.7)	
Warfarin	3866 (63.9)	5753 (65.6)	
Median (IQR) years of anticoagulant treatment	1.49 [0.66, 2.78]	1.51 [0.70, 2.84]	0.007
Year of RTI			0.059
2011	404 (6.7)	617 (7.0)	
2012	822 (13.6)	1302 (14.8)	
2013	905 (15.0)	1341 (15.3)	
2014	898 (14.8)	1342 (15.3)	
2015	890 (14.7)	1286 (14.7)	
2016	636 (10.5)	890 (10.2)	
2017	545 (9.0)	715 (8.2)	
2018	446 (7.4)	606 (6.9)	
2019	425 (7.0)	559 (6.4)	
2020	78 (1.3)	110 (1.3)	
Median (IQR) age on RTI date	76 [67–83]	76 [67–83]	0.044
Most recent recorded alcohol intake			0.008
Current drinker	2457 (40.6)	3579 (40.8)	
Ex-drinker	331 (5.5)	472 (5.4)	
Non-drinker	1372 (22.7)	2002 (22.8)	
Missing	1889 (31.2)	2715 (31.0)	
Most recent recorded smoking status			0.068
Current smoker	645 (10.7)	1052 (12.0)	
Ex-smoker	2404 (39.7)	3537 (40.3)	
Non-smoker	2829 (46.8)	4001 (45.6)	
Missing	171 (2.8)	178 (2.0)	
Cancer	872 (14.4)	1241 (14.2)	0.007
COPD	881 (14.6)	1424 (16.2)	0.046
Dementia	334 (5.5)	388 (4.4)	0.050
Depression	1730 (28.6)	2589 (29.5)	0.020
Diabetes	1113 (18.4)	1762 (20.1)	0.043
Heart failure	895 (14.8)	1256 (14.3)	0.013
Ischaemic heart disease	1500 (24.8)	2309 (26.3)	0.035
Hypertension	3468 (57.3)	4938 (56.3)	0.020
Stroke	917 (15.2)	1226 (14.0)	0.033
NSAIDS[a]	614 (10.2)	964 (11.0)	0.027
Antiplatelet[a]	2159 (35.7)	3218 (36.7)	0.021
Proton pump inhibitor[a]	3023 (50.0)	4432 (50.5)	0.011

TABLE 1 Characteristics of 14 817 adults consulting with a respiratory tract infection during their period of treatment with an oral anticoagulant, stratified by prescription for antibiotics. Values are numbers (%) unless otherwise stated.

Abbreviations: NSAIDS, non-steroidal anti-inflammatory drugs; RTI, respiratory tract infection; SMD, standardised mean difference.

[a]NSAID, antiplatelet, and proton pump inhibitor use determined from general practice prescription records in the 90 days prior to antibiotic exposure.

TABLE 2 Hazard ratios (HR) and 95% confidence intervals (CI) for major bleeding in people with and without antibiotics for respiratory tract infection.

	15 days		30 days	
	No antibiotic	Antibiotic	No antibiotic	Antibiotic
Number of patients	6049	8768	6049	8768
Number of events	34	18	39	35
Time at risk (years)[a]	244	355	478	699
Crude HR (95% CI)[b]	1	0.36 (0.21–0.64)	1	0.62 (0.39–0.97)
Adjusted HR (95% CI)[c]	1	0.38 (0.25–0.58)	1	0.65 (0.46–0.90)

[a]Total time from date of index respiratory tract infection (RTI) to end of follow-up. End of follow-up was earliest of death, end of data capture, or 30 days after index RTI.
[b]Crude HRs and 95% CIs estimated after multiple imputation but without inverse probability of treatment weighting (IPTW) or adjustment for any confounding variables.
[c]Adjusted HRs and 95% CIs were estimated after adjusting for confounders using IPTW and including the General Practice as a random effect to account for clustering.

TABLE 3 Hazard ratios (HR) and 95% confidence intervals (CI) for non-major bleeding in people with and without antibiotics for respiratory tract infection.

	15 days		30 days	
	No antibiotic	Antibiotic	No antibiotic	Antibiotic
Number of patients	6049	8768	6049	8768
Number of events	64	70	88	103
Time at risk (years)[a]	243	353	475	695
Crude HR (95% CI)[b]	1	0.75 (0.54–1.06)	1	0.80 (0.60–1.07)
Adjusted HR (95% CI)[c]	1	0.78 (0.61–0.99)	1	0.82 (0.67–1.00)

[a]Total time from date of index respiratory tract infection (RTI) to end of follow-up. End of follow-up was earliest of death, end of data capture, or 30 days after index RTI.
[b]Crude HRs and 95% CIs estimated after multiple imputation but without inverse probability of treatment weighting (IPTW) or adjustment for any confounding variables.
[c]Adjusted HRs and 95% CIs were estimated after adjusting for confounders using IPTW and including the General Practice as a random effect to account for clustering.

the two groups (68% vs. 73%). The immediate antibiotic group had a reduced risk of non-major bleeding at 15 days (adjusted HR 0.78, 95% CI 0.61 to 0.99) and 30 days (adjusted HR 0.82, 95% CI 0.67 to 1.00), but confidence intervals were close to the null. The reduced risk was driven by haematuria (15 days; adjusted HR 0.47, 95% CI 0.32 to 0.69, 30 days; adjusted HR 0.50, 95% CI 0.36 to 0.69), with no significant associations observed for haemoptysis or epistaxis (e-Table 2 in Supporting Information).

3.3 | Sensitivity analyses

Complete case analysis excluding people with missing smoking status data made little difference to estimates of major bleeding (e-Table 3 in Supporting Information). Censoring 1205 individuals in the no antibiotic group who were prescribed an antibiotic during the follow-up period (median time 9 days after the index RTI) made small differences to the magnitude of the risk estimates (e-Table 4 in Supporting Information). There was no difference to the direction of the estimates, but confidence intervals widened. We found no evidence that risk of bleeding differed between warfarin and DOAC users (p-value for interaction between the different anticoagulants and use of antibiotics for major bleeding 0.689 for 15 days, 0.939 for

30 days; p-value for interaction for non-major bleeding 0.467 for 15 days, 0.856 for 30 days). To assess the impact of a hospital admission on the same day as the index RTI, we excluded 488 people (8.1%) in the no antibiotic group, and 22 people (0.3%) in the antibiotic group. Again, confidence intervals widened but the significant reduction in risk of major bleeding at 15 days remained significant (e-Table 8 in Supporting Information). Adding alcohol status, gender, additional comorbidities, and use of corticosteroids, statins, proton-pump inhibitors, or antiplatelet, to the propensity score models made no appreciable difference to the risk estimates from the main analysis (e-Table 10 in Supporting Information). We explored whether bleeding could be due to an acute cardiovascular event triggered by the RTI, but only three cardiovascular events were identified during the 30-day post-RTI risk period; two people in the antibiotic group had a cardiovascular event (1 acute myocardial infarction, one ischaemic stroke) recorded on same day as a major bleed; one person in no antibiotic group had an ischaemic stroke recorded on the same day as their major bleed. The remaining sensitivity analyses maintained the direction of effect for all outcomes, but confidence intervals widened, and some included the null (e-Tables 5, 6, 7, 9 in Supporting Information). However, the significant reduction in risk of major bleeding at 15 days was consistent across all analyses, and at 30 days, across most analyses.

4 | DISCUSSION

4.1 | Principle findings

In this retrospective cohort study of warfarin and DOAC users consulting with General Practice for an RTI, immediate antibiotics were associated with a 62% reduction in relative risk of major bleeding at 15 days, and 35% at 30 days. This was consistent across several sensitivity analyses. Antibiotics were also associated with a reduced risk of non-major bleeding, but this finding was not significant across sensitivity analyses. We found no evidence of an increased risk of any bleeding amongst those prescribed antibiotics, suggesting that the effect of the infection on coagulation is clinically more important than any perceived concern about an antibiotic-anticoagulant drug–drug interaction.

4.2 | Strengths and limitations of this study

We used a large and representative data source with reliable and complete recording of prescription data to determine our population of oral anticoagulant users. Primary care is the key source of antibiotic prescriptions in the UK reducing the likelihood of misclassification of exposure except for individuals who may keep antibiotics at home (e.g., people with COPD). However, sensitivity analyses excluding these individuals found similar effects to the main analysis. We undertook a range of sensitivity analyses to test various assumptions from the main analysis and found findings for major bleeding to be consistent, but less so for non-major bleeding. Hence this outcome has been interpreted with caution.

This study had several limitations. Participants having an RTI were ascertained from General Practice records and represented an RTI for which the patient consulted a healthcare professional, and which led to a corresponding record in their health data. We were unable to capture RTIs seen in out-of-hours general practice or other forms of urgent primary care. Therefore, findings may not be applicable to RTIs that are self-managed or managed in settings other than in-hours General Practice. We were unable to ascertain the aetiology of the RTI, that is, viral, or bacterial. Our findings may be influenced by confounding by indication related to GPs identifying individuals at greater risk of bleeding and not prescribing them antibiotics. We were inadequately powered to assess any differential effect by the type of antibiotic prescribed. We were unable to determine whether people who were prescribed antibiotics for an RTI altered how they manage their anticoagulant use and acknowledge that some people may have temporarily stopped their anticoagulants during their antibiotic treatment due to fears of increased bleeding risk. We do not know if people in the no antibiotic group who had a hospital admission on the same day as the index RTI were given immediate antibiotics in hospital, and thus, may be misclassified. However, this represents only 8% of the no antibiotic group, and excluding these individuals in sensitivity analyses maintained the 15-day effect estimates for major bleeding seen in the main analysis. Findings for non-major bleeding had wide confidence intervals across several sensitivity analyses and should be interpreted cautiously.

4.3 | Comparison with other studies

Our study strengthens findings from the few previous studies that investigated the effect of community-acquired infection on the risk of bleeding. Clarke et al found that RTIs increased the risk of supratherapeutic anticoagulation irrespective of whether antibiotics were prescribed.[18] However, unlike our study, they did not detect a difference in rates of bleeding amongst those prescribed versus not prescribed antibiotics, likely due to the smaller sample size (6427 vs. 14 817) and inadequate power for a relatively rare outcome. A previous self-controlled case series found an increased risk of bleeding amongst warfarin and DOAC users in the 14-day period following an untreated (no antibiotic) RTI.[2] The magnitude of effect decreased when the cohort was expanded to include RTIs with antibiotic treatment, suggesting antibiotics may confer some protective effect. This aligns with the findings from our study.

We hypothesised that the RTI was the main driver of the risk of bleeding and therefore there would be no difference in bleeding rates amongst people with RTI prescribed antibiotics versus those not. Previous studies found that co-prescription of antibiotics and anticoagulants were associated with an increased risk of bleeding, but most were unable to account for the impact of the underlying infection.[14–17] We found that those prescribed antibiotics had a reduced risk of major bleeding. There may be several possible reasons for this. With RTI, it might be expected that increasing inflammation in the upper airways and trauma from coughing may increase the risk of epistaxis and haemoptysis. However, we did not observe this, suggesting that the relationship between infection and bleeding relates to more systemic changes. GPs may have selected those with greater likelihood of bacterial infection for antibiotics. Viral RTIs (e.g., influenza) may cause thrombocytopenia[39] and this might explain the greater bleeding rates in the no antibiotic group if they comprised a greater proportion of viral RTIs. Other systemic changes may relate to inflammation driving platelet activation, enhanced vascular permeability, and rapid platelet consumption,[40] all of which may be lessened by antibiotic treatment. Our finding of antibiotics potentially reducing the risk of bleeding is also indirectly supported by their recommended use for people with acute variceal bleeding.[41] Meta-analyses of randomised trials found that amongst people with acute variceal bleeding, antibiotics reduced the risk of re-bleeding, as well infection-related incidence and mortality.[42] Mechanisms are not well understood but are thought to relate to bacterial endotoxins increasing portal pressure, impairing liver function, and worsening haemostasis.[43] It is therefore plausible that bacterial RTIs may increase the risk of major bleeding, and antibiotic treatment may reduce this risk, but mechanisms need to be better understood.

5 | CONCLUSIONS

Amongst oral anticoagulant users consulting with General Practice for an RTI, immediate antibiotic prescriptions were associated with a reduced risk of major bleeding. Further work is warranted to better understand the mechanisms for this finding and identify specific subgroups of oral anticoagulant users where a lower threshold for antibiotic use in case of RTI may be beneficial. With major and non-major bleeding, we did not observe any increase in risk of bleeding relating to antibiotic use, suggesting that concerns about antibiotic-anticoagulant drug–drug interactions should not influence the decision to prescribe antibiotics if there is a clear clinical need.

AUTHOR CONTRIBUTIONS

All authors were involved in the design of the study. Haroon Ahmed did the statistical analysis and wrote the first draft. All authors contributed to further drafts and approved the final manuscript. Haroon Ahmed is guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

CPRD data agreement prevents data sharing but researchers can apply directly to CPRD for a data-set.

ETHICS STATEMENT

This study was approved by the independent scientific advisory committee (protocol number 20_175).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.