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Antibiotic prescribing patterns and risk of antibiotic-resistant infections and *Clostridium difficile* in Warfarin and Direct Oral Anticoagulant users: matched population-based cohort study

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Abstract

Background Warfarin and Direct Oral Anticoagulant (DOAC) users may have more frequent antibiotic prescriptions than non-users. The aim of this study was to estimate rates of common and resistant infections, and antibiotic prescribing amongst warfarin and DOAC users versus non-users.

Methods This matched retrospective cohort study used data from patients registered with General practices in England contributing to the Clinical Practice Research Datalink GOLD. We included 61,750 adults who initiated warfarin or a DOAC between 1st January 2011 and 31st December 2019, matched 1:1 to non-users. We estimated Incident Rate Ratios (IRR) and 95% Confidence Intervals for three common infections and all-cause antibiotic prescribing. We estimated hazard ratios (HRs) and 95% CIs for the risk of methicillin resistance *Staphylococcus aureus* (MRSA), other antibiotic-resistant organisms, or *Clostridium difficile*. We assessed the extent to which any of the effect of warfarin and DOAC use on antibiotic resistant infections or *Clostridium difficile* was mediated by antibiotic prescribing patterns.

Results 37,143 warfarin users and 24,607 DOAC users were matched 1:1 to non-users. Warfarin and DOAC users had greater relative consultation rates for respiratory, urinary, and skin infections. All-cause antibiotic prescribing was greater in warfarin and DOAC users (warfarin; adjusted IRR 1.47, 95% CI 1.45–1.50, DOAC; adjusted IRR 1.66, 95% CI 1.63–1.69). Largest effect sizes were observed for flucloxacillin (adjusted IRR 2.11, 95% CI 2.01–2.20), and erythromycin (adjusted IRR 2.32, 95% CI 2.00–2.70). Warfarin users had significantly higher risk of MRSA (adjusted HR 1.68, 95% CI 1.38–2.05) and hospital admission with antibiotic resistant infections (adjusted HR 1.91, 95% CI 1.11–3.30). DOAC users had significantly higher risk of MRSA (adjusted HR 1.57, 95% CI 1.20–2.06), hospital admission with antibiotic resistant infections (adjusted HR 2.13, 95% CI 1.61–2.82), and *Clostridium difficile* (adjusted HR 1.45, 95% CI 1.10–1.92). We found little evidence to suggest that the increased risks of studied outcomes were mediated by rates of antibiotic prescription.

Conclusion Warfarin and DOAC use was associated with greater rates of infection consultations, all-cause antibiotic prescribing, antibiotic resistant infections, and *Clostridium difficile*, but there was little evidence that antibiotic prescribing rates mediated risk of resistant infections or *Clostridium difficile*.

Keywords Antibiotic prescribing · Anticoagulants · Antimicrobial resistance

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1 Introduction

Warfarin and Direct Oral Anticoagulants (DOACs; apixaban, rivaroxaban, edoxaban, and dabigatran) are used to treat venous thromboembolism and prevent stroke [1]. Over six million prescriptions for warfarin and 11 million for DOACs were dispensed in England in 2019. [2] People who use Warfarin or DOACs may have significant comorbidities. In the four largest randomized trials of warfarin versus DOACs for atrial fibrillation, nearly 90% of participants had hypertension, 45% heart failure, 30% diabetes, and 30% coronary artery disease [3–6]. In large cohort studies using UK general practice databases (where recording of morbidities is likely to be less complete than trial data), around 60% of warfarin and DOAC users had hypertension, 14% heart failure, 20% diabetes, 25% coronary artery disease, and 8–12% had recently used corticosteroids [7]. At least some of these underlying morbidities can increase the risk of infection (e.g., diabetes) [8] and combinations of multiple morbidities and immunosuppressive medications (e.g., corticosteroids) may increase this risk further [9].

To date, no studies have adequately quantified the risk of infections in warfarin and DOAC users versus non-users. Indirect evidence for a greater incidence of infection can be inferred from studies of antibiotic prescribing which found significantly greater rates of antibiotic prescribing for people with diabetes, heart failure, coronary artery disease, and other comorbidities common amongst warfarin and DOAC users [10]. In addition to a greater volume of antibiotic prescribing, choice of drug may also differ between warfarin and DOAC users versus non-users due to the perceived potential for drug-drug interactions. Research to date suggests drug-drug interactions increase the risk of bleeding for co-prescriptions of warfarin with co-trimoxazole, quinolones, and macrolides, [11–13] and DOACs with clarithromycin [14]. Little is known about the volume and patterns of antibiotic prescribing for warfarin and DOAC users and subsequent outcomes. Of particular importance are subsequent antibiotic resistance which is driven by antibiotic use, [15] and infection with *Clostridium difficile* which is driven by broad-spectrum antibiotic use [16, 17]. Therefore, the aim of this study was to first estimate rates of three common infections in primary care amongst warfarin and DOAC users, and second describe antibiotic prescribing patterns and assess whether these mediated subsequent risk of infection with methicillin resistance *Staphylococcus aureus* (MRSA), other antibiotic-resistant organisms, or *Clostridium difficile*.

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) [18]. 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 [18]. Patient-level data are 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 2023, CPRD GOLD contained data for 2.9 million patients currently alive, with data deemed acceptable for research, registered at 369 Practices across the UK that use Vision® electronic health record software [19]. The CPRD GOLD sample represents 4.4% of the UK population and 4.6% of UK General Practices [18]. 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 [20]. 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 [21]. 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 [22].

The CPRD database contains coded and anonymised data from GP practices. No identifiable patient information is collected. Therefore, the need for individual consent to participate was waived by the Derby Research Ethics Committee (reference 21/EM/0265).

2.2 Study design, population, and follow-up

This was a retrospective matched cohort study. The source population were 4,553,515 people who contributed at least one 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 31st December of the year of their 18th birthday, and after the date their practice's data were regarded as "up-to-standard". The observation period began on the date of the first warfarin or DOAC prescription and ended on the earliest of: 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 [23].

Warfarin and DOAC users were matched 1:1 to non-users by the CPRD. Non-users were identified from the same source population of 4,553,515 people as users. To be eligible for matching with a user, non-users required at least one day of data in CPRD GOLD between 1st January 2011 and 31st December 2019, with data deemed acceptable for research, and eligible for linkage, but without any record of a warfarin or DOAC prescription. Non-users were matched to users on year of birth (± 5 years), sex, and practice. CPRD used index date matching. In this algorithm, the users index date (date of first warfarin or DOAC prescription) must fall between the follow-up start and follow-up end dates of the non-user. Matching was applied without replacement with non-users not eligible to be reused or matched to more than one user. Once data for matched pairs were received, each pair was assigned the same start and end of follow-up to match the duration of observation and calendar time covered. To do this, start of follow-up was the later of the users index date or non-users start date, and end of follow-up was the earlier of the users or non-users end date.

2.3 Exposure

The exposure was warfarin or DOAC use and thus the exposure period began on the date of the first warfarin or DOAC prescription and ended on the earliest of: end of warfarin or DOAC treatment period; death; end of CPRD data collection; or end of study period (31st March 2020).

2.4 Outcomes

The outcomes of interest were:

(1) Consultation rates for respiratory, urinary, or skin infections, which together account for almost 85% of antibiotic prescribing in UK General Practice; [24]
(2) All-cause antibiotic prescribing rates, because about 35% of antibiotics in UK General Practice are prescribed without a recorded indication; [24]
(3) Incident cases of infection with MRSA, other antibiotic-resistant organisms, or *Clostridium difficile*.

Rates of each outcome were compared between warfarin and DOAC users versus non-users during the exposure period. General Practice consultations for respiratory, urinary, and skin infections were identified using Read codes that represented diagnoses or symptoms of each infection of interest (tables e-1 to e-3). Antibiotic prescribing rates were calculated overall (any antibiotic listed in chapter 5 of the British National Formulary) and individually for the 10 most prescribed drugs. MRSA was identified from General Practice and hospital admission records using Read and International Classification of Disease version 10 (ICD-10) codes that represented carriage or infection (Table e-4), and prescriptions for eradication treatment (Table e-5). Infection with antibiotic-resistant organisms was identified from hospital admission records using relevant ICD-10 codes (Table e-6). Infection with *Clostridium difficile* was identified from General Practice and hospital admission records using Read and ICD-10 codes that represented infection or detection of antigen or toxin (Table e-7).

2.5 Statistical analysis

We described the sociodemographic and clinical characteristics of warfarin and DOAC users versus non-users. We calculated crude rates and Incidence Rate Ratios (IRR) for consultations for respiratory, urinary, and skin infections. Multiple infection-related consultations on the same day were only counted once. We also calculated crude rates and IRRs of overall and drug-specific antibiotic prescribing for each group during their observation period. IRRs [with 95% Confidence Intervals (CI)] were estimated using Poisson regression. Users and non-users were matched on year of birth, sex, and practice, and models were additionally adjusted for prior antibiotic prescribing rate (total number of antibiotic prescriptions/available observation time in the 12 months prior to index date), and a history of any of the following conditions determined from Read codes recorded prior to the index date: asthma, atrial fibrillation, cancer, chronic obstructive pulmonary disease, chronic kidney disease stage 3, 4 or 5, coronary artery disease, dementia, depression, diabetes, heart failure, hypertension, stroke.

To understand and assess the potential causal effect of warfarin and DOAC use on incident cases of infection with MRSA, other antibiotic-resistant organisms, or *Clostridium difficile,* we developed a Directed Acyclic Graph (DAG) to illustrate potential confounders and mediators of any causal relationship (Figure e-1). The DAG implied that the minimal sufficient adjustment set for estimating the total effect of warfarin or DOAC use on the outcomes of interest included age, calendar year, cancer, ischaemic heart disease, heart failure, number of GP contacts, and stroke. Co-morbidities were determined from Read codes recorded prior to the index date. Number of GP contacts were calculated as the total number of consultations/available observation time in the 12 months prior to index date. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CIs for the risk of each outcome amongst warfarin and DOAC users versus non-users [25]. The first model estimated HRs for users and non-users matched on year of birth, sex, practice, and observation time, without conditioning on any additional confounders, the second, for matched variables plus the minimal sufficient adjustment set from the DAG, and the third, for matched variables, minimal sufficient adjustment set, and additional variables thought to be potential causes of the outcomes. These included asthma, atrial fibrillation, cancer, chronic obstructive pulmonary disease, chronic kidney disease stage 3, 4 or 5, coronary artery disease, dementia, depression, diabetes, heart failure, hypertension, stroke, use of corticosteroids, statins, or proton pump inhibitors, and prior antibiotic prescribing rate. The absence of a record indicating a long-term condition or prescription drug was taken as absence of the condition or drug. There were no missing data for any of the required variables. We undertook mediation analysis to assess the extent to which any of the effect of warfarin and DOAC use on antibiotic resistant infections or *Clostridium difficile* was mediated by antibiotic prescribing patterns. To do this, we estimated hazard ratios for each outcome in multivariable Cox models with and without a measure of overall antibiotic prescribing during the observation period. Due to the non-collapsibility of hazard ratios, we repeated this with Aalen's additive regression models [26]. All analyses were performed in R version 4.2.1.

3 Results

We identified 37,143 eligible warfarin users and 24,607 eligible DOAC users that could be matched 1:1 to 61,750 non-users (Fig. 1). Warfarin users and non-users were well matched with 17,065 (45.9%) females in each group, mean age 70.65 years (standard deviation (SD) 14.64), and mean observation time of 1.05 years (SD 1.14) (Table 1). DOAC users and non-users were also well matched with 11,892 (48.3%) females in each group, mean age 72.19 years (SD 14.72), and mean observation time of 0.91 years (SD 1.00). Compared to non-users, warfarin and DOAC users had higher rates of infection-related consultations and antibiotic prescribing in the 12 months prior to index date, and higher rates of comorbidities.

3.1 Consultations for respiratory, urinary, and skin infections

Compared to non-users, warfarin and DOAC users had greater relative consultation rates for respiratory, urinary, and skin infections (Table 2). Effect sizes for respiratory and urinary tract infections were moderate and reduced once

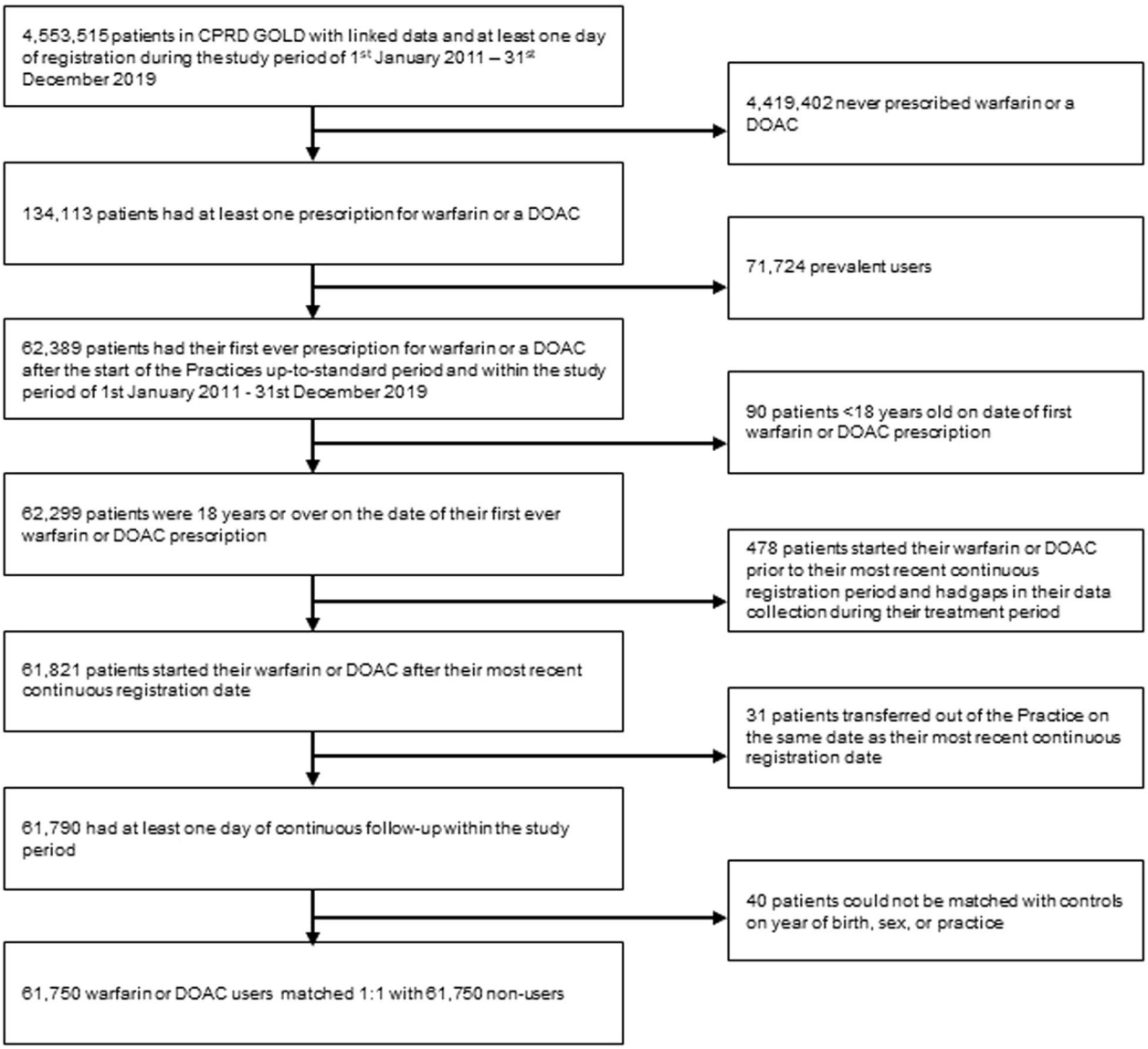

Fig. 1 Flow of patients into the cohorts

we adjusted for co-morbidities. Larger effect sizes were observed for cellulitis, and these were relatively consistent before and after adjustment for co-morbidities (adjusted IRR for warfarin users 2.76, 95% CI 2.54–2.99; adjusted IRR for DOAC users 3.09, 95% CI 2.77–3.45) (Table 2).

3.2 Antibiotic prescribing patterns

Over a total observation period of 38,895 years, there were 60,165 antibiotic prescriptions for warfarin users, and 38,247 for non-users, equating to crude rates of 154.68 and 98.33 per 100 person years respectively. Compared to non-users, warfarin users had a greater relative rate of antibiotic prescription (IRR 1.57, 95% CI 1.55–1.59) which reduced slightly once we adjusted for co-morbidities (IRR 1.47, 95% CI 1.45–1.50) (Table 2). Over a total observation period of 22,272 years, there were 37,561 antibiotic prescriptions for DOAC users, and 20,766 for non-users, equating to crude rates of 168.64 and 93.24 per 100 person years respectively. Compared to non-users, DOAC users had a greater relative rate of antibiotic prescription (IRR 1.81, 95% CI 1.78–1.84) which again reduced once we adjusted for co-morbidities (IRR 1.66, 95% CI 1.63–1.69) (Table 2). The 10 most prescribed antibiotics were amoxicillin, trimethoprim, flucloxacillin, nitrofurantoin, doxycycline, clarithromycin, co-amoxiclav, cefalexin, erythromycin, and ciprofloxacin (Table e-8). Estimation of IRRs by

Table 1 Characteristics of warfarin and DOAC users versus non-users

Characteristic	Warfarin users	Matched non-users	DOAC users	Matched non-users
N	37143	37143	24607	24607
Female	17065 (45.9)	17065 (45.9)	11892 (48.3)	11892 (48.3)
Age at cohort entry, mean [SD]	70.65 [14.64]	70.65 [14.64]	72.19 [14.72]	72.18 [14.71]
Total observation time (years), mean [SD]	1.05 [1.14]	1.05 [1.14]	0.91 [1.00]	0.91 [1.00]
GP consultations in 12 months prior to index date, mean [SD]				
All-cause	23.03 [15.21]	13.82 [12.52]	23.57 [15.73]	14.78 [12.79]
Respiratory tract infection	0.46 [0.99]	0.31 [0.81]	0.40 [0.90]	0.27 [0.74]
Urinary tract infection	0.18 [0.67]	0.15 [0.62]	0.18 [0.64]	0.14 [0.58]
Cellulitis	0.06 [0.42]	0.03 [0.27]	0.06 [0.35]	0.03 [0.23]
Antibiotic prescriptions in 12 months prior to index date, mean [SD]	1.27 [2.54]	0.93 [2.39]	1.36 [3.05]	0.90 [2.53]
Atrial fibrillation	18293 (49.3)	930 (2.5)	11103 (45.1)	522 (2.1)
Cancer	4721 (12.7)	3777 (10.2)	3405 (13.8)	2670 (10.9)
COPD	3239 (8.7)	2249 (6.1)	2226 (9.0)	1527 (6.2)
Ischaemic heart disease	8245 (22.2)	4666 (12.6)	4547 (18.5)	2891 (11.7)
Dementia	925 (2.5)	1673 (4.5)	1266 (5.1)	1430 (5.8)
Depression	8918 (24.0)	8249 (22.2)	6351 (25.8)	5576 (22.7)
Heart failure	3785 (10.2)	850 (2.3)	2038 (8.3)	527 (2.1)
Diabetes	6039 (16.3)	4762 (12.8)	4142 (16.8)	3392 (13.8)
Hypertension	19278 (51.9)	15693 (42.3)	12800 (52.0)	10661 (43.3)
Asthma	6063 (16.3)	4996 (13.5)	4088 (16.6)	3326 (13.5)
Stroke	4165 (11.2)	2097 (5.6)	2933 (11.9)	1486 (6.0)
Chronic kidney disease ≥ stage 3	7385 (19.9)	5576 (15.0)	4828 (19.6)	4187 (17.0)
Corticosteroid prescription	4662 (12.6)	2564 (6.9)	3106 (12.6)	1699 (6.9)
Statin prescription	17026 (45.8)	12893 (34.7)	11338 (46.1)	8875 (36.1)
Proton pump inhibitor prescription	15143 (40.8)	10411 (28.0)	10820 (44.0)	7434 (30.2)

Values are numbers (%) unless otherwise stated

antibiotic found increased relative rates of all 10 included antibiotics with the largest effect size amongst warfarin users being for flucloxacillin (adjusted IRR 2.11, 95% CI (2.01–2.20), and amongst DOAC users being for erythromycin (adjusted IRR 2.32, 95% CI 2.00–2.70) (Tables e-9 and e-10). Compared to non-users, prescription rates of cefalexin, ciprofloxacin, and co-amoxiclav (generally regarded as broad-spectrum with greater risk of *Clostridium difficile*) were 23%, 61%, and 75% greater in warfarin users, and 78 to 94% greater in DOAC users.

3.3 Antibiotic resistant infections and *Clostridium difficile*

Amongst warfarin users versus non-users matched on year of birth, sex, practice, and observation period, event counts for MRSA were 352 versus 154, hospital admission with antibiotic resistant infections were 45 versus 20, and *Clostridium difficile* were 170 versus 93 (Table 3). After adjusting for the minimal sufficient adjustment set from the DAG, warfarin users had significantly higher risk of MRSA (adjusted HR 1.68, 95% CI 1.38–2.05) and hospital admission with antibiotic resistant infections (adjusted HR 1.91, 95% CI 1.11–3.30). The adjusted HR for *Clostridium difficile* was 1.25 but the 95% CI crossed the null (0.96–1.62). Adjusting for co-morbidities in addition to the minimal sufficient adjustment set made little difference to estimates for MRSA or *Clostridium difficile* but strengthened the effect size for hospital admission with antibiotic resistant infections (adjusted HR 2.34, 95% CI 1.27–4.33). Event counts for matched DOAC users versus non-users were 185 versus 83 for MRSA, 208 versus 69 for hospital admission with antibiotic resistant infections, and 156 versus 78 for *Clostridium difficile*. After adjusting for the minimal sufficient adjustment set from the DAG, DOAC users had significantly higher risk of MRSA (adjusted HR 1.57, 95% CI 1.20–2.06), hospital admission with antibiotic resistant infections (adjusted HR 2.13, 95% CI 1.61–2.82), and *Clostridium difficile* (adjusted HR 1.45, 95% CI 1.10–1.92). Adjusting

Table 2 Incidence Rate Ratios (IRR) and 95% Confidence Intervals (CI) for antibiotic prescriptions and infection consultations amongst warfarin and DOAC users versus non-users

Outcome	Group	Number of events	Crude rate[a]	Matched IRR (95% CI)[b]	Adjusted IRR (95% CI)[c]
Antibiotic prescriptions	Non-users	38247	98.33	1	1
	Warfarin users	60165	154.69	1.57 (1.55–1.59)	1.47 (1.45–1.50)
Respiratory tract infections	Non-users	12377	31.82	1	1
	Warfarin users	17991	46.26	1.45 (1.42–1.49)	1.19 (1.16–1.23)
Urinary tract infections	Non-users	6239	16.04	1	1
	Warfarin users	9035	23.23	1.45 (1.40–1.50)	1.25 (1.20–1.30)
Cellulitis	Non-users	1086	2.79	1	1
	Warfarin users	2940	7.56	2.71 (2.53–2.90)	2.76 (2.54–2.99)
Antibiotic prescriptions	Non-users	20766	93.24	1	1
	DOAC users	37561	168.65	1.81 (1.78–1.84)	1.66 (1.63–1.69)
Respiratory tract infections	Non-users	5928	26.62	1	1
	DOAC users	8755	39.31	1.48 (1.43–1.53)	1.21 (1.16–1.26)
Urinary tract infections	Non-users	3236	14.53	1	1
	DOAC users	4780	21.46	1.48 (1.41–1.54)	1.42 (1.35–1.50)
Cellulitis	Non-users	517	2.32	1	1
	DOAC users	1566	7.03	3.03 (2.74–3.35)	3.09 (2.77–3.45)

[a]Total observation time was 38,895 years for warfarin users and matched non-users, and 22,272 years for DOAC users and matched non-users. Crude rate presented per 100 years

[b]Matched on year of birth, sex, practice, and observation period

[c]Additional adjustment for prior rate of the outcome and a history of any of the following conditions determined from Read codes recorded prior to the index date: asthma, atrial fibrillation, cancer, chronic obstructive pulmonary disease, chronic kidney disease stage 3, 4 or 5, coronary artery disease, dementia, depression, diabetes, heart failure, hypertension, stroke

Table 3 Hazard Ratios (HR) and 95% Confidence Intervals (CI) for risk of MRSA, antibiotic resistant infections, and *Clostridium difficile* amongst warfarin and DOAC users versus non-users

Outcome	Group	Number of events	Matched HR (95% CI)[a]	DAG adjusted HR (95% CI)[b]	Adjusted HR (95% CI)[c]
MRSA	Non-users	154	1	1	1
	Warfarin users	353	2.30 (1.91–2.78)	1.68 (1.38–2.05)	1.64 (1.30–2.05)
Hospital admission with antibiotic resistant infections	Non-users	20	1	1	1
	Warfarin users	45	2.25 (1.33–3.81)	1.91 (1.11–3.30)	2.34 (1.27–4.33)
Clostridium difficile	Non-users	93	1	1	1
	Warfarin users	170	1.83 (1.42–2.36)	1.25 (0.96–1.62)	1.29 (0.94–1.76)
MRSA	Non-users	83	1	1	1
	DOAC users	185	2.24 (1.73–2.90)	1.57 (1.20–2.06)	1.52 (1.12–2.07)
Hospital admission with antibiotic resistant infections	Non-users	69	1	1	1
	DOAC users	208	3.02 (2.30–3.97)	2.13 (1.61–2.82)	2.51 (1.85–3.43)
Clostridium difficile	Non-users	78	1	1	1
	DOAC users	156	2.00 (1.53–2.63)	1.45 (1.10–1.92)	1.38 (0.99–1.92)

[a]Matched on year of birth, sex, practice, and observation period

[b]As above and adjusted for cancer, ischaemic heart disease, heart failure, number of GP contacts, and stroke

[c]As above and additional adjustment for asthma, atrial fibrillation, cancer, chronic obstructive pulmonary disease, chronic kidney disease stage 3, 4 or 5, coronary artery disease, dementia, depression, diabetes, heart failure, hypertension, stroke, use of corticosteroids, statins, or proton pump inhibitors, and prior antibiotic prescribing rate

for co-morbidities again made little difference to estimates for MRSA or *Clostridium difficile* but strengthened the effect size for hospital admission with antibiotic resistant infections (adjusted HR 2.51, 95% CI 1.85–3.43). Adding antibiotic prescription rates during the observation period to the multivariable Cox models made little difference to the HRs and inspection of plots from the Aalen models found little evidence to suggest that the increased risks of studied outcomes were mediated by rates of antibiotic prescription.

4 Discussion

4.1 Principle findings

In this cohort study, we found that warfarin and DOAC users had significantly greater rates of consultations for respiratory, urinary, and skin infections. The relative rate for cellulitis consultations was almost three times greater than amongst matched non-users. Warfarin and DOAC users had around a 50% greater rate of antibiotic prescribing compared to non-users. Warfarin and DOAC use was associated with a 50–60% greater risk of MRSA and more than a two-fold increase in the risk of hospital admission with antibiotic resistant infection. DOAC users had significantly greater risk of *Clostridium difficile*.

4.2 Strengths and limitations of this study

We used a representative real-world sample of warfarin and DOAC users matched to non-users on year of birth, sex, practice, and observation period. Almost all prescriptions in UK General Practice are recorded electronically reducing the chances of misclassifying Warfarin and DOAC users and non-users. Matching was exact except for year of birth which applied a 5-year window, but 99.3% of pairs were matched exactly. Confounder adjustment was informed by a DAG, and although we may have some residual confounding, adjusting for additional covariates beyond those identified by the DAG made little difference to most of the risk estimates. Use of linked primary and secondary care data increased capture of outcomes of interest. We restricted to only the first event for each outcome to avoid double-counting. The outcomes were based on diagnostic codes (rather than laboratory results) which are subject to differential use. Read codes used for MRSA and *Clostridium difficile* included some that reflect carriage rather than infection but, (1) it is unlikely that GPs would screen asymptomatic patients, and (2) MRSA carriage alone is an important outcome that confers an increased risk of MRSA infection and indicates antibiotic resistance [27].

4.3 Comparison with other studies

We found that warfarin and DOAC users had greater rates of consultation for respiratory and urinary tract infections. Effect sizes were small and were appreciably reduced in models adjusted for co-morbidities versus models matched on age, sex, practice, and observation period. The observed associations are likely to be multi-factorial and could be explained by the (unmeasured) additive effect of co-morbidities strongly associated with greater rates of infection such as diabetes, stroke, COPD, and asthma [8, 28–30]. The observed rates may also reflect ascertainment bias, as warfarin and DOAC users are likely to be greater users of General Practice services for drug and disease monitoring. Effect sizes for cellulitis were more substantial. There are few reliable tests or tools to aid diagnosis of skin infections in primary care, and most clinicians rely on clinical judgment and experience [31, 32]. It is therefore difficult to determine the accuracy of diagnosed cellulitis amongst warfarin and DOAC users who may be more likely to have bruising and other non-infective skin changes. However, warfarin and DOACs are reported to cause skin necrosis, and although risks in a population-based cohort have not been quantified, this may partly account for our finding [33–35]. The greater rates of consultation for respiratory, urinary, and skin infections are the likely drivers of the observed rates of antibiotic prescribing. To date, no previous study has assessed warfarin and DOAC use as drivers of antibiotic prescribing, but cardiovascular and metabolic co-morbidities prevalent amongst warfarin and DOAC users are associated with a 37–70% increase in rates of antibiotic prescribing [10]. Despite concerns that perceived drug-drug interactions may affect antibiotic prescribing patterns, we observed increased rates of prescribing of all antibiotics. The 10 most prescribed antibiotics broadly reflected national patterns with some notable exceptions (e.g., Lymecycline, key indication is acne) due to the older population [36]. The highest rates were seen for flucloxacillin and erythromycin reflecting their roles in treatment of cellulitis [37].

We found that warfarin and DOAC use were associated with increased risks of MRSA, hospitalisation with antibiotic resistant infections, and *Clostridium difficile*. We found no previous studies describing this relationship. We expected this relationship to be mediated by the observed increase in antibiotic prescribing rates but found no quantifiable evidence to support this. However, it is well recognised that antibiotic use is the main driver for the spread of antibiotic resistant organisms [15] and *Clostridium difficile* infection is often triggered by recent antibiotic exposure [17]. Again, it is likely that the association is due to multiple factors including the patients' complex clinical phenotypes with an additive effect from several measured and unmeasured risk factors.

There are several implications of this research. First, we need to better understand the reasons for the increased rates of consultations for respiratory, urinary, and skin infections. Are these 'true' infections or clinically suspected with lower thresholds for antibiotic prescribing due to underlying co-morbidities? This is particularly important for skin infections. A key priority is to explore the challenges, needs, and potential solutions for patients and clinicians around skin infection diagnosis in the context of warfarin and DOAC use. Second, we need to understand whether antibiotic stewardship principles are followed for warfarin and DOAC users and the potential barriers to this in clinical practice. Third, there was little evidence that antibiotic-anticoagulant interactions affect antibiotic prescribing patterns. Electronic alerts/warnings based on weak evidence could be removed to reduce alert fatigues and focus on more clinically relevant issues (e.g., is this antibiotic clinically indicated). Fourth, we need to address the rates of antibiotic resistant infections and *Clostridium difficile* amongst warfarin and DOAC users and identify feasible strategies to drive these rates down and prevent the related morbidity and mortality.

5 Conclusions

In conclusion, warfarin and DOAC use was associated with increased rates of three common infections, all-cause antibiotic prescribing, antibiotic resistant infections, and *Clostridium difficile*. However, we found little evidence that rates of antibiotic resistant infections, and *Clostridium difficile* were mediated by greater overall antibiotic prescribing, suggesting that the causal mechanisms for this relationship may arise from the intrinsic characteristics of Warfarin and DOAC users themselves. However, warfarin and DOAC use appear to be adequate proxies for increased risk of common and resistant infections and may help to identify and target a primary care population where better infection prevention and antibiotic stewardship could improve outcomes.

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Data availability The data that support the findings of this study are available from the CPRD but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Declarations

Ethics approval and consent to participate This study was approved by the Independent Scientific Advisory Committee (ISAC) for CPRD (protocol number 20_175). The ISAC is a non-statutory expert advisory body providing scientific advice on research requests to access data provided by CPRD. The CPRD database contains coded and anonymised data from GP practices. No identifiable patient information is collected. Therefore, the need for individual consent to participate was waived by the Derby Research Ethics Committee (reference 21/EM/0265).

Consent for publication Not applicable.

Competing interests All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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