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ORIGINAL RESEARCH

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Impact of COVID-19 pandemic on the prescribing pattern of oral anticoagulants in the English primary care setting: a population-based segmented interrupted time series analysis of over 53 million individuals

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ABSTRACT

Background: The COVID-19 pandemic disrupted healthcare delivery, impacting oral anticoagulants (OAC) prescribing due to increased thromboembolic risks, Vaccine-induced immune thrombotic thrombocytopenia, and guidelines favoring Direct Oral Anticoagulants (DOACs) over warfarin. Previous studies were limited to short-term analyses.

Research design and methods: A segmented interrupted time series analysis was conducted using the English primary care Prescription Cost Analysis data from March/2018-March/2024 to assess the impact of the first and second COVID-19 lockdowns in March and November 2020, respectively. Trends in OAC utilisation were measured using number of items per 1,000 inhabitants (NIT) and defined daily dose per 1,000 inhabitants per day (DTD).

Results: Overall, oral anticoagulants prescribing increased significantly. Pre-pandemic, both NIT (β_1: 0.09; 95%CI: 0.02, 0.16) and DTD (β_1:0.13; 95%CI: 0.09, 0.16) showed positive trends. Post-first lockdown, DTD slope declined significantly (β_3:-0.22; 95%CI: −0.42, −0.03). Post-second lockdown, DTD rose in both immediate level (β_4:1.39; 95%CI: 0.34, 2.45) and slope (β_5: 0.20; 95%CI: 0.0015, 0.39). Warfarin usage declined initially but rebounded, while DOACs, particularly apixaban, increased substantially (β_4:0.96; 95%CI: 0.11, 1.81).

Conclusions: The COVID-19 pandemic significantly impacted oral anticoagulant prescribing patterns in England. While DOAC utilisation continued to rise, warfarin use declined significantly post-first lockdown but rebounded after the second lockdown.

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Anticoagulants; COVID-19; Warfarin; DOACs; prescribing patterns; primary care

1. Introduction

The COVID-19 pandemic and the associated lockdown measures had a profound and immediate impact on healthcare services worldwide including England, significantly disrupting routine medical practices and shifting priorities toward managing the pandemic and away from routine care [1–4]. This shift is illustrated by the notable reduction in planned/elective hospital admissions and outpatient visits in England, driven by fear of infection, suspension and cancellation of non-urgent services, and the reallocation of healthcare resources toward managing COVID-19 cases during lockdown [1–4]. The pandemic also had an appreciable impact on medication use including an increase in the prescribing of direct oral anticoagulants and the use of antibiotics across sectors [1–3,5–7].

Several factors may have contributed to or provided the basis for hypothesising that oral anticoagulant (OAC), encompassing both vitamin K antagonists and direct oral anticoagulants (DOACs), prescribing patterns were significantly impacted during the COVID-19 pandemic. One key factor was the elevated risk of thromboembolism in COVID-19 patients, particularly venous thromboembolism (VTE), likely influenced these prescribing patterns toward increased anticoagulant use [4,5,8–10]. Moreover, reports of rare thromboembolic events as side effects of the Oxford/AstraZeneca vaccine (Vaxzevria®) have necessitated using anticoagulants such as DOACs in specific clinical cases [11–13]. In response, the British Society for Hematology recommended using non-heparin-based therapies (including DOACs) to treat suspected or confirmed COVID-19 Vaccine-induced immune thrombotic thrombocytopenia (VITT) [14]. As the reported thromboembolic events were accompanied by thrombocytopenia, DOACs were also recommended for prophylaxis of thrombotic events when

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thrombocytopenia was present after receiving the COVID-19 vaccine [11–13]. In addition, NHS England guidance [4] issued in March 2020 likely influenced the shift from warfarin to DOACs.

Prior to the COVID-19 pandemic, DOACs were increasingly favored over warfarin due to their improved safety profile, comparable efficacy, predictable pharmacokinetics, reduced dietary restrictions, and diminished need for routine International Normalized Ratio (INR) monitoring [15–18]. This preference was reflected in a consistent year-on-year rise in DOAC dispensing prior to the pandemic [18,19]. During the initial phases of the pandemic, the recommendations from NHS England prompted a significant surge in DOAC prescribing [20]. Moreover, a further 19% increase in DOAC prescriptions between March 2020 and February 2021 alongside a 20% decline in warfarin prescriptions [20]. However, this period also witnessed an increase in potentially unsafe co-prescribing of warfarin and DOACs, prompting a national safety alert in April 2020, which emphasised the critical need for vigilant management of anticoagulant therapies [20]. Despite the initial surge, DOAC prescribing declined by approximately 15% between the first and second lockdowns (March 2020 to November 2020), with no significant recovery in prescribing rates observed before the second national lockdown [20].

Previous research on anticoagulant prescribing trends in the UK has largely focused on the immediate aftermath of the first COVID-19 lockdown [19–21], offering only a short-term perspective. This limited timeframe does not account for the sustained impact of the pandemic, including subsequent waves and policy changes that may have influenced prescribing practices. Long-term analyses are crucial for understanding persistent shifts in prescribing trends and their implications for healthcare system recovery. To date, no study has comprehensively examined anticoagulant prescribing over an extended period in relation to different pandemic phases. This study aimed to assess long-term prescribing patterns across England, identifying impact of the distinct pandemic stages. By evaluating significant changes in prescribing behavior, this research provides valuable evidence to inform future clinical practice and healthcare policy.

2. Method

2.1. Study design and data sources

This was a retrospective, repeated cross-sectional study design to analyse anticoagulant prescribing patterns in the primary care setting in England from March 2018 to March 2024 using Prescription Cost Analysis (PCA) data, an aggregated, publicly available dataset [22]. The PCA dataset contains comprehensive information about all medicines prescribed by General Practitioners (GPs) and dispensed in the community, providing detailed statistics on the cost and volume of prescriptions in England. This includes the total number of items dispensed, the dispensed quantity and strengths as well as associated costs, broken down by drug, therapeutic class, and prescribing entity. This dataset has been used widely to assess the impact of COVID-19 on other medication classes such as opioid and antibiotics [23,24], using similar methodology.

2.2. Study subjects and ethical approval

The study focuses on all oral anticoagulant prescriptions, stratified into two classes based on the British National Formulary (BNF) classification Chapter 2 (Cardiovascular System, particularly section 2.8.2 on oral anticoagulants) [25]. These were Vitamin K Antagonists (VKAs) such as warfarin and DOACs, including apixaban, dabigatran, edoxaban, and rivaroxaban. As the study used publicly available aggregated anonymous data, no ethical approval was required.

2.3. Study outcomes

The primary outcome of this study was the utilisation patterns of oral anticoagulants. Utilisation was measured using two key metrics: total Number of Dispensed Items per 1000 Inhabitants (NIT) and Defined Daily Dose (DDD) per 1000 Inhabitants per Day (DTD) [26,27]. DTD is an internationally recognized utilisation metric to standardise the comparison of drug use across different populations [28]. DDDs are defined by the WHO as the "assumed average maintenance dose of a drug per day for its main indication in adults" [29]. The calculation of DDD/1000 inhabitants/day involved summing the monthly total dispensed amount (mg) for each anticoagulant (by multiplying each quantity by its strength), dividing this sum by their WHO-assigned DDD value, and then dividing by the estimated mid-year population size (obtained from the UK Office for National Statistics) [30], multiplying by 1000, and dividing by the number of days in each month [24,27].

2.4. Data analysis

The impact of COVID-19 on anticoagulant utilisation was assessed over three distinct periods, which included the pre-COVID-19 period from March 2018 to February 2020, the Post-First Lockdown Period from April 2020 to October 2020 and the Post-Second Lockdown Period from November 2020 to March 2024 [21]. Changes in overall trends overtime were expressed as absolute and relative percentage changes and linear regression analysis was employed to assess the average monthly changes in utilisation.

Segmented interrupted time series analysis [31] was used to evaluate the impact of COVID-19 lockdowns, including the first and second national lockdowns in March and November 2020, respectively, on anticoagulant prescribing patterns. The analysis fit regression coefficients to the original scale of the monthly utilisation study outcome measures, and these coefficients were presented with their 95% confidence intervals. Specifically, the study included five regression coefficients: β_1, representing the baseline trend; β_2, indicating the level change immediately following the first lockdown in March 2020; β_3, the time trend after the first lockdown; β_4, the level change immediately following the second lockdown in November 2020; and β_5, the time trend after the second lockdown.

3. Results

3.1. Overall utilization trends of oral anticoagulants

Between March 2018 and March 2024, a total of 1,997.8 items of oral anticoagulants were dispensed per 1,000 inhabitants, with DOACs constituting 72.3% (1,445.2 NIT) of the total. Apixaban was the most dispensed DOAC, accounting for 51.3% (741.5/1,445.2) of total DOAC prescriptions. Overall, anticoagulant utilisation increased significantly over the study period. The total number of items dispensed (NIT) rose by 27.1% (absolute change = 6.47 NIT), increasing from 23.91 NIT in March 2018 to 30.38 NIT in March 2024, with an average monthly increase of 0.11 NIT (95% CI: 0.10–0.12) (Table 1; Figure 1). DOAC utilisation more than doubled, with a 113.6% increase (absolute change = 13.69 NIT), from 12.04 NIT in March 2018 to 25.73 NIT in March 2024, corresponding

Table 1. Absolute, relative, and average monthly changes in oral anticoagulant utilisation between March 2018 and March 2024 in the primary care setting in England.

Variable	Absolute Change	Relative Change (%)	Average Monthly Change (95% CI)
Number of items per 1000 inhabitants			
Total oral anticoagulant	6.47	27.06	0.11 (0.10, 0.12)
Total DOACs	13.69	113.64	0.20 (0.19, 0.21)
Warfarin	−7.21	−60.80	−0.09 (−0.10, −0.09)
Rivaroxaban	0.79	14.95	0.01 (0.01, 0.02)
Edoxaban	6.52	2089.35	0.09 (0.01, 0.02)
Apixaban	6.61	113.18	0.10 (0.09, 0.10)
Dabigatran	−0.24	−37.69	−0.0032 (−0.0036, −0.0029)
Defined daily dose per 1000 inhabitants per day			
Total anticoagulant	7.29	49.23	0.12 (0.11, 0.12)
Total DOACs	10.59	114.50	0.16 (0.15,0.17)
Warfarin	−3.30	−59.32	−0.04 (−0.05, −0.04)
Rivaroxaban	0.59	13.40	0.01 (0.01, 0.02)
Edoxaban	4.99	2179.04	0.07 (0.07, 0.08)
Apixaban	5.18	127.36	0.08 (0.07, 0.08)
Dabigatran	−0.17	−33.04	−0.0024 (−0.0027, −0.0022)

DOACs: Direct Oral Anticoagulants; Total DOACs includes rivaroxaban, edoxaban, apixaban and dabigatran.

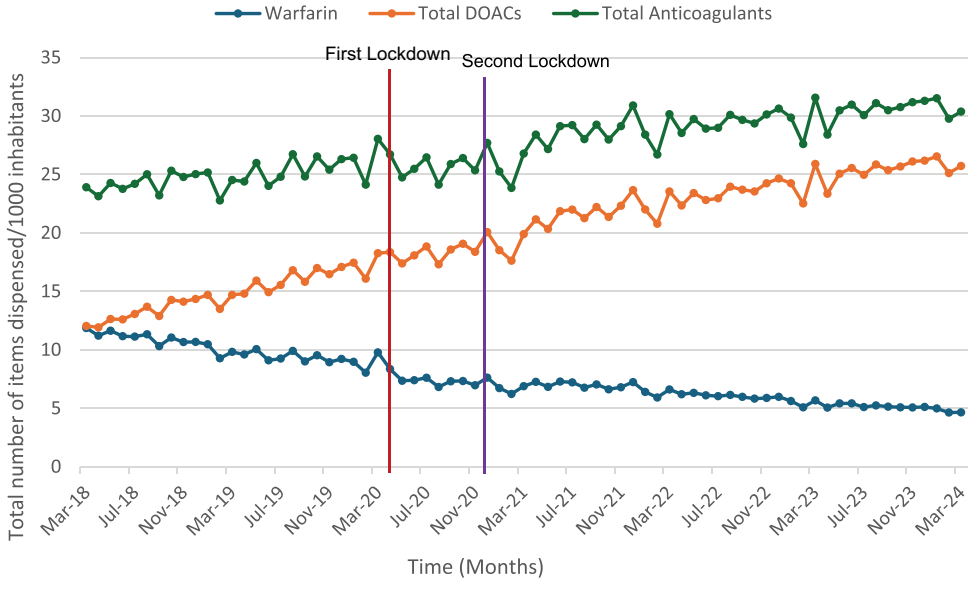

Figure 1. Total number of items dispensed/1000 inhabitants of oral anticoagulants dispensed in the primary care settings in England from March 2018 to March 2024.

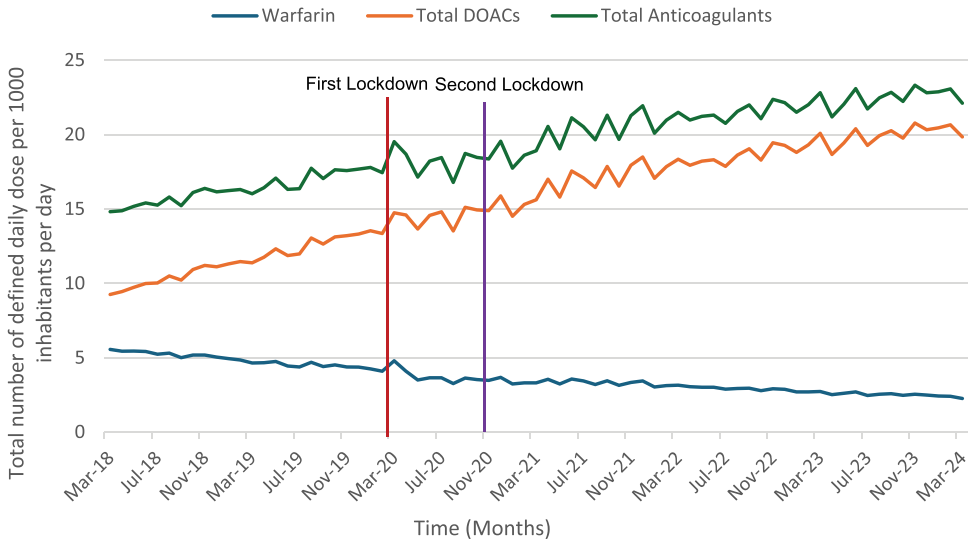

Figure 2. Total number of defined daily dose/1000 inhabitants/day of oral anticoagulants dispensed in the primary care settings in England from March 2018 to March 2024.

to a monthly rise of 0.20 NIT (95% CI: 0.19–0.21). In contrast, warfarin prescriptions decreased markedly by 60.8% (absolute change = −7.21 NIT), from 11.87 NIT in March 2018 to 4.65 NIT in March 2024, reflecting a monthly decline of −0.09 NIT (95% CI: −0.10–-0.09). Among individual DOACs, edoxaban exhibited the highest relative increase in NIT, rising by 2089.4% (absolute change = 6.52 NIT), with a monthly increase of 0.09 NIT (95% CI: 0.01–0.02), while apixaban remained the most frequently dispensed DOAC with a 113.2% increase (absolute change = 6.61 NIT) and an average monthly rise of 0.10 NIT (Table 1; Figure 3). The defined daily dose (DDD) trends mirrored the NIT results (Figure 2). Total anticoagulant DDD increased by 49.2% (absolute change = 7.29 DTD), with a monthly increase of 0.12 DTD. DOAC utilisation grew by 114.5% (absolute change = 10.59 DTD), with a monthly rise of 0.16 DTD (95% CI: 0.15–0.17). Edoxaban had the most pronounced relative increase in DDD (2179.0%, absolute change = 4.99 DTD), while apixaban remained the most utilised DOAC, increasing by 127.4% (absolute change = 5.18 DTD), with a monthly rise of 0.08 DTD (95% CI: 0.07–0.08) (Table 1; Figure 4).

3.2. Impact of COVID-19 on anticoagulant utilisation

Segmented regression analysis revealed significant changes in oral anticoagulant prescribing trends associated with the COVID-19 lockdowns (Table 2). Prior to the first lockdown, there was a positive baseline trend for total anticoagulants in both NIT (β_1: 0.09, 95% CI: 0.02–0.16) and DTD (β_1: 0.13, 95% CI: 0.09–0.16). However, the immediate impact of the first lockdown (β_2) on total anticoagulant prescribing was non-significant for both metrics. A significant decline in the DTD slope was observed post-first lockdown (β_3: −0.22, 95% CI: −0.42–-0.03), while NIT showed a non-significant downward

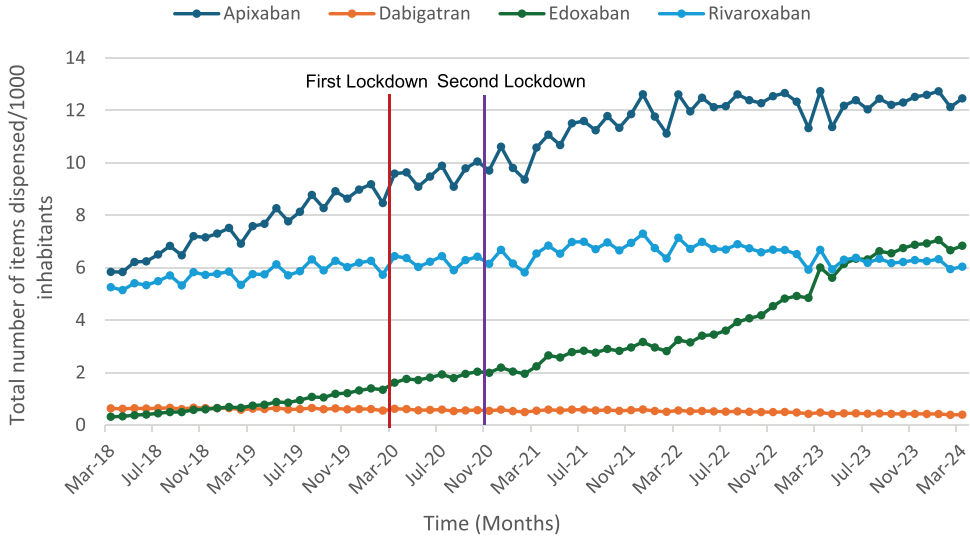

Figure 3. Total number of items dispensed/1000 inhabitants of individual direct oral anticoagulants dispensed in the primary care settings in England from March 2018 to March 2024.

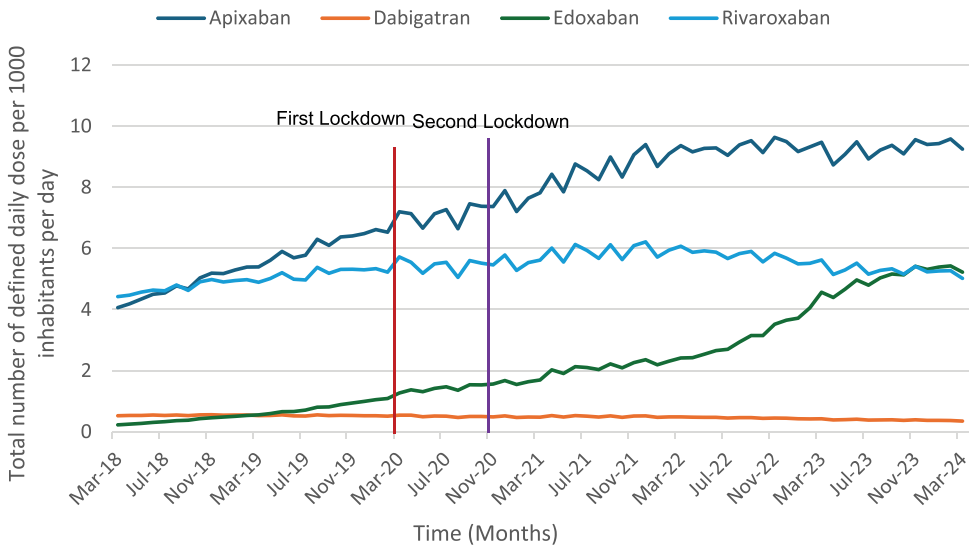

Figure 4. Total number of defined daily dose/1000 inhabitants/day of individual direct oral anticoagulants dispensed in the primary care settings in England from March 2018 to March 2024.

Table 2. Segmented regression analysis of the monthly utilisation of oral anticoagulants in the primary care setting in England between March 2018 and March 2024.

Variable	Baseline trend (β_1)	Level change immediately after first lockdown (β_2)	Time trend after first lockdown (β_3)	Level change immediately after second lockdown (β_4)	Time trend after second lockdown (β_5)
Number of items per 1000 inhabitants					
Total oral anticoagulant	**0.09 (0.02, 0.16)**	0.77 (−0.93, 2.48)	−0.29 (−0.63,0.06)	1.80 (−0.05,3.66)	0.31 (−0.03, 0.65)
Total DOACs	**0.22 (0.18, 0.27)**	0.45 (−0.75,1.65)	−0.14 (−0.38,0.11)	0.94 (−0.37, 2.25)	0.09 (−0.15, 0.33)
Warfarin	**−0.13 (−0.16,-0.11)**	0.32 (−0.25, 0.90)	**−0.15 (−0.27,-0.03)**	**0.86 (0.24, 1.49)**	**0.22 (0.10, 0.33)**
Rivaroxaban	**0.04 (0.02, 0.06)**	0.06 (−0.38,0.50)	−0.05 (−0.14,0.04)	**0.56 (0.08, 1.04)**	−0.0041 (−0.09, 0.08)
Edoxaban	**0.05 (0.03, 0.07)**	0.27 (−0.23,0.78)	0.0024 (−0.10, 0.10)	**−0.60 (−1.14, −0.05)**	0.09 (−0.01, 0.19)
Apixaban	**0.14 (0.11, 0.17)**	0.11 (−0.65,0.87)	−0.09 (−0.24,0.07)	**0.93 (0.10, 1.75)**	0.0010 (−0.1514, 0.1534)
Dabigatran	**−0.0019 (−0.0034, −0.0004)**	0.01 (−0.03,0.04)	−0.01 (−0.01,0.0018)	**0.05 (0.01,0.09)**	0.0035 (−0.0044, 0.0113)
Defined daily dose per 1000 inhabitants per day					
Total oral anticoagulant	**0.13 (0.09,0.16)**	0.63 (−0.34,1.61)	**−0.22 (−0.42,-0.03)**	**1.39 (0.34,2.45)**	**0.20 (0.0015,0.39)**
Total DOACs	**0.19 (0.16,0.22)**	0.47 (−0.32,1.25)	−0.14 (−0.30,0.02)	**0.96 (0.11,1.81)**	0.09 (−0.07,0.24)
Warfarin	**−0.06 (−0.07,-0.05)**	0.16 (−0.07,0.39)	**−0.08 (−0.13,-0.03)**	**0.44 (0.18,0.69)**	**0.11 (0.06,0.16)**
Rivaroxaban	**0.04 (0.03,0.05)**	0.08 (−0.25,0.42)	−0.06 (−0.12,0.01)	**0.57 (0.20,0.93)**	0.0019 (−0.07, 0.07)
Edoxaban	**0.04 (0.02,0.05)**	0.23 (−0.17,0.62)	−0.0025 (−0.08,0.08)	**−0.49 (−0.92,-0.06)**	0.08 (−0.0045,0.15)
Apixaban	**0.11 (0.09,0.13)**	0.15 (−0.37,0.67)	−0.08 (−0.18,0.03)	**0.83 (0.26,1.40)**	0.01 (−0.10,0.11)
Dabigatran	−0.0006 (−0.0018,0.0005)	0.0048 (−0.02,0.03)	**−0.0063 (−0.0122,-0.0004)**	**0.05 (0.02,0.08)**	0.003 (−0.0028,0.0089)

DOACs: Direct Oral Anticoagulants; Total DOACs includes rivaroxaban, edoxaban, apixaban and dabigatran.

trend (β3: −0.29, 95% CI: −0.63–0.06). Following the second lockdown, a significant immediate increase in DTD was observed (β_4: 1.39, 95% CI: 0.34–2.45) alongside a significant upward slope (β_5: 0.20, 95% CI: 0.002–0.39). The changes in NIT post-second lockdown remained non-significant. DOAC utilisation demonstrated a consistent upward baseline trend in both NIT (β_1: 0.22, 95% CI: 0.18–0.27) and DTD (β_1: 0.19, 95% CI: 0.16–0.22). Following the second lockdown, a significant increase in DOAC DTD was noted (β_4: 0.96, 95% CI: 0.11–1.81), though immediate changes after the first lockdown were non-significant. Among individual DOACs, apixaban exhibited significant increases in both NIT (β_4: 0.93, 95% CI: 0.10–1.75) and DTD (β_4: 0.83, 95% CI: 0.26–1.40) post-second lockdown. In

contrast, warfarin utilisation demonstrated a steady baseline decline in both NIT (β_1: −0.13, 95% CI: −0.16–-0.11) and DTD (β_1: −0.06, 95% CI: −0.07–-0.05). Post-first lockdown, warfarin use declined significantly in slope (β_3: −0.15, 95% CI: −0.27–-0.03 in NIT; β_3: −0.08, 95% CI: −0.13–-0.03 in DTD). However, an unexpected rebound in warfarin prescribing was observed post-second lockdown, with significant immediate increases in both NIT (β_4: 0.86, 95% CI: 0.24–1.49) and DTD (β_4: 0.44, 95% CI: 0.18–0.69).

4. Discussion

This study provides a comprehensive long-term analysis of OAC prescribing trends in England over 73 months, spanning pre-pandemic, pandemic, and post-pandemic periods. The findings highlight significant changes in OAC utilisation patterns, driven by healthcare disruptions during the COVID-19 pandemic, with important clinical and policy implications. The overall utilisation of oral anticoagulants demonstrated a clear upward trajectory, with a 27% increase in total prescriptions (NIT) and a 49% rise in defined daily dose (DTD). This trend likely suggests both an increase in the number of patients requiring anticoagulation therapy and potentially prolonged treatment durations or higher dosage intensity. The observed increase may reflect improved screening and diagnosis of atrial fibrillation (AF) and the elevated thromboembolic risks associated with COVID-19 infections [32,33].

The significant rise in DTD compared to NIT during lockdowns may also indicate the prescribing of larger quantities of anticoagulants to reduce the frequency of patient visits and minimise exposure risks during the pandemic. Furthermore, clinicians may have adopted a more cautious approach with intensified dosing to address the thrombotic complications linked to COVID-19 infections and VITT concerns [11–13,33]. Several factors may also have contributed to the observed changes in the different utilisation patterns for the different oral anticoagulants including changes in clinical practice, logistical challenges in warfarin monitoring, and heightened awareness of thrombotic risks. There was a notable increase in DOACs and a decline in warfarin use, with apixaban emerged as the most frequently prescribed DOAC, consistent with its favorable safety and efficacy profile compared to other anticoagulants, consistent with other studies [18–20]. The disruption in healthcare services during the lockdowns likely accelerated this shift, as clinicians faced challenges in maintaining face-to-face monitoring of warfarin therapy, which relies on regular International Normalized Ratio (INR) testing. The observed decline of 60.8% in warfarin prescriptions reflects these challenges and aligns with findings from other studies highlighting the pandemic's impact on warfarin management [3]. Interestingly, while National Institute for Health and Care Excellence (NICE) guidelines recommended transitioning eligible patients from warfarin to DOACs during the pandemic [4], our data did not clearly reflect this shift. This discrepancy may stem from the limitations of aggregated prescribing data, which cannot differentiate between newly initiated and prevalent patients. Prior research has shown that the impact of COVID-19 on medication prescribing patterns for other chronic conditions such as hypertension was primarily evident when focusing on newly initiated therapies [21]. Apixaban was the most utilised DOAC, possibly due to its favorable safety profile among other oral anticoagulants and NHS England's recommendations [4,15].

The segmented regression analysis provides further insights into prescribing behaviors during the pandemic. Following the first lockdown in March 2020, there was no significant immediate change in total anticoagulant prescriptions (NIT), suggesting that clinicians adapted quickly to maintain treatment continuity through remote consultations and medication stocking. However, the significant decline in DTD slope post-first lockdown indicates disruptions in treatment initiation, adherence, and monitoring, consistent with broader reports of reduced patient engagement with primary care [34,35]. This trend highlights the challenges of maintaining optimal anticoagulant management during periods of restricted healthcare access. In contrast, the period following the second lockdown in November 2020 revealed a significant rebound in anticoagulant utilisation, particularly in DTD. This suggests a more proactive approach to managing thromboembolic risks, likely driven by increased awareness of COVID-19-related complications such as venous thromboembolism (VTE) and AF. Reports of elevated thrombotic risks in patients with COVID-19 infection and VITT likely contributed to this observed intensification in treatment [12,13]. Additionally, concerns related to VITT emerged during this post-second lockdown period, following early reports of cases in March/April 2021, coinciding with the mass vaccination rollout. While VITT concerns may have influenced prescribing behavior, they should be considered alongside the aforementioned other factors rather than as the primary determinant of increased DOAC utilisation, especially our study was not designed to specifically assess the association between mass vaccination, subsequent concerns regarding VITT, and OAC prescribing patterns. In this context, findings from Bentounes et al. (2023) [36] on hemostasis testing trends in France provide valuable insights into how clinical concerns shaped clinical decision-making. Their study reported a decline in INR testing over time, aligning with our findings of increased DOAC prescribing, which may reflect both a preexisting shift away from warfarin and pandemic-driven challenges in routine INR monitoring. Additionally, they observed an overprescription of anti-PF4 antibody tests, D-dimer, and complete blood counts due to concerns surrounding VITT, driven in part by misinformation and disinformation. While our study focuses on prescribing trends rather than diagnostic testing, these findings suggest a broader pattern of clinical response to emerging thrombotic risks and vaccine-related concerns. The increased focus on thrombosis detection and prevention may have contributed to the observed rise in DOAC prescribing, particularly in the post-second lockdown period when VITT concerns were most prominent. The complex interplay of these influences underscores the need for further research to disentangle their relative contributions, particularly through patient-level data analysis that could directly assess the impact of vaccine-related concerns on anticoagulant prescribing. The decline in warfarin (NIT and DTD) post-first lockdown was consistent with other studies [19–21], likely due to healthcare

service disruptions. The increase in DTD for DOACs, without a corresponding rise in NIT, possibly suggests longer treatment durations or higher dosing intensity, reflecting adaptations to the pandemic's clinical challenges.

In contrast to previous studies that reported a significant increase in DOAC utilisation during the early phases of the pandemic [19–21], our study did not observe this trend immediately following the first lockdown. However, a notable increase in DOACs' defined daily dose (DDD) immediately after the second lockdown, without a corresponding rise in the number of prescriptions (NIT), might suggest a shift toward intensified therapy. This could reflect efforts to manage the increased thromboembolic risks associated with COVID-19, improved screening for AF, or clinical adaptations such as prescription consolidation to reduce patient visits during a period of ongoing disruption. Interestingly, warfarin utilisation exhibited an unexpected rebound following the second lockdown, with significant increases observed in both immediate levels (NIT) and trends for DTD. While this may initially appear counterintuitive given the ongoing preference for DOACs, it likely reflects the re-engagement of healthcare services as routine monitoring resumed. Clinicians were able to manage patients where warfarin remained clinically appropriate, such as those with mechanical heart valves or severe renal impairment, conditions where DOACs are contraindicated. This highlights the continued role of warfarin in specific clinical scenarios despite the broader shift toward DOACs as the standard of care. The significant increase in DOAC prescribing following the second lockdown, particularly for apixaban, warrants closer attention. Apixaban's dominance among DOACs is consistent with its favorable safety and efficacy profile, particularly in preventing stroke in patients with atrial fibrillation while minimising bleeding risks. The disproportionate rise in apixaban DDD, without a similar increase in prescription numbers, suggests longer treatment durations or higher dosing intensity. This likely represents a clinical response to the heightened thrombotic risks associated with COVID-19 infection and VITT. However, this trend also underscores the need for careful monitoring to ensure the benefits of intensified anticoagulant therapy are balanced against the potential for bleeding complications, particularly in vulnerable patients. Although some of the observed changes were statistically significant, the small magnitude of certain trends raises questions about their clinical relevance. Nonetheless, these findings highlight important adaptations in anticoagulant prescribing practices during the pandemic and reinforce the need for continued vigilance in balancing treatment efficacy with patient safety.

While our findings align with previous studies that reported increased DOAC prescribing during the pandemic [19,20], our long-term analysis did not demonstrate definitive evidence of warfarin switching to DOACs. This discrepancy may be attributed to differences in study design and data granularity. Unlike previous cohort studies that analysed patient-level data, our study used aggregated prescription data, which limits the ability to track individual patient transitions. Additionally, the longer study period allowed us to capture more sustained trends and post-pandemic recovery patterns that may not have been evident in earlier studies. These differences underscore the importance of long-term analyses to fully understand the impact of public health crises on prescribing behaviors.

The clinical implications of this study are significant. The findings reinforce the importance of DOACs as the preferred anticoagulant option for most patients, particularly during periods of healthcare disruption, when the reduced need for monitoring becomes a crucial advantage. At the same time, the challenges observed with warfarin management highlight the need for contingency strategies, such as home-based INR monitoring and enhanced telemedicine services, to ensure continuity of care during future public health crises. Furthermore, the observed increase in DTD underscores the importance of carefully balancing thrombotic and bleeding risks, particularly in the context of COVID-19-related complications, where intensification of anticoagulation therapy may be warranted.

It is worth noting that the observed increase in DOAC prescribing in England during the study period aligns with broader global trends favoring DOACs over warfarin, independent of the COVID-19 pandemic. Prior to the pandemic, studies had already documented a consistent shift toward DOACs due to their improved safety profile, predictable pharmacokinetics, reduced need for routine INR monitoring, and fewer dietary and drug interactions compared to warfarin. For instance, international research has highlighted similar trends, with a global rise in DOAC prescribing over warfarin across various healthcare settings [37]. Similarly, in Australia [38], anticoagulant prescribing data demonstrated an increasing preference for DOACs before the pandemic, suggesting that the shift observed in England was part of a broader international movement rather than an isolated trend. While our study focuses on the impact of COVID-19, it is important to recognise that this transition was already underway, and the pandemic has likely served as an accelerator to expedite this change rather than the primary driver for the changes in DOAC prescribing. The prescribing trends observed in this study are therefore consistent with global patterns, reinforcing the notion that the increased adoption of DOACs during COVID-19 must be interpreted in the context of a preexisting trajectory of rising utilisation.

4.1. Strengths and limitations

This study has several strengths, including the use of a comprehensive, population-based dataset from the PCA covering a 73-month period. The longitudinal nature of the analysis provides a robust framework for evaluating the sustained impact of the COVID-19 pandemic on prescribing patterns. The application of segmented interrupted time series analysis, a well-established statistical method frequently employed to assess the effects of significant events such as the COVID-19 pandemic, offers a detailed understanding of how prescribing behaviors evolved across distinct phases of the pandemic [24,31]. This method is widely recognised in health services research for its ability to evaluate interventions and external disruptions, making it particularly suitable for this investigation. Another notable strength lies in the use of two complementary utilisation metrics: the number of

items dispensed per 1,000 inhabitants (NIT) and the DDD per 1,000 inhabitants per day. Together, these measures provide a more nuanced understanding of anticoagulant prescribing patterns, accounting for both the volume of prescriptions and the intensity of treatment. The DDD metric, standardised per 1,000 inhabitants, enables reliable comparisons of usage trends over time and across populations, independent of population size. This dual approach is particularly valuable for identifying prescribing variations and informing future guidelines and healthcare policies. Despite these strengths, the study has some limitations. The use of aggregated data from the PCA dataset precluded the analysis of patient-level characteristics, such as clinical indications, demographics, and comorbidities, which are critical for understanding the factors influencing prescribing decisions. Additionally, the absence of a control group unaffected by the pandemic in the interrupted time series analysis limits the ability to isolate the direct impact of COVID-19 from other contemporaneous influences on prescribing trends. These limitations highlight the need for future studies utilising patient-level data to provide a deeper understanding of the drivers and clinical implications of these prescribing changes. Another limitation of this study is the use of monthly data points, which, while providing greater granularity, may introduce variability that could be perceived as statistical noise. However, this approach aligns with prescribing practices and habit in England, where most prescriptions are issued on a 28-day basis, allowing for a more precise capture of prescribing trends and minimising potential distortions caused by data aggregation. Additionally, the use of monthly data ensures a sufficient number of data points for a robust segmented interrupted time series analysis, as at least 12 observations before and after an intervention are recommended for meaningful statistical assessment [31]. In contrast, quarterly data would have significantly reduced the number of observations, limiting statistical power and the ability to detect meaningful changes in prescribing patterns. While quarterly data may offer a broader perspective on long-term trends, it would have potentially risked obscuring short-term prescribing fluctuations, particularly those driven by rapid policy shifts and healthcare disruptions during the COVID-19 pandemic. Therefore, the decision to use monthly data is methodologically justified and aligns with prior research [23,24], using PCA dataset, assessing the impact of COVID-19 on prescribing behaviors in England. Furthermore, we acknowledge the possibility that changes in reporting patterns, such as delays due to COVID-19, could contribute to the observed trends. However, this is unlikely in the English primary care setting, as prescription dispensing is predominantly electronic. Once a prescription is dispensed, an automated electronic message is transmitted to the central data warehouse, ensuring real-time data capture with minimal reporting delays. Given this system's robustness, the trends observed in our study are more likely to reflect actual changes in prescribing patterns rather than artifacts of reporting delays.

While this study provides a comprehensive analysis of prescribing trends and utilisation patterns of oral anticoagulants, it does not include a cost analysis. Understanding the financial implications of the observed changes, particularly the increased adoption of DOACs over warfarin, would be valuable for assessing the broader economic impact on healthcare expenditures. However, given the scope of this study and the nature of the available data, a detailed cost analysis was beyond our objectives. Additionally, interpreting cost analysis results in England would be challenging due to the fixed out-of-pocket fee for medicines, which does not reflect the actual cost of drugs to the NHS because the true cost of these medications remains confidential due to procurement and contracting agreements between the NHS and manufacturers. Furthermore, some other aspects of prescribing behavior also could not be assessed due to data limitations. Specifically, the PCA dataset does not include patient-level demographic information, such as age and sex, nor does it provide details on prescribed dosages. As a result, we were unable to determine whether specific demographic groups experienced shifts in anticoagulant prescribing patterns over time or whether there was an increase in the use of low-dose DOACs, potentially for prophylactic purposes, following COVID-19 and vaccination-related thrombotic concerns. Given the importance of these factors in anticoagulation management, future studies utilising patient-level datasets could provide further insights into whether prescribing adaptations occurred in response to evolving clinical guidance and thrombotic risk concerns. Such analyses would be particularly useful in determining whether age- or sex-related differences influenced prescribing patterns and whether DOAC dosing strategies were adjusted in response to increased awareness of COVID-19-associated thrombosis and VITT.

5. Conclusion

The COVID-19 pandemic significantly impacted oral anticoagulant prescribing patterns in England. While DOAC utilisation continued to rise, warfarin use declined significantly post-first lockdown but rebounded after the second lockdown. These findings reflect both clinical adaptations to the pandemic and the challenges associated with maintaining warfarin therapy during healthcare disruptions. The study highlights the importance of proactive strategies to ensure continuity of anticoagulant care during crises and underscores the need for further research using patient-level data to elucidate the underlying drivers of prescribing trends. The COVID-19 pandemic significantly impacted prescribing patterns, suggesting potential changes in dosage intensity, reflecting adaptations to healthcare service disruptions, as well as potential increase in the incidence of thromboembolic and AF event as a complication of COVID-19 infection. Further research using patient-level data is needed to better understand these trends and inform future healthcare policies.

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Declaration of interest

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Ethics statement

We confirm that our study adhered to the principles outlined in the Declaration of Helsinki. Ethical approval was not necessary as this investigation used aggregated level data which is publicly available and did not include any patient level information. Consequently, informed consent was not required. Furthermore, no identifiable information was used in the analyses.

Author contributions

All authors substantially contributed to the design, performance, analysis, reporting of the work and interpreting the relevant literature as well as had been involved in writing the manuscript and/or revised it for intellectual content. Further contributions include data collection, management and analysis: A Albutti; interpretation of results: all authors; and final approval: all authors.

Data availability statement

The data that support the findings of this study are publicly available.

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