

OpenSAFELY: impact of national guidance on switching from warfarin to direct oral anticoagulants (DOACs) in early phase of COVID-19 pandemic in England

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Background

Early in the COVID-19 pandemic the NHS recommended that appropriate patients anticoagulated with warfarin should be switched to direct acting oral anticoagulants (DOACs), requiring less frequent blood testing. Subsequently, a national safety alert was issued regarding patients being inappropriately co-prescribed two anticoagulants following a medication change, and associated monitoring.

Objective

To describe which people were switched from warfarin to DOACs; identify potentially unsafe co-prescribing of anticoagulants; and assess whether abnormal clotting results have become more frequent during the pandemic.

Methods

Working on behalf of NHS England we conducted a population cohort based study using routine clinical data from >17 million adults in England.

Results

20,000 of 164,000 warfarin patients (12.2%) switched to DOACs between March and May 2020, most commonly to edoxaban and apixaban. Factors associated with switching included: older age, recent renal function test, higher number of recent INR tests recorded, atrial fibrillation diagnosis and care home residency. There was a sharp rise in co-prescribing of warfarin and DOACs from typically 50-100 per month to 246 in April 2020, 0.06% of all people receiving a DOAC or warfarin. INR testing fell by 14% to 506.8 patients tested per 1000 warfarin patients each month. We observed a very small increase in elevated INRs (n=470) during April compared with January (n=420).

Conclusions

Increased switching of anticoagulants from warfarin to DOACs was observed at the outset of the COVID-19 pandemic in England following national guidance. There was a small but substantial number of people co-prescribed warfarin and DOACs during this period. Despite a national safety alert on the issue, a widespread rise in elevated INR test results was not found. Primary care has responded rapidly to changes in patient care during the COVID-19 pandemic.

Background

Following the onset of the COVID-19 pandemic and the implementation of “lockdown”, the NHS responded to deliver healthcare services in a manner that minimised risk of transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Most Patients taking the anticoagulant warfarin require frequent blood tests, the International Normalised Ratio (INR) test, potentially increasing their chance of exposure to SARS-CoV-2. NHS England issued guidance in late March 2020 [1] to support local NHS organisations to manage their anticoagulant services; this included identifying people suitable for switching from warfarin to direct oral anticoagulants (DOACs), which require less frequent blood testing. Subsequently, in October 2020, the Medicines and Healthcare products Regulatory Authority (MHRA) issued a safety alert, warning about an increase in the number of people with substantially elevated INR levels observed during the pandemic and also warned that of some people for whom warfarin was inadvertently continued after switching to DOACs [2].

Anticoagulants are prescribed to people at risk of, or for treatment of thromboembolism, which in some cases can result in stroke. Warfarin, a vitamin K antagonist, has been the mainstay of oral anticoagulant treatment for decades. Unlike most medicines, a patient’s specific dose of warfarin is adjusted based upon frequent blood tests which determine their INR, a measurement of blood clotting time. Factors such as changes in diet, alcohol intake, acute illness and concomitant medications can affect blood levels of warfarin and the INR, requiring a temporary increase in frequency of testing. The quality of the anticoagulation control is assessed by the proportion of time in therapeutic range (TTR). DOACs’ (rivaroxaban, dabigatran etexilate, apixaban, and edoxaban) mechanism of action does not alter the INR and therefore people taking DOACs only require less frequent drug safety monitoring (for example renal function), in line with many other commonly-prescribed medications. Nationally, the prescribing of DOACs has increased steadily since their recommendation by NICE for atrial fibrillation in 2012 [3], but they remain more expensive than warfarin.

In late May 2020 NHS England wrote to Clinical Commissioning Groups (CCGs), the local NHS bodies responsible for medicines use, advising that apixaban or rivaroxaban should be prescribed in place of warfarin for people able to change, [4] following a procurement exercise that secured additional stock at reduced prices. Subsequently, in October 2020, the Medicines and Healthcare products Regulatory Authority (MHRA) issued their safety alert about co-prescribing of warfarin and DOACs and elevated INRs [2]; however this document gave no indication of the scale of these problems.

Using a retrospective cohort study design, we set out to: evaluate the proportion and characteristics of prior warfarin users who switched to DOACs, and how many subsequently reverted; identify potentially unsafe co-prescribing of warfarin and DOACs; measure the frequency of INR testing during the pandemic for people taking warfarin, any changes to TTR, and the extent to which elevated INRs were observed. This was conducted as a “proof of concept” for the use of the new OpenSAFELY analytics platform to rapidly understand service impacts during the COVID-19 pandemic and inform support for primary care.

Methods

Study design

Prescribing and testing practice was analysed by conducting a retrospective cohort study using data from English NHS general practices.

Data sources

Primary care records managed by the GP software provider The Phoenix Partnership (TPP) were assessed using OpenSAFELY, a data analytics platform created by our team on behalf of NHS England to address urgent COVID-19 research questions (<https://opensafely.org>). OpenSAFELY provides a secure software interface allowing the analysis of pseudonymized primary care patient records from England in near real-time within the EHR vendor's highly secure data centre, avoiding the need for large volumes of potentially disclosive pseudonymized patient data to be transferred off-site. This, in addition to other technical and organisational controls, minimizes any risk of re-identification. Similarly pseudonymized datasets from other data providers are securely provided to the EHR vendor and linked to the primary care data. The dataset analysed within OpenSAFELY is based on 24 million people currently registered with GP surgeries using TPP SystemOne software (40% of England's population). It includes pseudonymized data such as coded diagnoses, medications and physiological parameters, but no free text data. Further details on our information governance can be found on page 17, under information governance and ethics.

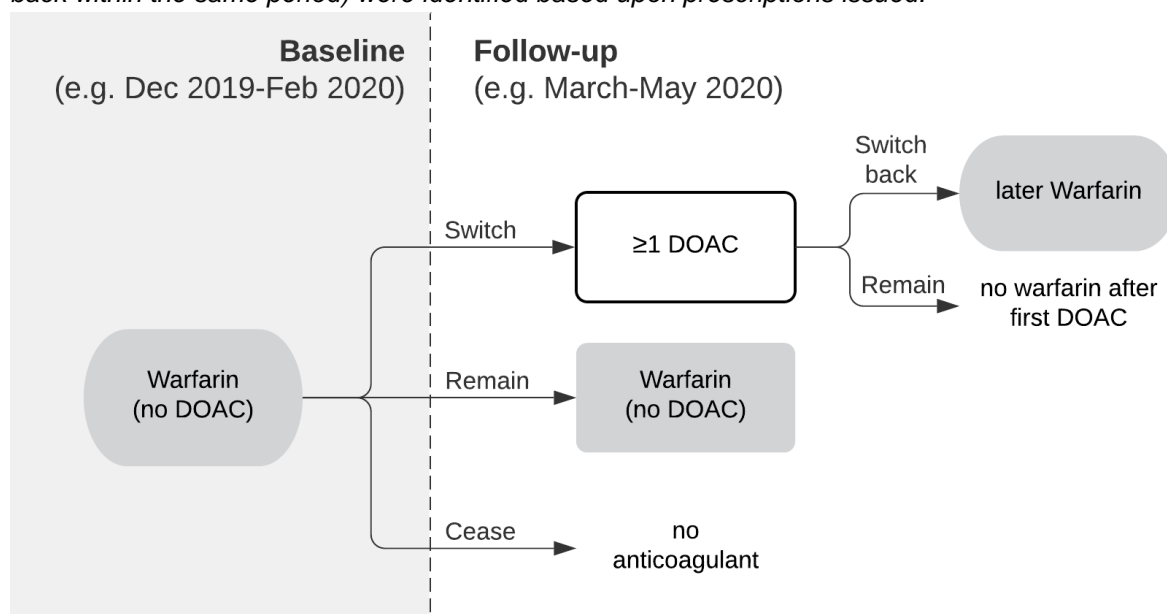
Data processing

We extracted data for all people who were issued with a prescription or had an active repeat prescription for warfarin or DOACs between January 2019 and August 2020, and the relevant dates of each prescription and INR test-related activity. We used warfarin, DOAC and INR codelists from OpenSAFELY [5,6] to identify these activities, with "high INRs" classified as INR results values >8 / ≥ 8 (as indicated) in line with thresholds relied upon by the MHRA [7] . We identified recorded INR time in therapeutic range (TTR) using the following CTV3 codes 'YavzQ', '42QE2' (redundant), 'Xaa68'.

People switching from warfarin to DOACs following NHS England guidance

We identified people issued a prescription for warfarin (but no DOACs) between December 2019-February 2020, and assessed how many received at least one DOAC ("switched") in March-May 2020, or only received warfarin (Figure 1). Of those switching, we counted how many later received warfarin again during this period ("switched back"). Of those remaining on warfarin we counted how many received an INR test, a high INR value, or had a TTR recorded. This analysis was repeated for the subsequent 3-month period (warfarin March-May 2020, switching June-August 2020), and for the corresponding periods in the previous year. Descriptive tables were generated to describe the cohort.

Figure 1. Flow chart illustrating how patients switching from warfarin to DOACs (and those switching back within the same period) were identified based upon prescriptions issued.



We also assessed the overall rate of people starting new DOAC repeat prescriptions each month from January 2019-August 2020 (with “new” defined as people having no DOAC repeat prescription ending within the previous three months). We assessed how many of whom had switched from warfarin, defined as people having a warfarin repeat prescription with an end date in the previous three months. Figures were plotted on a time trend chart.

Potentially unsafe co-prescribing of warfarin and a DOAC

For each month, January 2019-August 2020, patients were identified who: a) were issued a prescription for DOAC and warfarin on the same day, or b) had a repeat medication initiated for both DOAC and warfarin on the same day. We identified whether these people had at least one of these prescriptions ended the same day. Figures were plotted on a time trend chart.

INR blood tests during the COVID-19 period

Each month, INR tests and TTR values were identified for people on warfarin (defined as people with warfarin issued within the previous 3 months, and no DOAC issued after the latest warfarin). We plotted the rate per 1000 warfarin patients (and for TTRs, also the rate per 1000 INR tests and the rate per 1000 people tested) on time trend charts.

Factors associated with switching from warfarin to a DOAC during the pandemic

We investigated the factors associated with switching from warfarin to DOAC using mixed effects logistic regression. We included the variables in Table 1 as factors in the model. We also planned to include the patient’s practice but this was later removed to allow the model to converge. The population was: people aged 18-110 at the start of the follow-up period; registered with a single practice for the six months prior to the follow-up period (to ensure completeness of covariate data); prescribed warfarin at least once in the baseline period; first prescribed warfarin at least 6 months ago (to exclude very recent initiations); not prescribed a DOAC during the baseline period; and prescribed at least one DOAC or warfarin during the follow-up period (to exclude people who ceased treatment or died before

receiving any prescription in this period). The outcome was the prescription of at least one DOAC during the follow-up period. Baseline period: 3 months prior to the national “stay at home” order (16 December 2019-15 March 2020); follow-up period: the following 3 months (16 March 2020-15 June 2020).

Table 1: Variables used to assess factors associated with switching (present on the first day of the follow-up period unless otherwise stated).

Factor	Detailed information on coding	Codelist (where applicable)
Age Group	<65, 65-74, 75+	
Ethnicity	6 categories. Ethnicity will be missing for ~30% of people so will not be included in the primary model.	https://codelists.opensafely.org/code-list/opensafely/ethnicity/2020-04-27/
Indices of deprivation (IMD)	Deciles based on residential postcode	Supplied by TPP
Sustainability and transformation partnership (STP) membership	STP of current registered practice - modelled as a random effect	STP are NHS administrative regions made up of one or more CCGs Linkage to national STPs carried out by TPP
Care / nursing home residence status	Yes/no	Classification supplied by TPP based on patient’s residential address at 1 Feb 2020 linked to CQC care home register.
Diagnosis of atrial fibrillation	Yes/no; any time prior to follow-up period	https://codelists.opensafely.org/code-list/opensafely/atrial-fibrillation/2020-07-09/
Renal Function	Latest eGFR function (<30, 30-59, ≥60) in the 12 months to the end of the baseline period (or “no evidence” for those with no creatinine recorded in this period).	eGFR calculated from creatinine records. Creatinine clearance is recommended renal function assessment for tailoring DOAC doses for individual people. Automated calculation of CrCl is not yet available in OpenSAFELY and eGFR is used as pragmatic alternative.
Recent Renal Function Test	Yes/no; within last 4 months and up to the end of the study period (this conservatively allows tests slightly outside of the recommended 3 month period, and any time during the switching period).	Creatinine test, or: <ul style="list-style-type: none"> • “451..” Renal function test • “XacUK” eGFR using creatinine (CKD-EPI) per 1.73 square metres
Number of INR tests	0, 1-3, 4-6, or 7+ tests during the baseline period	https://codelists.opensafely.org/code-list/opensafely/international-normalised-ratio-inr/2020-10-22
Length of time on warfarin*	Categorised as: <ul style="list-style-type: none"> • ≤ 2 years (since 16 March 2018) • ≤ 6 years (since June 2014, date of latest NICE AF guidance [8]) • ≤ 8 years (since March 2012, date of first NICE Technology Appraisal for a DOAC for AF [9]) 	https://codelists.opensafely.org/code-list/opensafely/warfarin/2020-10-05/

	• > 8 years	
Previously prescribed DOACs*	Yes/no; any time prior to the baseline period	https://codelists.opensafely.org/code-list/opensafely/direct-acting-oral-anticoagulants-doac/2020-10-05/
Explicitly Recorded contraindication to DOAC	Yes/no; any time prior to the follow-up period	https://codelists.opensafely.org/code-list/opensafely/explicit-contraindication-to-doacs-direct-acting-anticoagulants/2020-10-19/

*The earliest actual date of an event may be missing due to incomplete patient records (e.g. lost in transfer between practices), but the earliest recorded date can be used as an approximation.

Software and reproducibility

Data management was performed using Python 3.8 and SQL, and regression analysis using Stata 16.1. All code for the OpenSAFELY platform, and for data management and analyses for this study, are available for inspection and reuse under open licenses on GitHub (<https://github.com/opensafely/anticoagulant-switching-research>). All codelists are available for inspection and re-use from <https://codelists.opensafely.org/>.

Patient and Public Involvement

Patients were not formally involved in developing this specific study design that was developed rapidly in the context of a global health emergency. We have developed a publicly available website <https://opensafely.org/> through which we invite any patient or member of the public to contact us regarding this study or the broader OpenSAFELY project.

Results

Patients switching from warfarin to DOACs following NHS England advice

164,000 people were prescribed warfarin between December 2019-February 2020, of whom 12.2% (20,000) were prescribed a DOAC between March-May 2020 (Table 2). This is substantially higher than the previous year (3.5%), and the following three months (4.4%) (Table 2). Of those who switched to a DOAC, 5.8% (n=1,200) also received a subsequent prescription for warfarin (switched back), compared to 4.1% the previous year (Table 2). Of those remaining on warfarin, 80.1% had at least one INR test recorded during March to May compared to 83.7% the previous year, 38.6% had at least one recorded INR TTR (37.9% the previous year), and 0.5% had a high INR (≥ 8) result (0.4% the previous year; Table 2). During March-May 2020, edoxaban and apixaban were the most commonly selected DOACs (38.1% and 33.5% respectively; Table 3). During June-August 2020, apixaban had increased to 40.3%, with edoxaban dropping to 33.4% (Table 3).

Table 2: Warfarin patients switching to DOACs or remaining on warfarin. Number and percentage of warfarin patients who continued on warfarin, received a DOAC ("switched") or had no anticoagulants, during March-May 2020 compared to 2019, and similarly for June-August. Also showing the percentage of those switching to a DOAC who later received warfarin "switched back" (within the same three month period); and the percentage of those remaining on warfarin who had at least one INR test, INR TTR, or high INR (≥ 8) recorded. Patient counts are rounded to the nearest 100.

Period	Patient Count, thousands (percentage)			
	March-May		Jun-Aug	
	2020	2019	2020	2019
baseline warfarin patients*	164,000	195,000	143,200	185,900
switched	20,000 (12.2%)	6,900 (3.5%)	6,300 (4.4%)	5,900 (3.2%)
continued warfarin	136,100 (83.0%)	177,300 (90.9%)	128,200 (89.5%)	169,900 (91.4%)
no anticoagulants†	7,900 (4.8%)	10,800 (5.6%)	8,700 (6.1%)	10,100 (5.4%)
switched back (% of switchers)	1,200 (5.8%)	300 (4.1%)	300 (4.7%)	300 (4.4%)
at least one INR (% of continued)	109,100 (80.1%)	148,400 (83.7%)	101,100 (78.8%)	140,000 (82.4%)
at least one TTR (% of continued)	52,600 (38.6%)	67,200 (37.9%)	50,300 (39.2%)	66,500 (39.1%)
high INR (≥ 8) (% of continued)	700 (0.5%)	700 (0.4%)	400 (0.3%)	600 (0.3%)

*Baseline warfarin patients for each period were those issued warfarin at least once (but no DOACs) in the three months immediately prior to the period shown. †Those with no anticoagulants (referring to warfarin and DOACs only) in the follow-up period may have discontinued anticoagulant treatment, moved to a non-TPP practice, died, or simply had a long period without a new prescription from their GP (e.g. due to a hospital stay or longer than usual prescription duration).

Table 3: Types of DOAC selected. Number and percentage of warfarin patients switched to each of the four types of DOAC between March-May 2020 compared to 2019, and similarly for June-August, for people who were prescribed warfarin during the previous three month period. Patient counts are rounded to the nearest 10. Percentages may not add to exactly 100 due to rounding.

period	year	Apixaban		Edoxaban		Rivaroxaban		Dabigatran etexilate		Total
		patient count	%	patient count	%	patient count	%	patient count	%	
March-May	2020	6,700	33.5	7,620	38.1	5,550	27.8	120	0.6	19,990
	2019	3,510	51.1	1,040	15.2	2,190	31.9	120	1.8	6,860
June-Aug	2020	2,550	40.3	2,110	33.4	1,620	25.6	40	0.6	6,320
	2019	2,900	49.5	1,110	18.9	1,760	30	90	1.6	5,860

The initiation of repeat prescriptions for DOACs to new patients increased ~1.5-fold during March and April 2020, and subsequently dropped slightly below normal levels (Figure 2). Much of this increase was attributable to people switching from warfarin (40.3% in March 57.5% in April), compared to the normal rate of ~15% per month (Figure 2, Table 4).

Figure 2. Patients newly initiated on DOAC repeats. Number of people having a new DOAC repeat prescription initiated per month (where the patient had no prior DOAC repeat ending within the previous three months), indicating whether or not patients had previously had a repeat prescription for warfarin (ending same month or within previous three months).

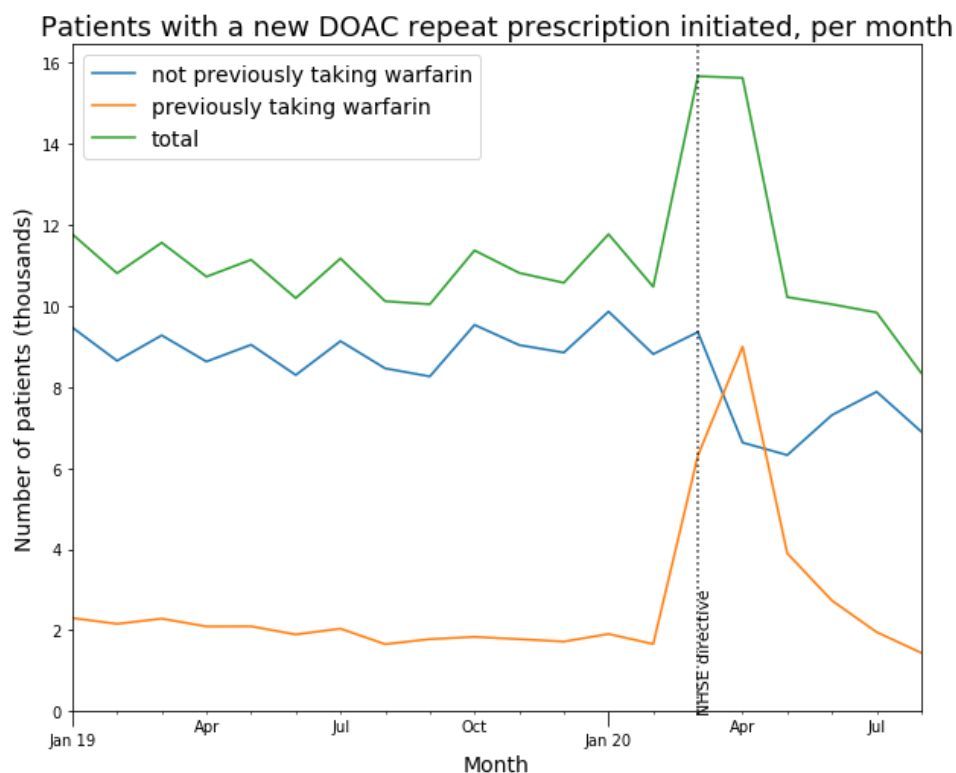


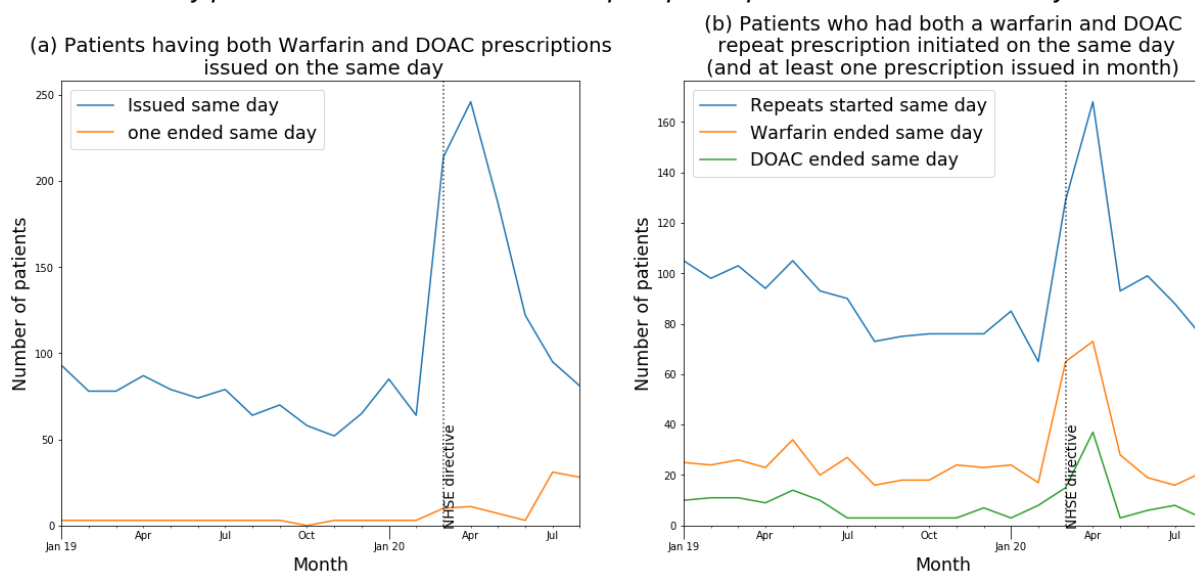
Table 4. Number of people having a DOAC repeat prescription initiated per month, and the percentage of whom had previously been issued with warfarin (within the previous three months). Patient counts are rounded to the nearest 100.

Month	Patients starting DOACs	Previously taking warfarin (%)
Jan 20	11,800	16.2
Feb 20	10,500	15.8
Mar 20	15,700	40.3
Apr 20	15,700	57.5
May 20	10,200	38.1
Jun 20	10,100	27.2
Jul 20	9,900	19.8
Aug 20	8,400	17.2
Sep 20	9,500	15.0

Potentially unsafe co-prescribing of warfarin and a DOAC

Prior to the pandemic period, typically 50-100 people per month had both warfarin and a DOAC issued on the same day, rising sharply to 246 in April 2020 (0.06% of all people receiving a DOAC or warfarin) before declining gradually to almost baseline by August 2020 (Figure 3a). Only a small proportion of these patients had at least one of their co-prescriptions ended on the same day. Prior to the pandemic, 60-110 patients per month had both warfarin and a DOAC repeat prescription initiated on the same day (Figure 3b). This figure reached a peak of ~170 in April, and declined rapidly to near-normal levels from May 2020. However, this rise was compensated by an increase in the number of repeat prescriptions that ended the same day (usually warfarin).

Figure 3. Number of patients having (a) both warfarin and a DOAC prescription issued on the same day, also indicating how many patients for whom one of those prescriptions ended the same day; (b) both warfarin and a DOAC repeat prescriptions initiated on the same day (restricted to patients who also had at least one warfarin or DOAC prescription issued in the given month), also indicating how many patients for whom one of those repeat prescriptions ended the same day.



INR blood tests during the COVID-19 period

Of 164,000 people on warfarin prior to March 2020, 80.1% had an INR test recorded and 35% had a TTR recorded between March and May 2020 (Table 2). The number of warfarin patients tested each month was approximately constant prior to the pandemic (589 per 1000 eligible patients per month, Jan 2019-March 2020) but with a small reduction during the pandemic (Figure 4). The monthly testing rate reduced by 14%, to 506.8 (April-Aug 2020), a reduction of 82.4 per 1000 patients being tested per month (14.0% reduction). The number of TTRs recorded followed a similar pattern (Figure 5a), and where TTR was recorded the mean value for those who were still on warfarin remained relatively constant (Figure 5b). Figure 6 illustrates the rate of high INRs per 1000 warfarin patients, per 1000 INR tests and per 1000 patients tested. A small peak is observed in April, but the absolute number of high INR results (≥ 8) was 470, only slightly higher than January's figure of 420 (Table S1).

Figure 4. Number of patients having an INR test per month, and the rate per thousand warfarin patients.

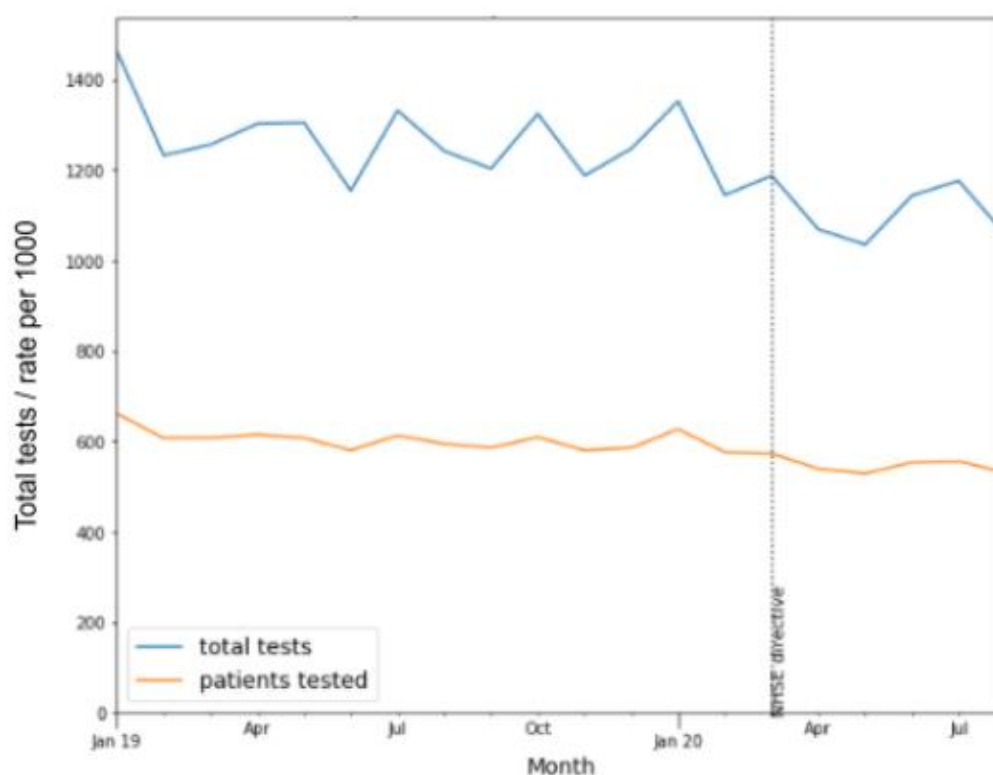
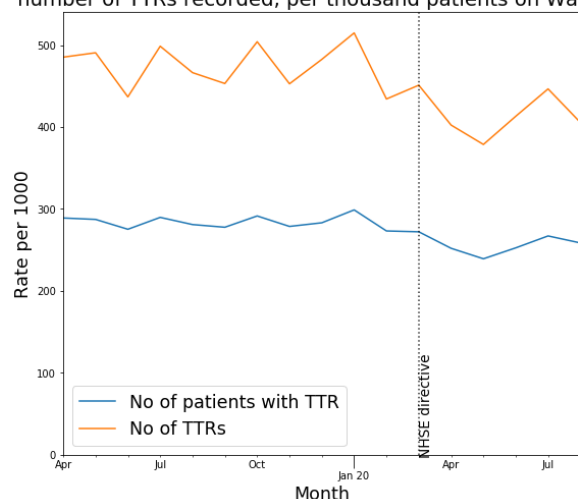


Figure 5: INR TTRs recorded in warfarin patients.

(a) Number of patients with a TTR recorded per month, and number of TTRs recorded, per thousand patients on Warfarin



(b) Mean INR TTR for warfarin patients

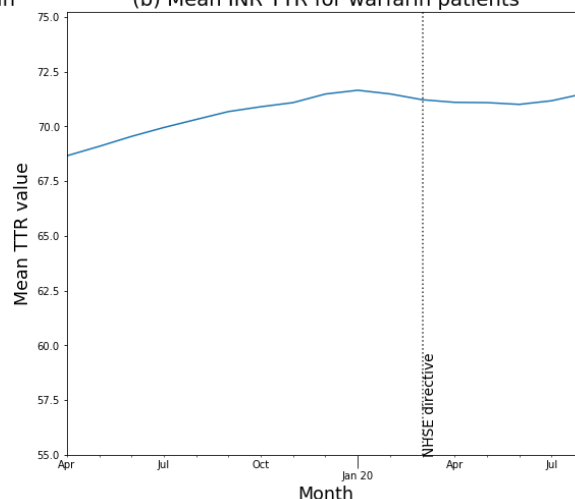
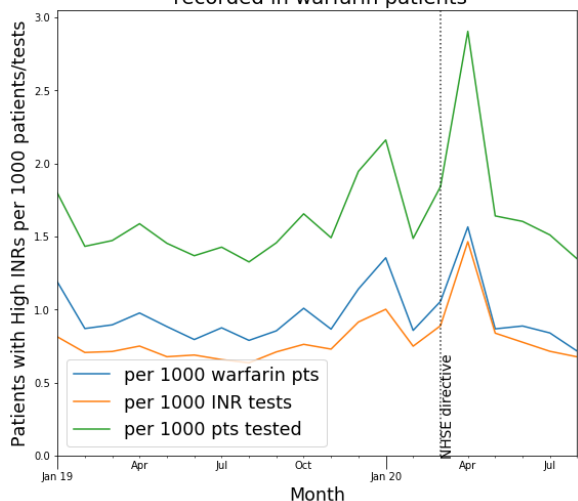
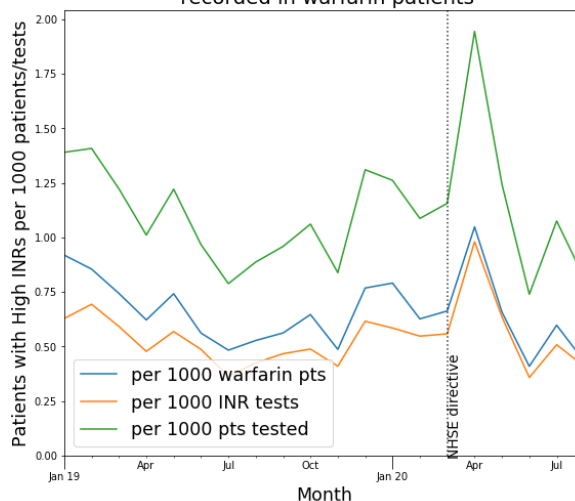


Figure 6: Monthly rate of elevated INRs (showing >8 or equal to 8 separately) recorded for warfarin patients relative to the total number of patients, INR tests, or patients tested.

Monthly rate of high INRs (over 8) recorded in warfarin patients



Monthly rate of high INRs (equal to 8) recorded in warfarin patients



Factors associated with switching from warfarin to a DOAC during the pandemic

The results of our logistic regression model are presented in Table 4. People who had a recent renal function test were much more likely to switch from warfarin to DOAC (OR 3.40, 95% CI 3.26-3.55), as were people with multiple recent INR tests (over seven vs none recorded, OR 2.04, 95% CI 1.92-2.15); older people (over 75 vs under 65, OR 1.93, 95% CI 1.82-2.05); people living in a care home (OR 1.33, 95% CI 1.12 - 1.52); and people with a diagnosis of atrial fibrillation (OR 1.93, 95% CI 1.85 - 2.01). People with a recorded contraindication for a DOAC were less likely to be switched (OR 0.36, 95% CI 0.25-0.51), as were people with reduced kidney function. We also found that STP membership, when modelled as a random effect, was a significant driver of variation ($p < 0.0001$).

Table 4: Factors associated with switching from warfarin to a DOAC during the pandemic

		Univariable logistic regression			Mixed effects logistic regression*		
		Odds ratio	95%CI		Odds ratio	95%CI	
Age	Under 65	Ref			Ref		
	65 to 74	2.04	1.93	2.17	1.52	1.43	1.62
	75 and over	2.87	2.72	3.03	1.93	1.82	2.05
Index of Multiple Deprivation	Least deprived	Ref			Ref		
		1.13	1.07	1.19	1.07	1.01	1.13
		1.20	1.14	1.26	1.07	1.01	1.12
		1.18	1.12	1.24	1.03	0.98	1.09
	Most deprived	1.20	1.14	1.26	1.03	0.97	1.08
Care home	No	Ref			Ref		
	Yes	1.47	1.29	1.68	1.32	1.15	1.52
Atrial fibrillation	No	Ref			Ref		
	Yes	2.47	2.38	2.57	1.93	1.85	2.01
eGFR	Not measured	Ref			Ref		
	>=60	1.36	1.31	1.41	0.72	0.69	0.75
	30-59	1.52	1.46	1.59	0.63	0.60	0.66
	<30	0.84	0.76	0.93	0.33	0.29	0.36
Recent renal function test	No	Ref			Ref		
	Yes	2.99	2.88	3.10	3.40	3.26	3.55
Number of recent INR tests	0	Ref			Ref		
	1-3	1.53	1.45	1.61	1.39	1.32	1.47
	4-6	1.99	1.88	2.10	1.78	1.69	1.88
	7+	2.03	1.92	2.15	1.87	1.77	1.99
Length of warfarin prescription	<= 2 years	Ref			Ref		
	2-6 years	1.68	1.53	1.85	1.25	1.14	1.38
	6-8 years	1.88	1.71	2.06	1.31	1.19	1.45
	>8 years	1.57	1.44	1.72	1.14	1.04	1.25
Previous DOAC prescription	No	Ref			Ref		
	Yes	0.65	0.60	0.70	0.65	0.60	0.70
DOAC contraindication	No	Ref			Ref		
	Yes	0.40	0.28	0.57	0.36	0.25	0.51

*Adjusted for the variables in the table STP membership as a random effect

Discussion

Summary

We observed a very substantial increase in people switching from warfarin to a DOAC after NHS England advice to do so during the COVID-19 pandemic. We were able to identify in the data that a small but substantial number of people (n=246, 0.06%) were simultaneously issued with warfarin and a DOAC in April 2020, and were potentially at risk of serious adverse effects. Overall the rate of INR testing for those on warfarin dropped by 14%, although we observed no substantial change in the proportion tests that reported a clotting time outside the desired range. Factors associated with switching from warfarin to DOACs included older age, higher number of recent INR tests, diagnosis of atrial fibrillation, recent record of a renal function test, and care home residency.

Strengths and weaknesses

The key strength of this study is the scale, timeliness and completeness of the underlying data. The OpenSAFELY platform runs analyses across the full, raw, single-event-level medical records of all patients at 40% of all GP practices in England, including all tests, treatments, diagnostic events, and other salient clinical and demographic information. We also recognise some limitations. We assessed the number of prescriptions issued, or initiated on repeat prescriptions. We cannot currently access information on which medications were dispensed. An individual appearing to receive warfarin and a DOAC may therefore not receive, or take, both medications: for example a doctor might notice the co-prescribing some time after the consultation, and cancel the prescription before it leaves the practice; or a pharmacist may decline to dispense both medications at once to the same patient for safety reasons. Finally, a patient may be informed not to take the medicine by their healthcare professional even if they received a dispensed medicine. Nonetheless these subsequent remedial interventions do not diminish the finding that co-prescribing of warfarin and DOACs occurs, and that incidence increased substantially during COVID-19 to over two hundred people in one month. Another limitation relates to missing INR data: people in England often have their warfarin managed by an “anticoagulation clinic” in a community service, hospital outpatient department or indeed a neighbouring general practice with specialist expertise; these clinics typically use bespoke software to record all relevant results related to INR, which may not be transferred in structured data into GP records; but would commonly be visible through some other means to a clinicians delivering direct care for a patient; this could explain the apparent absence of INR tests for some people but not negatively impact clinical care.

Findings in Context

A recent systematic review of healthcare utilisation during the pandemic found that utilisation reduced by approximately one third during the pandemic [10] but we are not aware of any published studies assessing switching of anticoagulant therapy during the pandemic or implementation of NHS England anticoagulation guidance. We found that edoxaban and apixaban were favoured DOACs when switching from warfarin, not wholly in line with NHS England advice from May 2020,[4] which recommends only apixaban and rivaroxaban. In October, NICE published draft guidance on Atrial Fibrillation recommending apixaban and dabigatran; however, we found dabigatran was prescribed in a very small proportion of switches [11]. In England, general practitioners have autonomy in the selection of treatments they prescribe, but are obliged to consider a wide number of factors which may influence choice of DOACs[12]. Our previous research has shown NHS England guidance advising

GPs to stop prescribing certain medicines did not cause an immediate noticeable change in prescribing patterns [13] and CCG membership has a strong association with GP prescribing choices [14–17]. Our study shows evidence of switching after the guidance and although we were not able to directly assess CCG membership, our study did find that STPs, an administrative region made up of one or more CCGs, were a significant driver of variation. The MHRA safety alert on anticoagulation identified a “small number of patients” co-prescribed warfarin and a DOAC, but provided no further information on the scale of the problem. One Swiss hospital found 0.8% of its patients on anticoagulant therapy (121/15812) were co-prescribed two anticoagulants in a single year, 2017/2018 [18]. However, 88.7% of these cases involved co-prescription of DOACs and injectable low-weight molecular heparins, not included in our study. As regards INR blood tests, the MHRA reports appears to have been triggered by a root cause analysis from a single centre in London,[19] reporting that between 1st March and 17th April 2020, 0.9% (30/3214) of INRs were high (>8.0) compared to 0.1% (6/4079) the previous year. Analysing the full records of 40% of patients in England we found only a small peak in high INRs, and with no obvious change in the mean TTR recorded for those still on warfarin.

Policy Implications for research and practice

The COVID-19 pandemic has brought new challenges for the NHS to deliver safe and effective routine care. NHS England issued anticoagulant guidance at the peak of the pandemic and a substantial number of people were switched in line with this guidance. This study using OpenSAFELY demonstrates it is possible to use routinely collected raw EHR data on a specific clinical area to support evaluation of national guidance and safety alerts during the COVID-19 pandemic. There is a need for high quality applied practical research to support healthcare organisations' responses to the pandemic; OpenSAFELY can be used by NHS England, the MHRA and others such as NICE to rapidly assess in near-real time the impact of policy and clinical guidance as well as informing future versions of guidance. Specific areas of focus for anticoagulants during COVID-19 could include: identifying people eligible for switching who haven't switched yet; assessing the scale of clinical work needed; evaluating completeness of uptake; prioritising risk groups; understanding causes of co-prescription of warfarin and DOACs; evaluating variation in organisations response to new guidance [16]; and better understanding the factors identified by MHRA as being associated with elevated INRs such as co-prescribing of antibiotics [2].

OpenSAFELY is now using full patient records to measure and mitigate the indirect health impacts of Covid-19. Our aim is to give early warning on clinical work displaced, such as cancer referrals, cardiovascular management, and vaccinations; and to monitor clinical impact on patients. We have titled this work the *OpenSAFELY NHS Service Restoration Observatory*. We can help identify NHS organisations in need of additional support as the pandemic evolves; and rapidly identify success stories from new best practices that others can learn from. Working in collaboration with NHS England and other stakeholders, short data reports will be available soon on www.OpenSAFELY.org assessing individual clinical areas and making recommendations such as research questions for examination by the research community, findings that require further analysis and actionable insights to inform care at a national, local and practice level.

Summary

We observed increased switching of anticoagulants from warfarin to DOACs at the outset of the COVID-19 pandemic in England. We did not find a widespread rise in elevated INR test results which may be reassuring after a recent MHRA safety alert although we did observe a small but substantial number of people who were co-prescribed warfarin and DOACs.

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Conflicts of Interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare the following: BG has received research funding from the Laura and John Arnold Foundation, the NHS National Institute for Health Research (NIHR), the NIHR School of Primary Care Research, the NIHR Oxford Biomedical Research Centre, the Mohn-Westlake Foundation, NIHR Applied Research Collaboration Oxford and Thames Valley, the Wellcome Trust, the Good Thinking Foundation, Health Data Research UK (HDRUK), the Health Foundation, and the World Health Organisation; he also receives personal income from speaking and writing for lay audiences on the misuse of science. IJD has received unrestricted research grants and holds shares in GlaxoSmithKline (GSK).

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The views expressed are those of the authors and not necessarily those of the NIHR, NHS England, Public Health England or the Department of Health and Social Care.

Information governance and ethical approval

NHS England is the data controller; *TPP are the data processors* and the key researchers on OpenSAFELY are acting on behalf of NHS England. This implementation of OpenSAFELY is hosted within the TPP environment which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant;[20,21] patient data has been pseudonymised for

analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymised datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is via a virtual private network (VPN) connection, restricted to a small group of researchers; the researchers hold contracts with NHS England and only access the platform to initiate database queries and statistical models; all database activity is logged; only aggregate statistical outputs leave the platform environment following best practice for anonymisation of results such as statistical disclosure control for low cell counts.[22] The OpenSAFELY research platform adheres to the data protection principles of the UK Data Protection Act 2018 and the EU General Data Protection Regulation (GDPR) 2016. In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 (COPI) to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure; this sets aside the requirement for patient consent.[23] Taken together, these provide the legal bases to link patient datasets on the OpenSAFELY platform. GP practices, from which the primary care data are obtained, are required to share relevant health information to support the public health response to the pandemic, and have been informed of the OpenSAFELY analytics platform.

This study was approved by the Health Research Authority (REC reference 20/LO/0651) and by the LSHTM Ethics Board (reference 21863).

Guarantor

BG is guarantor.

References

- 1 NHS England. Clinical guide for the management of anticoagulant services during the coronavirus pandemic. 2020. https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/C0077-Specialty-guide_Anticoagulant-services-and-coronavirus-v1-31-March.pdf (accessed 20 Jul 2020).
- 2 Warfarin and other anticoagulants – monitoring of patients during the COVID-19 pandemic. <https://www.gov.uk/government/publications/warfarin-and-other-anticoagulants-monitoring-of-patients-during-the-covid-19-pandemic/warfarin-and-other-anticoagulants-monitoring-of-patients-during-the-covid-19-pandemic> (accessed 16 Oct 2020).
- 3 The DataLab. Direct Oral Anticoagulants (DOACs) Measure. OpenPrescribing. <https://openprescribing.net/measure/doacs/national/england/> (accessed 30 Sep 2020).
- 4 NHS England. Supply of additional direct oral anticoagulants (DOACs) during COVID-19. 2020. https://www.worcslmc.co.uk/cache/downloads/C0517-DOAC-briefing-for-CCGs_27-May.pdf
- 5 Curtis HJ, MacKenna B, Croker R. OpenSAFELY Codelists: Direct Acting Oral Anticoagulants (DOAC). 2020. <https://codelists.opensafely.org/codelist/opensafely/direct-acting-oral-anticoagulants-doac/2020-10-05/> (accessed 28 Oct 2020).
- 6 Curtis HJ, MacKenna B, Croker R. OpenSAFELY Codelists: Warfarin. 2020. <https://codelists.opensafely.org/codelist/opensafely/warfarin/2020-10-05/> (accessed 28 Oct 2020).
- 7 OpenSAFELY Codelists: International normalised ratio (INR). <https://codelists.opensafely.org/codelist/opensafely/international-normalised-ratio-inr/2020-10-22/> (accessed 3 Nov 2020).
- 8 NICE. Overview | Atrial fibrillation: management | Guidance. <https://www.nice.org.uk/guidance/cg180> (accessed 30 Sep 2020).
- 9 NICE. NICE Key Therapeutic Topic: Anticoagulants, including direct-acting oral anticoagulants (DOACs). 2016. <https://www.nice.org.uk/advice/ktt16/resources/anticoagulants-including-directacting-oral-anticoagulants-doacs-pdf-58757956094149#:~:text=Following%20appropriate%20assessment%2C%20NICE%20recommends,taking%20bleeding%20risk%20into%20account.> (accessed 30 Sep 2020).
- 10 Moynihan R, Sanders S, Michaleff ZA, *et al.* Pandemic impacts on healthcare utilisation: a systematic review. *medRxiv* Published Online First: 2020. <https://www.medrxiv.org/content/10.1101/2020.10.26.20219352v1.abstract>
- 11 Consultation | Atrial fibrillation: management | Guidance. NICE. <https://www.nice.org.uk/guidance/indevelopment/gid-ng10100/consultation/html-content-2> (accessed 28 Oct 2020).
- 12 NHS England. Standard General Medical Services Contract. <https://www.england.nhs.uk/gp/investment/gp-contract/>
- 13 Walker AJ, Bacon S, Curtis H, *et al.* Six months on: NHS England needs to focus on dissemination, implementation and audit of its low-priority initiative. *J R Soc Med*

2018;;141076818808429. doi:10.1177/0141076818808429

- 14 Walker AJ, Curtis HJ, Bacon S, *et al.* Trends, geographical variation and factors associated with prescribing of gluten-free foods in English primary care: a cross-sectional study. *BMJ Open* 2018;**8**:e021312. doi:10.1136/bmjopen-2017-021312
- 15 Croker R, Walker AJ, Goldacre B. Why did some practices not implement new antibiotic prescribing guidelines on urinary tract infection? A cohort study and survey in NHS England primary care. *J Antimicrob Chemother* Published Online First: 22 December 2018. doi:10.1093/jac/dky509
- 16 Walker AJ, Pretis F, Powell-Smith A, *et al.* Variation in responsiveness to warranted behaviour change among NHS clinicians: novel implementation of change detection methods in longitudinal prescribing data. *BMJ* 2019;**367**:l5205. doi:10.1136/bmj.l5205
- 17 MacKenna B, Curtis HJ, Walker AJ, *et al.* Trends and variation in unsafe prescribing of methotrexate: a cohort study in English NHS primary care. *British Journal of General Practice* 2020 doi: [10.3399/bjgp20X710993](https://doi.org/10.3399/bjgp20X710993)
- 18 Rahmzade R, Cabrera Diaz F, Zaugg C, *et al.* Therapeutic duplication of anticoagulants: a retrospective study of frequency and consequences in a tertiary referral hospital. *Thromb J* 2020;**18**:14. doi:10.1186/s12959-020-00227-w
- 19 Speed V, Patel RK, Byrne R, *et al.* A perfect storm: Root cause analysis of supra-therapeutic anticoagulation with vitamin K antagonists during the COVID-19 pandemic. *Thromb Res* 2020;**192**:73–4. doi:10.1016/j.thromres.2020.05.024
- 20 BETA – Data Security Standards - NHS Digital. NHS Digital. <https://digital.nhs.uk/about-nhs-digital/our-work/nhs-digital-data-and-technology-standards/framework/beta---data-security-standards> (accessed 30 Apr 2020).
- 21 Data Security and Protection Toolkit - NHS Digital. NHS Digital. <https://digital.nhs.uk/data-and-information/looking-after-information/data-security-and-information-governance/data-security-and-protection-toolkit> (accessed 30 Apr 2020).
- 22 ISB1523: Anonymisation Standard for Publishing Health and Social Care Data - NHS Digital. NHS Digital. <https://digital.nhs.uk/data-and-information/information-standards/information-standards-and-data-collections-including-extractions/publications-and-notifications/standards-and-collections/isb1523-anonymisation-standard-for-publishing-health-and-social-care-data> (accessed 30 Apr 2020).
- 23 Secretary of State for Health and Social Care - UK Government. Coronavirus (COVID-19): notification to organisations to share information. 2020. <https://web.archive.org/web/20200421171727/https://www.gov.uk/government/publications/coronavirus-covid-19-notification-of-data-controllers-to-share-information>

Supplementary

Table S1 High INRs. Patient count and test count for high INR results per month of 2020, rounded to the nearest 10.

		8 exactly	over 8	Total (≥8)
Patient count	Jan 2020	160	260	420
	Feb 2020	120	160	280
	Mar 2020	120	200	320
	Apr 2020	190	280	470
	May 2020	110	150	260
	Jun 2020	70	140	210
	Jul 2020	90	130	220
	Aug 2020	60	110	170
	Sep 2020	80	140	220
Test count	Jan 2020	200	310	510
	Feb 2020	160	190	350
	Mar 2020	160	240	400
	Apr 2020	250	340	590
	May 2020	130	180	310
	Jun 2020	90	180	270
	Jul 2020	110	160	270
	Aug 2020	80	120	200
	Sep 2020	100	170	270

Table S2 Co-prescribing. Patients issued warfarin and DOAC scripts on the same day. Values below 5 are shown as “1-5”.

Month	Warfarin and DOAC issued same day	One ended same day
Jan 2019	93	1-5
Feb 2019	78	1-5
Mar 2019	78	1-5
Apr 2019	87	1-5
May 2019	79	1-5
Jun 2019	74	1-5
Jul 2019	79	1-5
Aug 2019	64	1-5
Sep 2019	70	1-5
Oct 2019	58	0
Nov 2019	52	1-5
Dec 2019	65	1-5
Jan 2020	85	1-5
Feb 2020	64	1-5
Mar 2020	214	10
Apr 2020	246	11
May 2020	187	7
Jun 2020	122	1-5
Jul 2020	95	31
Aug 2020	81	28

Table S3: Number of patients included in regression for factors associated with switching from warfarin to a DOAC during the pandemic, stratified by the outcome of whether the patient was switched to a DOAC.

Factor		DOAC switched?	
		No	Yes
Age	Under 65	25,028	1,717
	65 to 74	32,872	4,531
	75 and over	69,839	13,469
Ethnicity	Unknown	36,892	5,697
	White	87,375	13,715
	Mixed	307	27
	South Asian	1,888	159
	Black	730	67
	Other	547	52
IMD	Least deprived	26,334	3,322
		25,611	3,830
		25,481	4,330
		25,332	4,110
	Most deprived	24,981	4,125
Care home	No	126,394	19,431
	Yes	1,345	286
Atrial fibrillation	No	44,456	3,587
	Yes	83,283	16,130
eGFR	Not measured	53,451	6,780
	>=60	43,965	7,497
	30-59	26,382	5,012
	<30	3,941	428
Recent renal function test	No	58,742	4,329
	Yes	68,997	15,388
Number of recent INR tests	0	23,164	2,244
	1-3	52,680	7,590
	4-6	30,079	5,732
	7+	21,816	4,151
Length of warfarin prescription	<= 2 years	5,996	569

	2-6 years	30,528	4,797
	6-8 years	24,194	4,289
	>8 years	67,021	10,062
Previous DOAC prescription	No	120,886	18,965
	Yes	6,853	752
DOAC contraindication	No	127,224	19,682
	Yes	515	35