Safety of direct-acting oral anticoagulant (DOAC) prescribing during the COVID-19 pandemic

September 2022

Introduction

During the COVID-19 pandemic many patients were switched from warfarin to a direct-acting oral anticoagulant (DOAC): Eliquis® (apixaban), Lixiana® (edoxaban), Pradaxa® (dabigatran), or Xarelto® (rivaroxaban), to reduce the frequency of monitoring and visits to GP practices and anticoagulant clinics. The NHS England and NHS Improvement (NHSEI) clinical guide for the management of anticoagulant services during the coronavirus pandemic, published in November 2020 and last updated in February 2021, contained a table with advice on DOAC dosing in non-valvular atrial fibrillation (NVAF) based on body weight, serum creatinine and creatinine clearance for each of the DOACs. A suggested process, undertaken remotely where possible, for safe switching from warfarin to a DOAC was outlined. This included checking the GP clinical system for urea and electrolytes (U&Es), recording weight, calculating creatinine clearance (CrCl) and prescribing the DOAC at an appropriate dose.[1]

Before a DOAC is initiated, renal function should be assessed by calculating the CrCl using the Cockcroft-Gault method.[2,3] Guidance on dosage adjustments in renal impairment and assessing renal function before treatment are available in the British National Formulary (BNF) and the Summary of Product Characteristics (SPCs). DOAC doses are either reduced or are not recommended in patients with impaired renal function, in line with the SPCs.[2, 4-7] The Medicines Healthcare products Regulatory Agency (MHRA) published a Drug Safety Update in 2019 advising that for DOAC dosing CrCl should be used to determine the correct dosage instead of using estimated Glomerular Filtration Rate (eGFR). CrCl should be calculated using the Cockroft-Gault formula.[3] The MHRA also warns that DOACs should be used with caution in older patients and those with low body weight or renal impairment.[8]

This research, conducted through the OpenSAFELY platform, sought to identify the number of patients and proportion of the population prescribed a DOAC from January 2018 to December 2021 and determine any change in prescribing behaviour broken down by age and sex. The data analysis was re-run in August 2022 to include data up to July 2022. We also sought to determine the proportion of patients prescribed a DOAC who had a recorded weight, eGFR, serum creatinine or CrCl. We also examined the proportion of patients on a DOAC with a diagnosis of NVAF and whether there was a CrCl recorded. For those patients on a DOAC with NVAF we determined the proportion of patients that may be at risk of harm whilst prescribed the incorrect dose of DOAC according to their renal function during the COVID-19 pandemic. https://www.opensafely.org/approved-projects/#project-21

Methods

Access to the OpenSAFELY-TPP COVID-19 datasets were granted for this research. Data for this report were obtained from the TPP system which covers approximately 40% of all primary care practices in England, with a total population of approximately 18.6 million in January 2018, rising to approximately 19.9 million in July 2022.

The data were used to answer the following questions:

1. The number of patients prescribed DOACs (Jan 18-July 22).
2. The change in prescribing behaviour related to DOACs (Jan 18-July 22) broken down by patient demographics (age and sex).
3. The number and proportion of patients on a DOAC who had a weight recorded (Aug 21-July 22).
4. The number and proportion of patients on a DOAC that had a recorded eGFR (Aug 21-July 22).
5. The number and proportion of patients on a DOAC that had a recorded serum creatinine (Aug 21-July 22).
6. The number and proportion of patients on a DOAC that had a recorded CrCl (Aug 21-July 22).
7. The proportion of patients with NVAF who were prescribed a DOAC in the last 12 months (Aug 21-July 22).
8. The proportion of patients with NVAF who were prescribed a DOAC and had a Cr Cl recorded in the last 12 months (Aug 21-July 22).
9. The number and proportion of patients with NVAF who were not prescribed the correct dose of DOAC for their CrCl (Aug 21 to July 22).

The full study definition codes, codelists, and results are available in attachment 1: DOACs all data analysis.

The codelist outlines the name and code terms used in the analysis to identify people who were on a DOAC. These will also be available through the OpenSAFELY platform once published.

For each of the analyses, the number of people on a DOAC extracted from the data, were those people with a SNOMED CT code entitled ‘DOACs’ in the codelist sheet and the additional criteria applied as outlined under each figure.

The date of first lockdown has been marked on all the charts, to show the impact on prescribing.

Results

Figure 1. The number of people prescribed a DOAC; Jan 18-July 22: is a registered patient; has not died; aged between 18 and 120 (question 1)

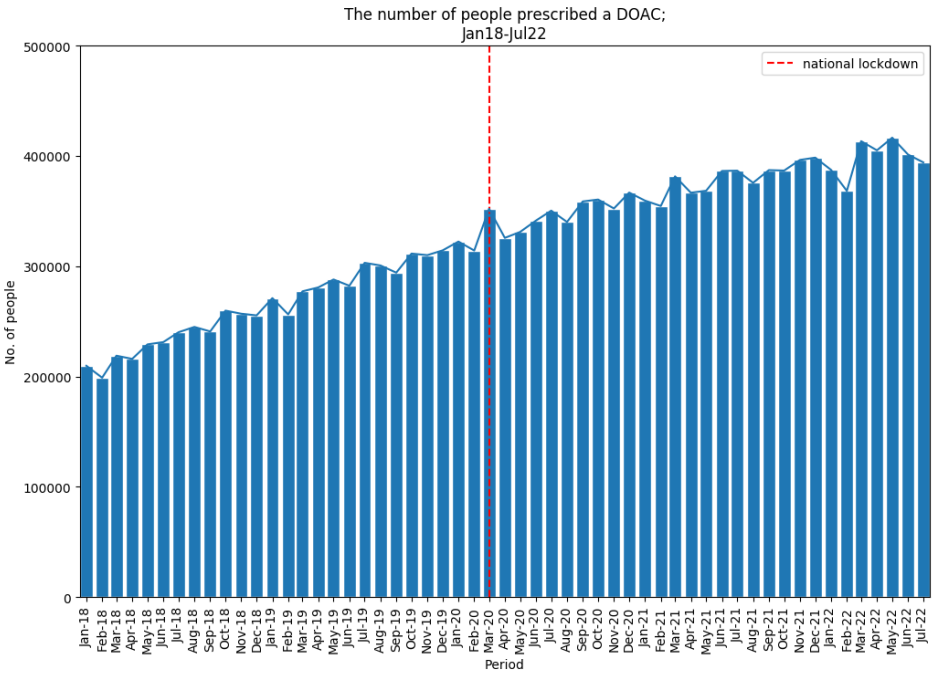

Figure 1 shows that an additional 184,407 people were prescribed a DOAC in July 2022 compared to January 2018, an increase of 87%. A small increase in prescribing can be seen in the first month of lockdown.

Figure 2. Percentage of people prescribed a DOAC out of total population; Jan 18-July 22: (question 1)

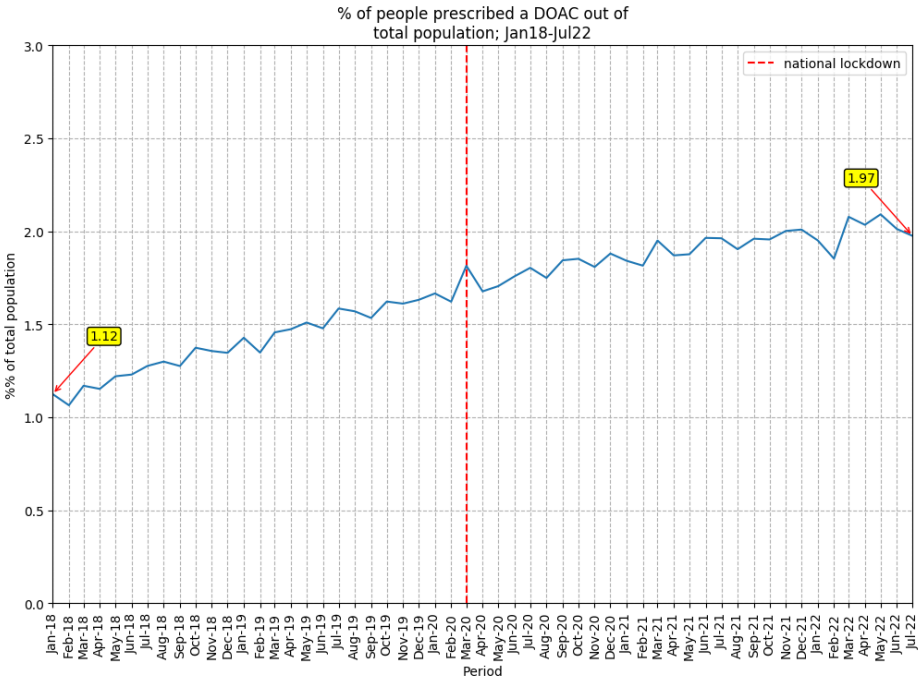

Figure 2 illustrates that the percentage of the population (number of patients) receiving a DOAC increased from 1.12% to 1.97% from January 2018 to July 2022, an increase of 76%. The small increase in prescribing during the first month of lockdown is reflected here too. To verify this we looked at prescribing data (England only) which shows that between January 2021 and July 2022, DOAC prescribing went from 1.39% to 1.57% of the total English population (NHSBSA, pseudo anonymised patient level prescribed and dispensed data set January to July 2022). This is in line with the findings in this study which used a smaller population size.

Figure 3. Number of people prescribed a DOAC by age band; Jan 18-July 22: (question 2, grouped by age into age bands, excluding patients with a missing age)

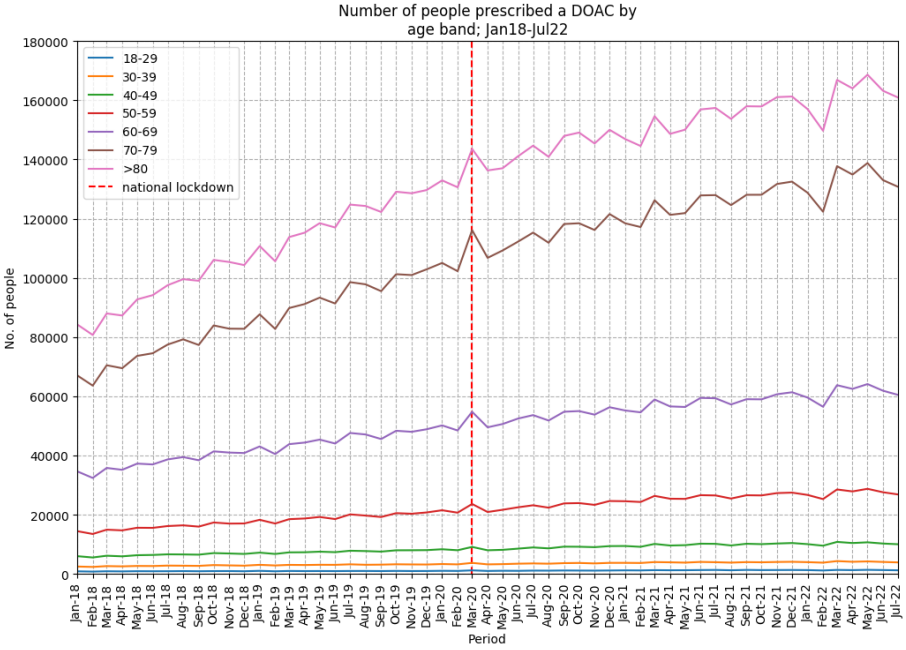

Figure 3 shows the number of people aged over 80 years, 70 to 79 years, 60 to 69 years, 50 to 59 years, and 40 to 49 years, prescribed a DOAC, increased by 91%, 94%, 75%, 86% and 67% respectively from January 2018 to July 2022. The largest increase in absolute number of people prescribed a DOAC was in the over 80 years age group (76,670) followed by the 70 to 79 years age group (62,263) and then 60 to 69 years age group (25,838).

Figure 4. Number of people per 100,000 population prescribed a DOAC by age band; Jan 18-July 22: (question 2, grouped by age into age bands, excluding patients with a missing age)

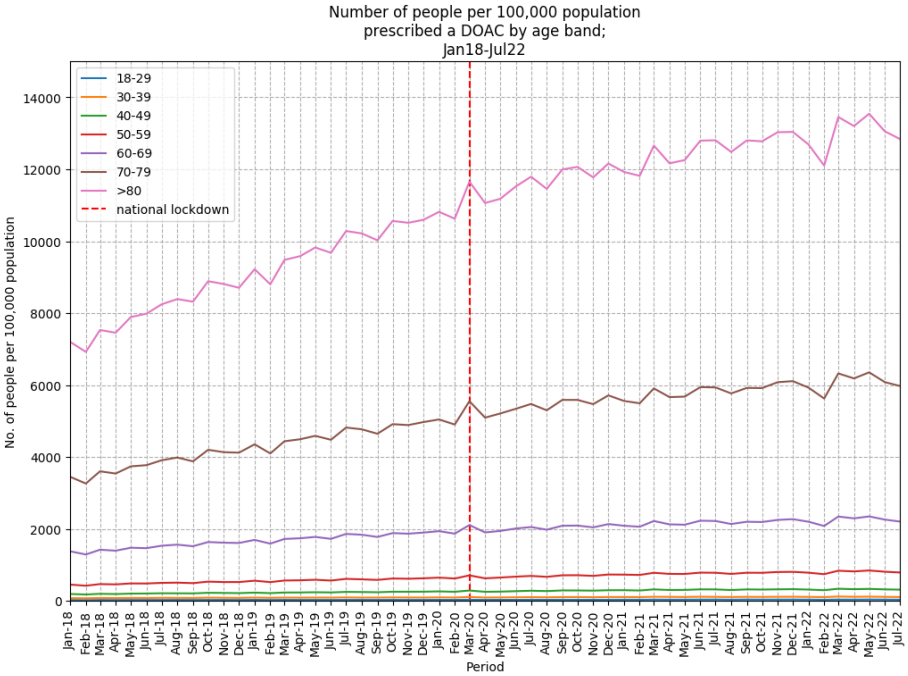

Figure 4 shows the number of people per 100,000 population (of the age band) prescribed a DOAC in the over 80 years, 70 to 79 years, 60 to 69 years, 50 to 59 years, and 40 to 49 years age bands was 12,841; 5,975; 2,206; 790; and 313 respectively in July 2022, increases of 78%, 73%, 60%, 74% and 63% respectively since January 2018.

Figure 5. Number of people prescribed a DOAC by gender; Jan 18-July 22: (question 2, grouped by gender, excluding patients where gender not recorded)

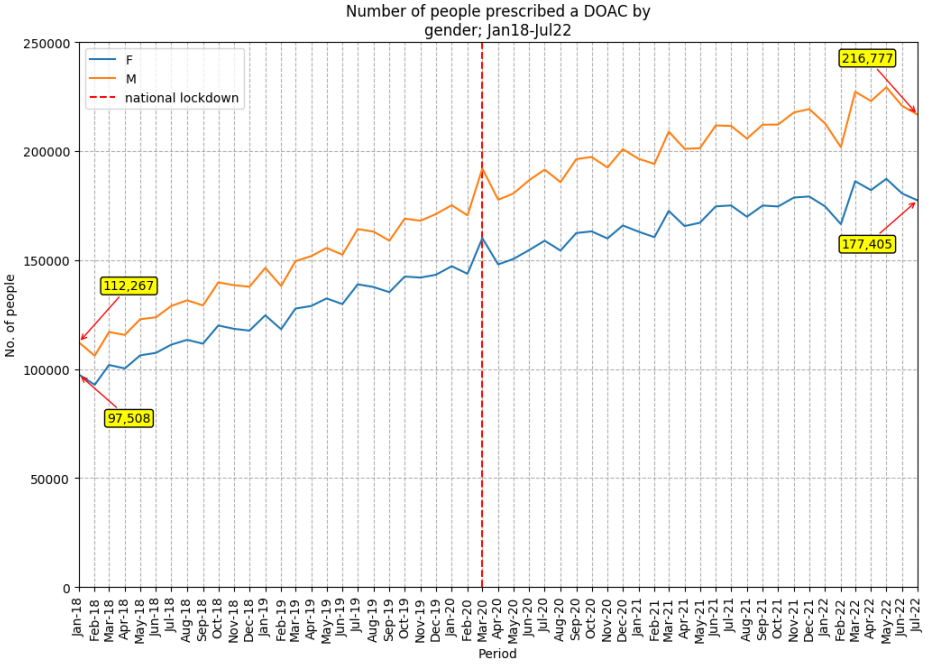

Figure 5 shows that consistently from January 2018 to July 2022 there were more males prescribed a DOAC than females. In July 2022, 54% of people prescribed a DOAC were males compared to 51% in January 2018.

Figure 6. Number of people per 100,000 population prescribed a DOAC by gender; Jan 18-July 22: (question 2, grouped by gender, excluding patients where gender not recorded)

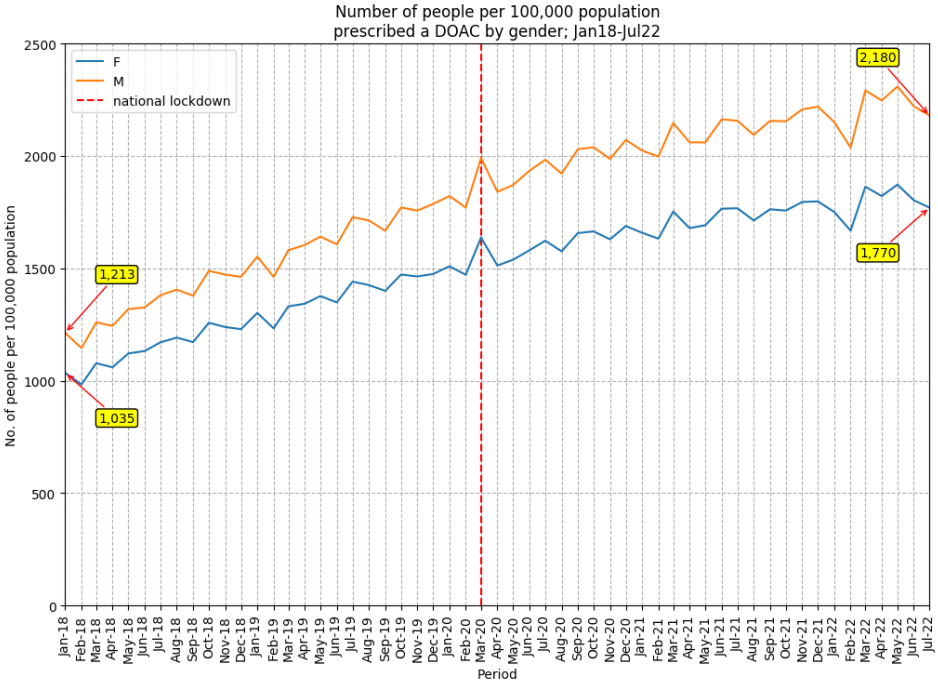

Figure 6 illustrates that more males than females per 100,000 population were prescribed a DOAC from January 2018 to July 2022.

Figure 7. Percentage of people prescribed a DOAC with a weight recorded in the last 12 months; Aug 21-July 22: (question 3 - those patients with clinical events recorded by using SNOMED CT codes "27113001", "162763007")

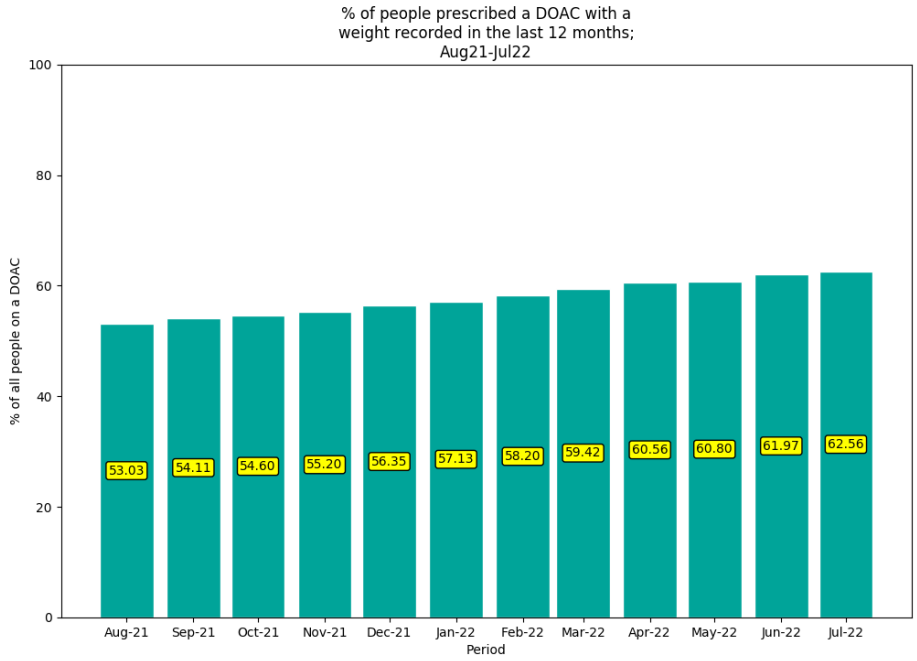

Figure 7 illustrates that the percentage of people on a DOAC with a weight recorded increased from 53.03% to 62.56% from August 2021 to July 2022. However, 37.44% of patients prescribed a DOAC did not have a weight recorded in the last 12 months as of July 2022.

Figure 8. Percentage of people prescribed a DOAC with a eGFR recorded in the last 12 months; Aug 21-July 22: (question 4 - those patients with clinical events recorded by using SNOMED CT codes 'eGFR' on codelist sheet)

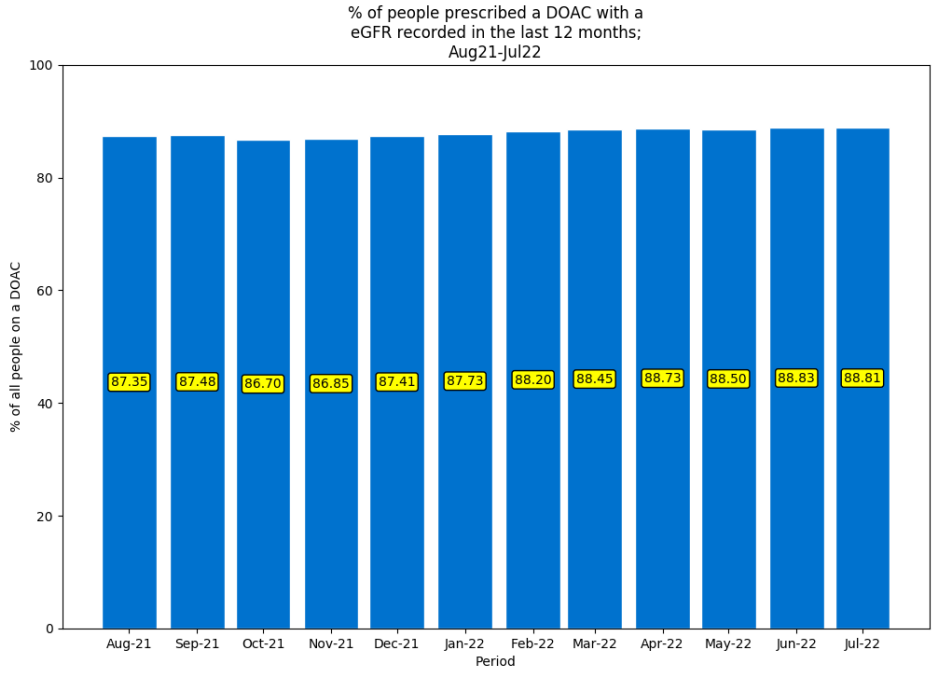

Figure 8 shows that the percentage of people prescribed a DOAC with an eGFR recorded in the last 12 months increased from 87.35% to 88.31% from August 2021 to July 2022. However, 11.19% of patients on a DOAC did not have an eGFR recorded in the last 12 months as of July 2022.

Figure 9. Percentage of people prescribed a DOAC with a serum creatinine level recorded in the last 12 months; Aug 21-July 22: (question 5 - those patients with clinical events recorded by using SNOMED CT codes 'serum creatinine' on codelist sheet)

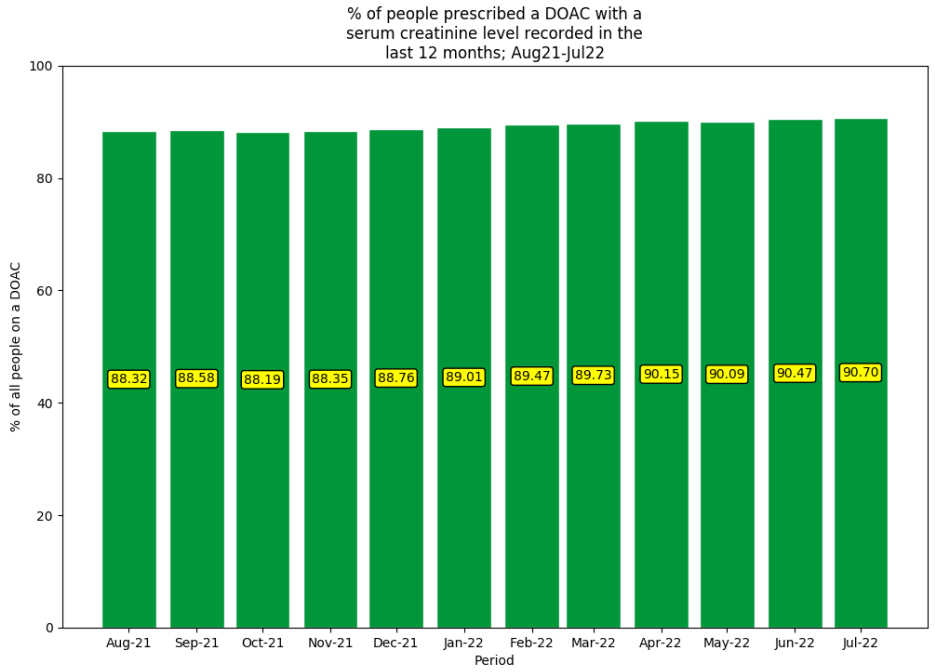

Figure 9 illustrates the percentage of people prescribed a DOAC with a serum creatinine recorded in the last 12 months, increased from 88.32% to 90.70% from August 2021 to July 2022. 9.3% of patients on a DOAC did not have a serum creatinine recorded in the last 12 months as of July 2022.

Figure 10. Percentage of people prescribed a DOAC with a CrCl recorded in the last 12 months; Aug 21-July 22: (question 6 - those patients with clinical events recorded by using SNOMED CT codes 'CrCl' on codelist sheet)

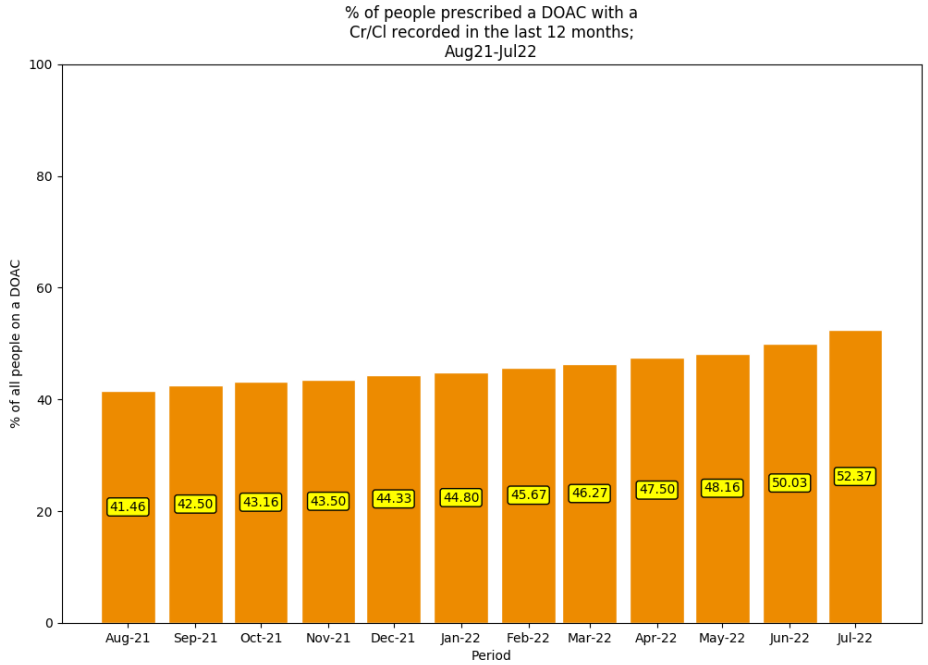

Figure 10 shows the percentage of people prescribed a DOAC with a coded CrCl recorded in the last 12 months increased from 41.46% to 52.37% from August 2021 to July 2022. However, 47.63% of patients prescribed a DOAC did not have a coded CrCl recorded in the last 12 months as of July 2022.

Figure 11. Percentage of people prescribed a DOAC with a serum creatinine level but no CrCl recorded in the last 12 months; Aug 21-July 22: (question 5 - those patients with clinical events recorded by using SNOMED CT codes 'serum creatinine' and 'CrCl' on codelist sheet)

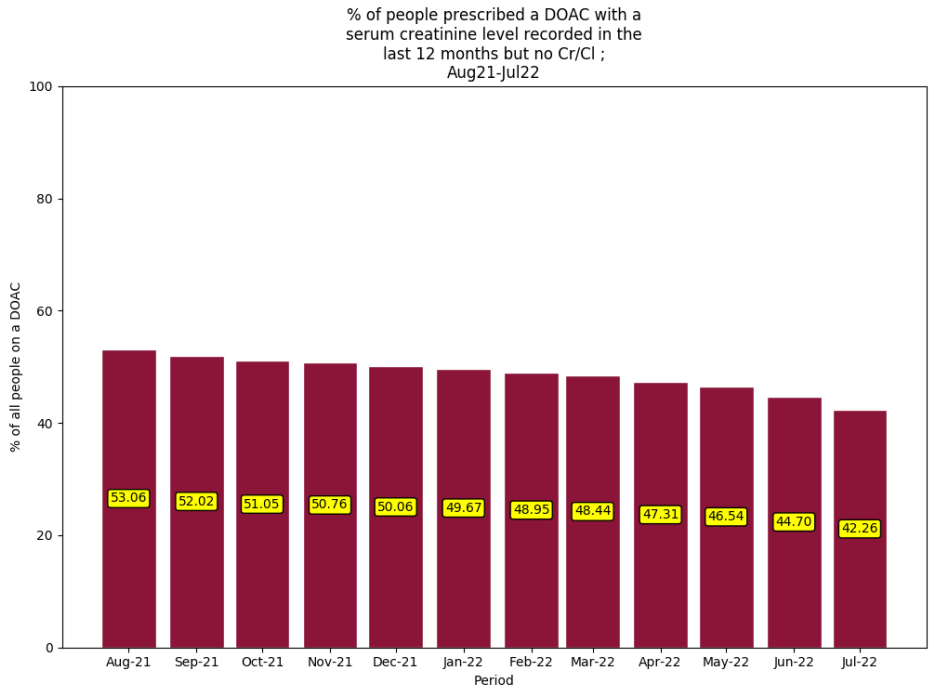

Figure 11 illustrates the percentage of people prescribed a DOAC with a serum creatinine level recorded but no CrCl recorded in the last 12 months, decreased from 53.06% to 42.26% from August 2021 to July 2022. This shows that the recording of CrCl has improved.

Figure 12. Percentage of people prescribed a DOAC with NVAF in the last 12 months; Aug 21-July 22: (question 7 - those patients with clinical events recorded by using SNOMED CT codes 'afib' on codelist sheet)

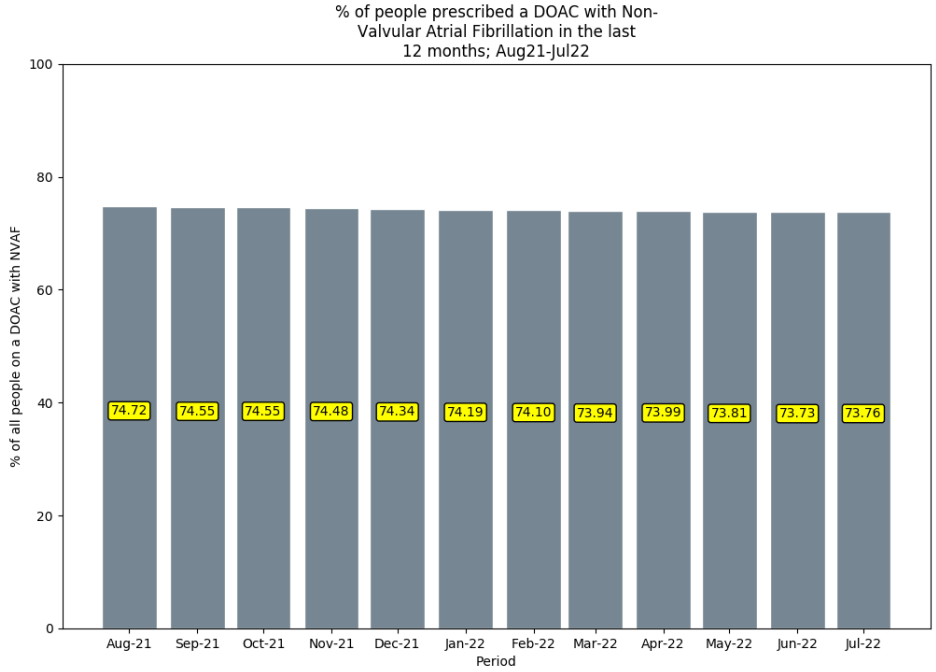

Figure 12 shows that approximately 75% of people were prescribed a DOAC for NVAF from August 2021 to July 2022. Approximately 25% of people were prescribed a DOAC for conditions other than non-valvular atrial fibrillation.

Figure 13. Percentage of people prescribed a DOAC with NVAF and CrCl recorded in the last 12 months; Aug 21-Jul 22: (question 8 - those patients with clinical events recorded by using SNOMED CT codes 'afib' and 'CrCl' on codelist sheet)

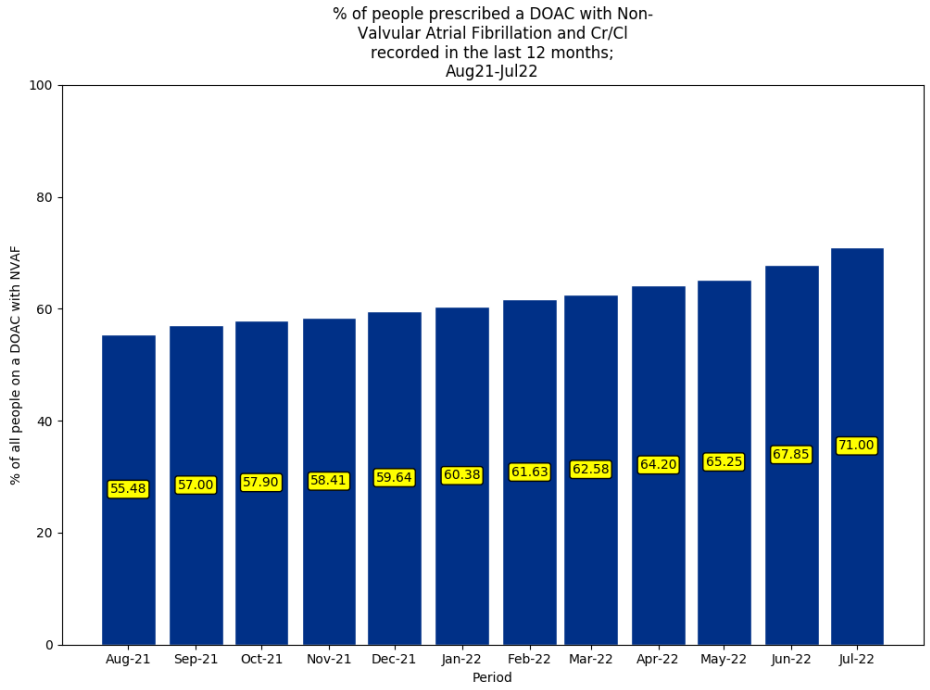

Figure 13 shows that the percentage of people prescribed a DOAC with NVAF and a CrCl recorded, rose from 55.48% in August 2021 to 71% in July 2022. However, there were 29% of people prescribed a DOAC with NVAF who did not have a CrCl recorded/coded on the clinical system in the last 12 months.

Figure 14. Percentage of people prescribed a DOAC with NVAF and with CrCl recorded in the last 12 months, where the recommended dose (calculated using recorded CrCl) does not match the prescribed dose in the last 12 months; Aug 21-July 22: (question 9 - using NICE guidance and the actual recorded CrCl only, analysis was done to find the % of people not on the recommended dose, breaking this down into 'over' and 'under' dosing)

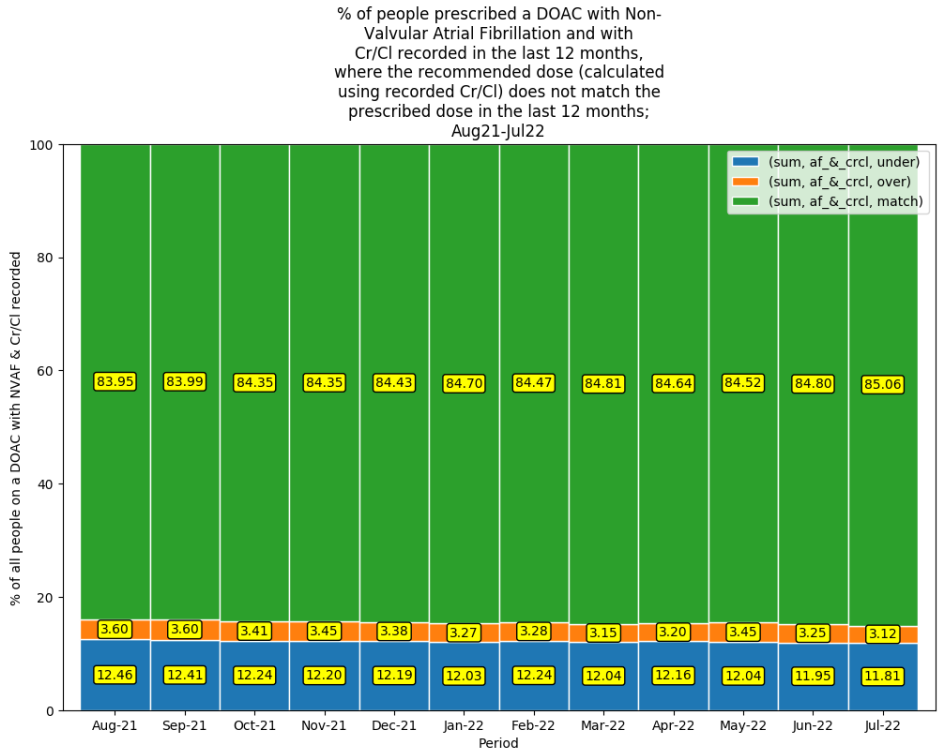

Figure 14 illustrates that in July 2022, 85.1% of patients prescribed a DOAC for NVAF were prescribed the correct dose based on their creatinine clearance. 11.8% of people prescribed a DOAC for NVAF received a DOAC dose lower than their calculated dose

(underdose/subtherapeutic) using their recorded CrCl. 3.1% of people prescribed a DOAC for NVAF received a dose higher than their calculated dose (overdose) using their recorded CrCl.

Discussion

Data analysis from this research, which covers 40% of GP practices in England, indicates that the number of people prescribed a DOAC was 394,182, equivalent to 1.9% of the population, as of July 2022. This represents an 76% increase in DOAC prescribing from January 2018. The age band with the largest number of people prescribed a DOAC was the 80 years and over group, followed next by the 70 to 79 years age group. The largest increases in DOAC prescribing from January 2018 to July 2022 were seen in the 80 years and over age group with a prescribing rate of 12,841 per 100,000 population followed by the 70 to 79 years age group with 5,975 per 100,000, and then the 60 to 69 years age group with 2,206 per 100,000. More males than females were prescribed a DOAC with a steady increase in the percentage of males receiving a DOAC compared to females over the study period from January 2018 (51% males) to July 2022 (54% males). This data is all in line with an expected increase in DOAC prescribing based on national guidance.

The NHSEI clinical guide for the management of anticoagulant services during the coronavirus pandemic contained a table with advice on DOAC dosing in NVAF based on body weight, serum creatinine and CrCl for each of the DOACs. The suggested process, undertaken remotely where possible, for safe switching from warfarin to a DOAC included checking the GP clinical system for U&Es, recording weight, calculating CrCl and prescribing the DOAC at an appropriate dose. The clinical guide excludes switching patients from warfarin to a DOAC if their CrCl is less than 15ml/min.[1] It is therefore important to know the CrCl of the patient in order to comply with the national guideline.

The Summary of Product Characteristics (SPCs) for Pradaxa® (dabigatran) and Lixiana® (edoxaban), specify that the method used to estimate renal function (CrCl in mL/min) is the Cockcroft-Gault method.[5,6] The Cockcroft-Gault method requires the input of the person's age, sex, weight and serum creatinine. The actual body weight is used in the calculation. However, guidance around how to calculate the CrCl is ambiguous and calculation tools use different body weights in the calculations (actual vs. ideal vs. adjusted) and there is no national advice available to clarify which weight to use. Online calculators are available to assist with calculating CrCl (Cockcroft-Gault equation) https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation [9] which highlight the issues around which body weight to use (in particular for patients at extremes of BMI). For obese or morbidly obese people and for underweight people, the online calculators offer a range for the CrCl which also takes into account adjusted body weight and ideal body weight. Online calculators are also available to show how the ideal and adjusted body weight can be calculated https://www.mdcalc.com/ideal-body-weight-adjusted-body-weight.[10] There are also tools available in the GP clinical systems which support calculation of CrCl using the Cockcroft-Gault equation but these may use different body weights (ideal vs. actual) and it is important to be aware of which body weight is being used in calculations. This situation

has led to confusion amongst prescribers on how to use the Cockcroft-Gault equation to calculate CrCl correctly.

The SPCs for Eliquis® (apixaban) and Xarelto® (rivaroxaban) do not state the method that should be used to calculate the CrCl or which body weight to use in the calculation.[4,7] However, all clinical trials for the DOACs used actual body weight in the dosing calculations.[11] The Cockcroft-Gault equation is not routinely reported by labs. In contrast, eGFR is routinely reported by labs. However, eGFR can overestimate renal function and therefore the dose to be prescribed, and increase the risk of bleeding events with DOACs.[8] The MHRA advises that for DOAC dosing, the Cockcroft-Gault formula should be used to calculate CrCl[3], however does not advise on which weight to use in the calculation.

This analysis has shown that in July 2022, 37.44% of people on a DOAC had no weight recorded, 11.2% had no eGFR recorded and 9.3% had no serum creatinine recorded in the last 12 months. It is important that these markers are checked on an annual basis to ensure that patients are on the correct dose and that their renal function is not declining. 47.63% had no CrCl recorded on the GP clinical system, there could be many reasons for this. For example, the study could only look at records where creatinine clearance is coded in the notes, if it has been calculated outside of the clinical system and then added as free text, the study would not pick these up. Also if it has been coded using a code other than those that were used to run the searches and identified in the codelists, these would not be picked up. As there is no national guidance on how to correctly calculate CrCl for DOAC dosing, there is much confusion around which body weight to use and clinicians will often use online calculators outside of the clinical systems and then record the CrCl as free text in the notes. Almost 90% of patients on a DOAC are having their renal function checked, this could imply that some clinicians are using their clinical judgement to assess whether a dose is appropriate for the patient and this is not recorded or coded in the clinical systems. 42.6% of people prescribed a DOAC with a recorded serum creatinine level did not have a CrCl level recorded.

People with NVAF for the prevention of stroke and systemic embolism receiving higher DOAC doses than required for their CrCl (overdosing) are at higher risk of bleeding and adverse effects from the DOAC. Conversely people prescribed lower DOAC doses than required for their CrCl (underdosing/subtherapeutic doses) are at risk of not being protected from developing a stroke or systemic embolism. Since August 2021, there has been a significant increase in the number of people prescribed a DOAC for NVAF with their CrCl recorded in the last 12 months. In July 2022, of the 71% of people with NVAF prescribed a DOAC and who had their CrCl recorded, 11.8% were prescribed an underdose/subtherapeutic dose and 3.1% were prescribed an overdose of DOAC according to their calculated renal function. This means that these people may be at risk of harm from their DOAC.

Recommendations

- There should be national guidance on how to correctly calculate creatinine clearance for DOAC dosing including which weight to use including at extremes of weight. The Drug and Therapeutics Bulletin have also called for this in 2019.[12]
- GP system supplier internal CrCl software should be reviewed for compliance to appropriate standards for calculating and coding CrCl.
- All patients prescribed a DOAC should have their weight, serum creatinine and calculated creatinine clearance recorded (and coded) in their notes annually with the necessary DOAC dosage adjustments made in line with the SPC.
- Current patients on a DOAC without these values recorded or dosage adjustments made should be identified and prioritised for a DOAC review to ensure they are on the correct dose.

About us

OpenSAFELY is an open source publicly funded trusted research environment (TRE) created during COVID-19 by the University of Oxford in collaboration with NHS England, The London School of Hygiene and Tropical Medicine, and Electronic Health Record software companies TPP and EMIS. It is currently executing code across 58 million patients' full GP records linked onto other datasets such as HES/SUS, vaccination and death certificates, with a large number of completed and published research outputs in high impact journals.

OpenSAFELY has implemented various technical features to support privacy, transparency, and open science. Analysts use standardised tools for data curation, meaning all code can be reviewed, understood, improved and re-used by other users.

All technical and user documentation for the platform is openly available online. All code executed against patient records is logged and automatically published when results are published; most code is amenable to review and re-use as it follows standard structures.

PrescQIPP CIC is a non-profit company working with the NHS currently providing services to the UK Intregrated Care Systems in England and Health Boards in, Wales, Northern Ireland, Jersey, Isle of Man and half of the Scottish Health Boards. PrescQIPP is solely funded by the NHS for the NHS and most bulletins are publicly available 12 months after publication. We produce evidence-based resources, data analysis and implementation tools for primary care commissioners, and provide a platform to share innovation and good practice across the NHS.

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Appendix 1

Acknowledgements

This project was approved by NHS England, https://www.opensafely.org/approved-projects/#project-21We are very grateful for all the support received from TPP technical Operations team throughout this work, and for generous assistance from the information governance and database teams at NHS England and the NHS England Transformation Directorate

Methods - Data Sharing or Data Source headings

All data were linked, stored, and analysed securely within the OpenSAFELY platform: **https://opensafely.org/**. Data include pseudonymised data such as coded diagnoses, medications, and physiological parameters. No free text data are included. All code is shared openly for review and re-use under MIT open license https://github.com/opensafely/doacs-covid19/

Detailed pseudonymised patient data is potentially re-identifiable and therefore not shared.

Software and Reproducibility

Data management was performed using Python 3.8.8 with analysis carried out using Python/Jupyter Notebook Code for data management and analysis, as well as codelists, are archived online https://github.com/opensafely/doacs-covid19/

Information governance and ethical approval

NHS England is the data controller for OpenSAFELY-TPP; TPP is the data processor; all study authors using OpenSAFELY have the approval 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.[1]

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.[2]

The OpenSAFELY research platform adheres to the obligations of the UK General Data Protection Regulation (GDPR) and the Data Protection Act 2018. 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.[3] This was extended in July 2022 for the NHS England OpenSAFELY COVID-19 research platform.[4] In some cases of data sharing, the common law duty of confidence is met using, for example, patient consent or support from the Health Research Authority Confidentiality Advisory Group.[5]

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.

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