

## **Trends in direct oral anticoagulant (DOAC) prescribing in English primary care**

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**Short title:** Trends in DOAC prescribing in English primary care

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### **Conflicts of interest**

MJ, XF, JW, MF and SdeL are employees of Oxford University, which received funding from Bristol Myers Squibb and Pfizer to undertake this study. KGP, BS, and JA are employees of Bristol Myers Squibb Pharmaceuticals Ltd. SE is a postgraduate doctoral student with SdeL at University of Surrey. SdeL is Director of the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) and has also received funding through his university from Daiichi Sankyo for AF research. JS receives funding from the Wellcome Trust/Royal Society via a Sir Henry Dale Fellowship (ref: 211182/Z/18/Z) and an NIHR Oxford Biomedical Research Centre (BRC) Senior Fellowship. BCTF has acted as a consultant, speaker or received grants from Abbott Diabetes, AstraZeneca, Boehringer Ingelheim, Eli Lilly, GSK, Janssen, Medtronic, MSD, Napp, Novo Nordisk and Sanofi. This research was funded in part, by the Wellcome Trust [211182/Z/18/Z]. For the purpose of open access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. FDRH acknowledges part support as Director of the NIHR Applied Research Collaboration (ARC) Oxford Thames Valley, and Theme Lead of the NIHR OUH BRC. FDRH has also received occasional fees or expenses for speaking or consultancy from AZ, BI, Bayer, BMS/Pfizer, and Novartis.

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## ABSTRACT

**Background:** In England, most prescribing of direct-acting oral anticoagulants (DOACs) for atrial fibrillation (AF) is in primary care. However, there remain gaps in our understanding of dosage and disparities in use.

**Objective:** To describe trends in DOAC prescribing, including dose reduction in people with renal impairment and other criteria, and adherence.

**Methods:** Using English primary care sentinel network data from 2014-2019, we assessed appropriate DOAC dose adjustment with creatinine clearance. We used logistic regression to study adherence (defined as proportion of days prescribed) reporting odds ratios (OR) with 95% confidence intervals (95%CI).

**Results:** Of 6,464,129 people in the cohort, 2.3% were aged  $\geq 18$  years with a diagnosis of AF, and 30.8% of these were prescribed vitamin K antagonist, and 69.1% DOACs. Appropriate DOAC prescribing following creatinine clearance measures improved between 2014-2019; dabigatran from 21.3% (95% CI 15.1-28.8) to 48.7% (45.0-52.4); rivaroxaban from 22.1% (16.7-28.4) to 49.9% (48.5-53.3); edoxaban from 10.0% (0.3-44.5) in 2016 to 57.6% (54.5-60.7) in 2019; apixaban from 30.8% (9.1-61.4) in 2015 to 60.5% (57.8-63.2) in 2019.

Adherence was highest for Factor Xa inhibitors, increasing from 50.1% (47.7-52.4) in 2014 to 57.8% (57.4-58.2) in 2019. Asian and black/mixed ethnicity was associated with non-adherence (OR 1.81, 1.56-2.09) as was male gender (OR 1.19, 1.15-1.22), higher socioeconomic status (OR 1.60, 1.52-1.68), being an ex-smoker (OR 1.12, 1.06 -1.10), and hypertension (OR 1.07, 1.03-1.17).

**Conclusions:** Year-on-year, the volume and quality of DOAC prescribing has improved. Future interventions to improve quality of anticoagulant management should target disparities in adherence.

**Keywords:** Atrial Fibrillation; Stroke, Medication Adherence; Anticoagulants; Inappropriate prescribing; Renal insufficiency; General Practice; Medical record systems, computerized.

## **Key messages**

### **What is already known on this topic**

Guidelines recommend using direct-acting oral anticoagulants (DOACs) for non-valvular atrial fibrillation (NVAf). However, DOACs require complex dose adjustments that vary between preparations.

### **What this study adds**

DOACs are being increasingly used for NVAf, surpassing VKAs. In addition, we found that whilst there remains a prescribing gap for appropriate dose reductions, this aspect of therapy improved year-on-year across all DOACs. The persistence with DOACs was superior to vitamin K antagonists. However, disparities in adherence persist in people of non-white ethnicity, male gender, higher socioeconomic status, in ex-smokers and some disease groups.

### **How this study might affect research, practice or policy**

Primary care chronic disease management programmes could be extended to further improve DOAC prescribing, and to reduce disparities in care.

## INTRODUCTION

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia.<sup>1,2</sup> The global prevalence of AF in 2019 was estimated at 59.7 million with nearly 5 million new cases occurring every year.<sup>1</sup> Both the prevalence and incidence of AF are expected to increase, due to an ageing population, improved survival of individuals with coronary artery disease and heart failure, and improved diagnosis.<sup>3</sup> AF increases the risk of stroke five-fold and cardio-embolic strokes associated with AF are more likely to be fatal, recurrent, and cause more severe disability.<sup>4</sup>

Direct oral anti-coagulants (DOACs) have been increasingly adopted over vitamin K antagonists (VKAs) such as warfarin for management of non-valvular AF (NVAF). This is likely due to an improved efficacy/safety ratio, fewer food and drug interactions, favourable bleeding profile, simple dosing regimen and less routine monitoring.<sup>5,6</sup> In NVAF, DOACs have demonstrated at least non-inferior clinical efficacy over VKAs in reducing the risk of stroke and systemic thromboembolism and lowering bleeding risk, particularly with respect to reductions in intracranial haemorrhage.<sup>7</sup> Hence, DOACs are currently indicated as first-line anti-coagulation therapy for NVAF patients with at least one risk factor for stroke or systemic embolism in men and two risk factors in women.<sup>8</sup> Recent guidelines, including NICE 2021 and ESC 2020 guidelines similarly favour DOACs over warfarin in patients with NVAF.<sup>9,10</sup>

To reduce the risks of bleeding and stroke, DOACs should be prescribed with an appropriate dose and patients should adhere to treatment. However, few studies have explored this or examined which clinical groups have poor rates of adherence and persistence. Research in primary care has largely focussed on overall rates of prescribing, adherence, and persistence, without exploring how dosages were adjusted, based on individual DOAC summary of product characteristics and national guidelines.<sup>11,12</sup> There has been limited research as to whether dose reduction has occurred in renal impairment, this is important because some of these medicines are mainly excreted via the kidney and have a narrow therapeutic index.<sup>13</sup>

We conducted this study to report trends and changes in the quality of anticoagulant prescribing in primary care between 2014 and 2019; we specifically explored appropriate dose reduction with a focus on patients with renal impairment. We also explored the patient factors associated with adherence and compared persistence in DOACs with VKAs.

## METHODS

### Data source

We used data from the Oxford-Royal College of General Practitioners (RCGP) Clinical Informatics Digital Hub (ORCHID).<sup>14,15</sup> We used ORCHID data collected from our primary care sentinel cohort (PCSC), a subset of 722 general practices, with 6.46 million currently registered patients at the time of this study.

PCSC data provided an accurate denominator, long-term use of computerised medical records (CMR), plus financially incentivised chronic disease management. Over the period of this study, pseudonymised NHS Number provided a unique identifier across the NHS ensuring key data flowed into GP CMR system. This included all registration, de-registration and death

data, pathology data, and prescription data. NHS number also facilitates the transmission of prescriptions electronically to the patient's registered pharmacist. A pay-for-performance system has rewarded annual review of people with AF since 2006.<sup>14</sup> The variables for this study were recorded in the primary care CMR using the systematised nomenclature of medicine clinical terminology (SNOMED CT) and carefully curated. The PCSC has previously been involved in AF research including the development of a quality improvement dashboard.<sup>16-18</sup>

### **Population and study period**

Our retrospective cohort included individuals aged  $\geq 18$  years with non-valvular AF diagnosed between January 2014 and December 2019. We did not include 2020 due to the onset of the COVID-19 pandemic, which may have distorted trends in AF management in primary care, particularly in older people.<sup>19</sup> The first prescription of VKA/DOAC was on or after the date of AF diagnosis. The date of first prescription became the index date.

For inclusion, patients needed  $\geq 90$  days of follow-up. Individuals with  $\geq 1$  prescription of VKA/DOAC were eligible for inclusion in adherence/persistence analyses. We excluded patients taking an anticoagulant for other indications (e.g., deep vein thrombosis and pulmonary embolism). Follow-up was until an outcome event, death, or patient leaving the practice.

### **Study variables**

The population of interest were people with a diagnosis of AF, who were prescribed anticoagulants. Only those with two or more consecutive prescriptions were included in the adherence and persistence analysis (Figure 1). Our analysis included sociodemographic data of age, gender, ethnicity, deprivation indices and co-morbidities (Table 1). An ontological approach was used to describe ethnicity, and was categorised as White, Asian, Black, mixed, and other ethnicity.<sup>20</sup> We combined black, mixed, and other due to low numbers. The socioeconomic status was calculated using the Index of Multiple Deprivation (IMD), which was divided into quintiles, where quintile 1 signifies most deprived, and quintile 5 the least deprived.<sup>21</sup> The IMD is unique in its inclusion of a measure of geographical access as an element of deprivation and in its direct measure of poverty (through data on benefit receipts). This has the potential to provide a missing dimension of deprivation in rural areas.

We recorded smoking status classified as current, ex- and non-smokers; and heavy drinking defined as over 14 drinks/units of alcohol per week. We reported medication using the individual anticoagulant's generic name, or by type. We classified anticoagulants into: VKAs (Warfarin); factor Xa inhibitors (apixaban, edoxaban and rivaroxaban); and dabigatran. The other variables included were respiratory disease (asthma and chronic obstructive pulmonary disease [COPD]); cardiometabolic disease including hypertension, chronic kidney disease (CKD, only including stages 3-5), ischaemic heart disease (IHD), ischaemic and haemorrhagic stroke, heart failure, peripheral arterial disease (PAD), vascular dementia, and diabetes mellitus (combining all types of diabetes); we also included neoplasms (solid tumours), liver disease and epilepsy.

### **Outcome measures**

Our primary areas of interest were the quality of and disparities in prescribing trends. Our primary outcome measures were the use of lower doses of DOACs in renal impairment (defined using creatinine clearance as reported in the product characteristics). We also report patient factors associated with non-adherence and compared persistence of DOACs with VKAs.

**Table 1: Characteristics of study population (n=82,367)**

| Variables            | VKA<br>(n=25,429) | Factor Xa inhibitors<br>(n=53,518) | Dabigatran<br>(n=3,420) | <i>p</i> |
|----------------------|-------------------|------------------------------------|-------------------------|----------|
|                      | Mean (SD)         | Mean (SD)                          | Mean (SD)               |          |
| Age                  | 76.7 (8.9)        | 75.4 (9.8)                         | 74.3 (9.2)              | <0.001   |
| <b>Gender:</b>       |                   |                                    |                         |          |
| Female               | 10,020 (39.4)     | 23,057 (43.1)                      | 1,259 (36.8)            | <0.001   |
| Male                 | 15,409 (60.6)     | 30,461 (56.9)                      | 2,161 (63.2)            |          |
| <b>Ethnicity</b>     |                   |                                    |                         |          |
| White                | 21,010 (82.6)     | 43,672 (81.6)                      | 2,805 (82.0)            |          |
| Asian                | 342 (1.3)         | 746 (1.4)                          | 31 (0.9)                | <0.001   |
| Black/Mixed/Other    | 241 (0.9)         | 538 (1.0)                          | 20 (0.6)                |          |
| Unknown              | 3,836 (15.1)      | 8,562 (16.0)                       | 564 (16.5)              |          |
| <b>IMD quintile</b>  |                   |                                    |                         |          |
| 1 (most deprived)    | 3,034 (11.9)      | 263 (7.7)                          | 5,907 (11.0)            | <0.001   |
| 2                    | 4,195 (16.5)      | 464 (13.6)                         | 8,570 (16.0)            |          |
| 3                    | 5,376 (21.2)      | 717 (21.0)                         | 11,126 (20.8)           |          |
| 4                    | 5,938 (23.4)      | 902 (26.4)                         | 12,958 (24.2)           |          |
| 5 (least deprived)   | 6,859 (27.0)      | 1,072 (31.4)                       | 14,908 (27.9)           |          |
| <b>Comorbidities</b> |                   |                                    |                         |          |
| Asthma               | 3,435 (13.5)      | 8,169 (15.3)                       | 513 (15.0)              | <0.001   |
| COPD                 | 2,243 (8.8)       | 5,210 (9.7)                        | 296 (8.7)               | <0.001   |
| Hypertension         | 18,407 (72.4)     | 36,960 (69.1)                      | 2,331 (68.2)            | <0.001   |
| No CKD               | 17,490 (68.8)     | 39,870 (74.5)                      | 2,710 (79.2)            | <0.001   |
| CKD stage 3          | 7,450 (29.3)      | 13,086 (24.5)                      | 705 (20.6)              |          |
| CKD stage 4          | 415 (1.6)         | 522 (1.0)                          | 4 (0.1)                 |          |
| CKD stage 5          | 74 (0.3)          | 40 (0.1)                           | 1 (0.0)                 |          |
| IHD                  | 9,635 (37.9)      | 16,800 (31.4)                      | 1,090 (31.9)            | <0.001   |
| TIA                  | 2,509 (9.9)       | 5,083 (9.5)                        | 372 (10.9)              | 0.013    |
| Ischaemic stroke     | 958 (3.8)         | 2,258 (4.2)                        | 155 (4.5)               | 0.005    |
| Liver disease        | 1,169 (4.6)       | 2,637 (4.9)                        | 181 (5.3)               | 0.059    |
| PAD                  | 281 (1.1)         | 608 (1.1)                          | 26 (0.8)                | 0.126    |
| Diabetes             | 6,103 (24.0)      | 11,531 (21.5)                      | 675 (19.7)              | <0.001   |
| Epilepsy             | 503 (2.0)         | 989 (1.8)                          | 70 (2.0)                | 0.368    |

## Quality of DOAC dosage adjustment

We conducted repeated analysis in each year from 2014 to 2019 to explore whether there was a trend in the quality of DOAC prescribing (Table 2). Good quality prescribing was defined as dose reduction of DOACs guided by prior measurement of creatinine clearance. This was identified from codes for creatinine clearance in the CMRs, or by calculating the creatinine clearance using the Cockcroft-Gault formula if its components were available within the CMR.<sup>22</sup> We also conducted a sensitivity analysis (Supplementary file 3) exploring whether an estimate of glomerular filtration rate (eGFR) had been used as a substitute measure of renal function.

DOAC dose reduction was indicated according to the following criteria (see table 2): For apixaban, age, weight and serum creatinine >133micromol/l were considered; for edoxaban, weight and certain medications that inhibit P-glycoprotein; for rivaroxaban, no additional patient variables are needed to determine dose reduction. Dabigatran prescription additionally requires assessment of the risk of gastrointestinal bleeding, older age and special consideration given to people on concurrent medication such as verapamil.

**Table 2. Criteria for dose reduction of DOACs (CrCl; creatinine clearance)**

| Dosing Criteria for AF  | Edoxaban   | Apixaban  | Dabigatran  | Rivaroxaban          |
|---|--|---|---|----------------------|
| Normal Dosing Regime  | 60 mg od   | 5 mg bd   | 150 mg bd   | 20 mg od             |
| Reduced Dosing Regime   | 30 mg od   | 2.5 mg bd   | 110 mg bd   | 15 mg od             |
| Criteria for Dose Reduction (SmPC recommended <sup>17</sup> ) | ≥1 of following:<br>Body weight ≤ 60 kg<br>On Cyclosporin, Dronedarone<br>Erythromycin or Ketoconazole | ≥2 of following<br>Age > 80 y<br>Body weight ≤ 60 kg<br>Serum creatinine 133 µmol/L | ≥1 of following:<br>Age > 80 y<br>On verapamil<br>Reflux/Gastritis<br>Age 75-80<br>“Bleed Risk” |                      |
| Renal Criteria for Dose Reduction                             | CrCl<br>15-50 ml/min   | CrCl<br>15-29 ml/min  | CrCl<br>30-50 ml/min  | CrCl<br>15-50 ml/min |

## Adherence

We report adherence for 2019, the most recent year prior to the COVID-19 pandemic. Adherence was estimated by proportion of days covered (PDC) over the year following index date. This measure is superior to other measures of adherence<sup>23</sup>. The definition of adherence is:

$$PDC = \frac{\text{number of days covered with drug } (\leq 365)}{\text{Number of days between first and last prescription (+30 days) or 365 days *}}$$

*Whichever is the shorter*

Adherence was defined as PDC >80%, in-line with other studies.<sup>24</sup> Crude rates of adherence were estimated and presented together with 95% CIs stratified by year and anticoagulant. A multilevel logistic regression model was generated to estimate adjusted rates of non-adherence. Baseline variables and type of anticoagulant were covariates included in the model.

### **Persistence**

We reported persistence over the last three years of our study period to provide the most contemporary data pre-pandemic. Individuals were deemed persistent if no gaps of >90 days appear in the prescription history in the year following the index date. We ascertained the proportion of patients persistent at one year. Persistence was measured using the product limit KM estimator.<sup>25</sup>

### **Statistical Analysis**

Patients were stratified by type of anticoagulant prescribed as well as year of study, to determine whether adherence rates changed over time. Factor Xa inhibitors were grouped together when evaluating adherence and persistence as the intention of this study was to explore trends in prescribing of Factor Xa inhibitors in comparison to dabigatran and VKAs, and not to relate differences in outcomes between DOACs. Adherence was modelled via logistic regression, with explanatory variables of the anticoagulant prescribed, along with other baseline characteristics entered as individual univariate predictors. Persistence of anticoagulants over time were modelled through Cox regression and presented via a Kaplan-Meier curve. All statistical analyses were performed using the R statistical programming language version 4.1.0.

### **Ethical considerations**

We used pseudonymised data from the RSC database for analysis within the Oxford-RCGP Clinical Informatics Digital Hub (ORCHID) a secure trusted research environment (TRE) 34,35. This TRE meets the requirements of NHS Digital's Data Security and Protection (DSP) Toolkit, Organisational Data Service (ODS) number EE133863-MSD-NDPCHS 28.

This study was defined by the Health Research Authority's Decision Tool as being a Service Evaluation (assessment of current practice) not needing formal NHS Ethical review 28. The study was approved by the University-RCGP Joint Research and Surveillance Centre Committee (JRSCC).

### **Patient and Public Involvement**

The RSC has a patient panel, drawn from member practices, which is informed of all our studies including this one. There was no patient member of the study team.

## **RESULTS**

### **AF prevalence, anticoagulation, and DOAC utility**



At the end of 2019, the prevalence of NVAf in our population of people  $\geq 18$  years and eligible for our study was 2.3% (149,635/6,464,129), compared with 1.15% (68,765/6,001,675) in 2014. 55% of patients with AF (n=82,367) in 2019 were anticoagulated; 30.8% (n=25,427) with a VKA, 69.1% (n=56,940) with DOACs. Of the people anticoagulated with a DOAC in 2019, 94% (53,518) were anticoagulated with a factor Xa inhibitor (apixaban, rivaroxaban, and edoxaban), with the remaining 6% receiving dabigatran (figure 2). Those in the most deprived IMD quintile were least likely to be prescribed any oral anticoagulant with the proportion prescribed increasing through the IMD quintiles (table 1).

Overall oral anticoagulant prescribing increased between 2014 and end of 2019 (figure 2). The number of VKAs prescribed increased then declined over the study period, the final number of prescriptions issued at the end of 2019 was 5% greater than in 2014. Over the study time period, the number of prescribed DOACs surpassed that of VKAs. The prescribing of factor Xa inhibitors increased 30-fold (1,796 to 53,518) while dabigatran prescriptions increased 3-fold (1,120 to 3,340) over the same period. Our supplementary file shows the details of the change in prescribing (supplementary file, table S1).

### **Dose adjustment of DOACs in renal impairment**

The proportion of people with AF who were prescribed a reduced dose of DOAC in renal impairment increased across the 5 year study period (Figure 3). Prescriptions for apixaban in renal impairment (CrCl 15-30 ml/min) increased from 30.8% (95%CI: 9.1-61.4) in 2015 to 60.6% (95%CI: 57.8-63.2) in 2019. Similarly, for edoxaban, appropriately reduced dose in renal impairment (CrCl 15-30 ml/min) increased from 10% (95%CI: 0.3-44.5%) in 2016 to 57.6% (95%CI: 54.5-60.7) in 2019. For rivaroxaban, the reduced dose range is for CrCL 15-50 ml/min, and correct dosage reduction was 22.1% in 2014 (95%CI: 16.7-28.4) with an increase to 49.9% (95%CI: 48.5-51.3) in 2019. Appropriately reduced dosing of dabigatran in renal impairment (30-50 ml/min) also improved from 21.3% (95%CI 15.1-28.8) in 2014 to 48.7% (95%CI 45.0-52.4) in 2019.

Our sensitivity analysis did not suggest that there was widespread substitution of eGFR for CrCl (Supplementary file: Table S2 and Figure S1). Whilst the proportion of cases correctly dosed if eGFR were substituted for CrCl in primary care, the rate of adjustment was lower and grew less. The change was 17.2% to 25.1% across DOACs in 2014, to 27.5% to 31.2% in 2019). There was no evidence that GPs were substituting eGFR for CrCl.

### **Adherence and non-adherence**

Unadjusted analyses showed that between 2014 and 2019 adherence with anticoagulants was only around 50%. Adherence was superior for DOACs compared with VKA. In 2019, the last year of the study, 46% (95%CI: 46-47%) of patients prescribed a VKA were adherent compared with 58% (95%CI: 57-58%) of people prescribed factor Xa inhibitors and 57% (95%CI: 56-59%) prescribed dabigatran (Supplementary file, Table S3).

Multi-variate logistic regression estimated adjusted rates of non-adherence (table 3). Non-adherence was greater in males than females, (OR= 1.19, 95%CI: 1.15-1.22,  $p < 0.0001$ ), and was also more likely in all non-white ethnicities, non-smokers and ex-smokers, and was greater with increasing socioeconomic status (table 3). It would appear that whilst the more affluent were prescribed a higher proportion of these medicines (table 1), they were less adherent. Of

all considered sociodemographic risk factors, only increasing age was associated with improved adherence.

Of all comorbidities, only hypertension was associated with higher odds of non-adherence (OR= 1.07, 95%CI: 1.03-1.10,  $p<0.0001$ ). Both COPD and asthma were associated with improved adherence, as were IHD, ischaemic stroke (OR= 0.83, 95%CI: 0.77-0.89,  $p<0.0001$ ), heart failure, dementia, diabetes and epilepsy. Other comorbidities did not have any statistically significant association with adherence, including TIA and haemorrhagic stroke.

**Table 3: Odds ratio (OR) associated with OAC non-adherence**

|  |                     | <b>OR</b> | <b>LCI</b> | <b>UCI</b> | <b>p</b> |
|--|---------------------|-----------|------------|------------|----------|
| <b>OAC</b><br>(Ref VKA)                        | Factor Xa Inhibitor | 0.60      | 0.58       | 0.62       | <0.0001  |
|  | Dabigatran          | 0.58      | 0.54       | 0.62       | <0.0001  |
|  | Age (continuous)    | 0.98      | 0.98       | 0.98       | <0.0001  |
|  | Gender (Ref Female) | 1.19      | 1.15       | 1.22       | <0.0001  |
| <b>Ethnicity</b><br>(Ref White)                | Asian               | 1.89      | 1.67       | 2.14       | <0.0001  |
|  | Black/Mixed/Other   | 1.81      | 1.56       | 2.09       | <0.0001  |
|  | Unknown             | 1.15      | 1.10       | 1.19       | <0.0001  |
| <b>IMD Quintile</b><br>(Ref 1 - most deprived) | IMD Quintile 2      | 1.19      | 1.12       | 1.26       | <0.0001  |
|  | IMD Quintile 3      | 1.23      | 1.16       | 1.29       | <0.0001  |
|  | IMD Quintile 4      | 1.33      | 1.27       | 1.40       | <0.0001  |
|  | IMD Quintile 5      | 1.60      | 1.52       | 1.68       | <0.0001  |
| <b>Smoking Status</b><br>(Ref Current Smoker)  | Ex-smoker           | 1.12      | 1.06       | 1.19       | <0.0001  |
|  | Non-smoker          | 1.10      | 1.03       | 1.17       | 0.002    |
|  | Heavy Drinking      | 0.91      | 0.74       | 1.12       | 0.394    |
| <b>Co-morbidities</b><br>(Ref None)            | COPD                | 0.86      | 0.82       | 0.90       | <0.0001  |
|  | Asthma              | 0.95      | 0.91       | 0.99       | 0.010    |
|  | Hypertension        | 1.07      | 1.03       | 1.10       | <0.0001  |
|  | CKD Stage 3         | 1.01      | 0.97       | 1.04       | 0.6286   |
|  | CKD Stage 4         | 1.03      | 0.90       | 1.18       | 0.6600   |
|  | CKD Stage 5         | 1.04      | 0.71       | 1.52       | 0.843    |
|  | IHD                 | 0.93      | 0.90       | 0.96       | <0.0001  |
|  | TIA                 | 0.98      | 0.93       | 1.03       | 0.3801   |
|  | CVA-Haemorrhagic    | 0.88      | 0.75       | 1.03       | 0.116    |
|  | CVA-Ischaemic       | 0.83      | 0.77       | 0.89       | <0.0001  |
|  | Heart Failure       | 0.81      | 0.78       | 0.84       | <0.0001  |
|  | Dementia            | 0.52      | 0.47       | 0.57       | <0.0001  |

|                   |      |      |      |         |
|-------------------|------|------|------|---------|
| Diabetes Mellitus | 0.86 | 0.83 | 0.89 | <0.0001 |
| PAD               | 0.91 | 0.79 | 1.04 | 0.163   |
| Liver Disease     | 1.00 | 0.93 | 1.07 | 0.962   |

## Persistence

We measured persistence from 2017 and patients had poorer persistence with VKA than with the DOACs (figure 4). There was no significant difference between factor Xa inhibitors and dabigatran. Overall persistence reduced to approximately 80% over the three-year observation period (2017-2019). Compared with VKA, the HR for non-persistence was 0.75 (95%CI: 0.69-0.81,  $p<0.0001$ ) for dabigatran, and 0.69 (95%CI: 0.66-0.71;  $p<0.0001$ ) for factor Xa inhibitors. The difference between persistence with dabigatran and factor Xa inhibitors was non-significant.

## Discussion

Between 2014-2019, there was a doubling in NVAF prevalence (1.15 to 2.3%) in the study population. Importantly, despite the higher case detection of NVAF, leading to more than 50% rise in patients where need for OAC management needed to be assessed and initiated where indicated, there was year-on-year increased volume and quality of DOAC prescribing in primary care. Appropriate reductions in dose prescribed, particularly in renal impairment, also improved over time.

However, our study has identified areas where there is scope for quality improvement. Almost half (45%) of NVAF patients were not anticoagulated over an extended period and many of these had only a single prescription for an anticoagulant. Adherence also appeared to be a significant clinical problem and additionally there were disparities in both who is prescribed, and adherent to their anticoagulant. We found that the most affluent by deprivation quintile are most likely to be anticoagulated and most likely not to persist to their OAC therapy. Non-white ethnicity was also associated with non-adherence. For patients with co-morbidities, it was important to see those with ischaemic stroke were more likely to be adherent to their anticoagulant, but also that comorbidities associated with increased stroke risk, such as CKD, were not associated with improved adherence. We also noted that overall adherence with DOACs was superior to VKA.

### *Implication of the findings:*

There is increasing volume and improving quality in primary care prescribing of OAC therapy, although focused interventions are needed to target gaps. There is a need to ensure eligible patients are anticoagulated, and that any disparities in socioeconomic status around commencing therapy are addressed, and a further need to intervene to improve adherence in non-white ethnicities and ensure that there is better adherence to anticoagulants, particularly those with high-risk conditions such as hypertension. People with dementia prescribed anticoagulants are noted to have a very low odds of non-adherence, perhaps demonstrating that when the right care plan is in place, adherence can be good.

The trend in increased diagnosis of NVAF, probably due to improved detection as well as to increased prevalence, with commensurate prescription of DOACs over VKA has been reported elsewhere.<sup>18</sup> Anticoagulation of patients with AF includes more prescribed DOACs than VKA in line with guidelines, with increasing use of Factor Xa inhibitors rather than dabigatran.<sup>26</sup> Education of primary care clinicians concerning the product characteristics (SmPCs) approved by the European Medicines Agency may have helped improve quality.<sup>27</sup>

Ethnicity has been identified as an important factor in poor adherence to anti-hypertensive treatment, and poor adherence has generally been associated with higher levels of deprivation.<sup>28,29</sup> Our findings are consistent with previous studies which have shown associations between increased comorbidities and reduced risk of non-adherence, although the finding that affluence is associated with non-adherence to DOACs is at odds with this and may reflect residual confounding.<sup>18</sup> Our low odds of non-adherence in dementia may not have been anticipated, generally adherence falls with cognitive decline. However it is plausible that our primary care professionals were only selecting people with appropriate support in place. Poor adherence and persistence have implications on drug cost and therapy effectiveness, at a population level.<sup>28</sup> Most importantly, they have a deleterious effect on stroke and systematic embolism outcomes.

This is one of the largest contemporary studies of prescribing of DOAC for NVAF in England, enhanced by the high data quality within the primary care sentinel network. The limitations of our study include lack of data on time in therapeutic range (TTR), which is a better measure of VKA monitoring. Consequently, our findings may be more uncertain for the quality of VKA prescribing than for DOACs. UK general practice commonly uses near-patient testing of the INR and a dose calculator for VKA management. Access to these data may have better enabled us to monitor VKA persistence and adherence. We also used prescribing, rather than dispensing data, so patients may have been issued prescriptions but not had them dispensed. However, the use of prescriptions as a surrogate is an established approach in evaluating medicine usage at a population level.<sup>24</sup>

## **Conclusion**

In a large retrospective study of five-year use of anticoagulants in people with AF, there has been growth in the number and type of anticoagulants prescribed. There has also been improvement in the quality of DOAC prescribing, especially in those with impaired renal function. However, there may be disparities in who is prescribed an anticoagulant, and gaps in the management of people with known AF. These include improving uptake and adherence, noting disparities and poor adherence in some at-risk groups. Whilst it is reassuring that primary care teams show these areas of improvement, future interventions to improve quality of anticoagulant management should target disparities in adherence and close the quality gap.

## **Acknowledgements**

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## **Contributorship Statement**

SdL, KGP, BS, JA, SE and MJ created the study concept. GD provided study oversight. MJ, SE and XF performed statistical analysis of the data. All other co-authors were responsible for clinical discussion relating to the analysis and iterative drafting of the manuscript. SdL and

KGP are responsible for the overall content as guarantors.

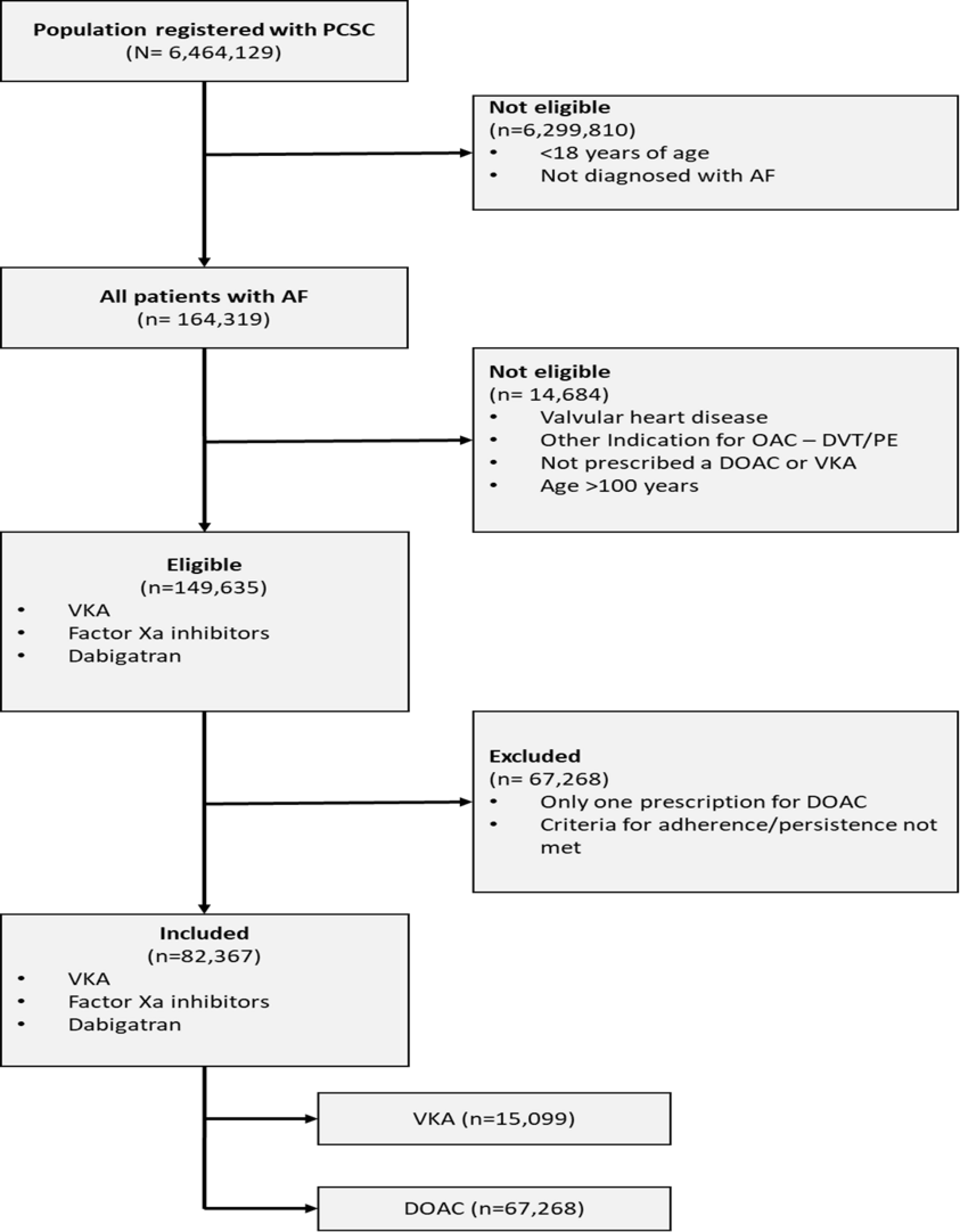
## References

1. Roth, Gregory A et al. "Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update from the GBD 2019 Study." *J Am Coll Cardiol* 2020; 76; 2982-3021.
2. Gage BF, Cardinalli AB, Albers GW, et al. Cost-Effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA* 1995; 274:1839–45.
3. Wu J, Zhang Y, Liao X, Lei Y. Anticoagulation therapy for non-valvular atrial fibrillation: a mini-review. *Front Med* 2020;7.
4. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death the Framingham Heart Study. *Circulation*, 1998, vol. 98 (pg. 946-952)
5. Shen NN, Zhang C, Wang N, Wang JL, Gu ZC, Han H. Effectiveness and Safety of Under or Over-dosing of Direct Oral Anticoagulants in Atrial Fibrillation: A Systematic Review and Meta-analysis of 148909 Patients From 10 Real-World Studies. *Front Pharmacol*. 2021 Mar 18;12:645479. doi: 10.3389/fphar.2021.645479. PMID: 33815125; PMCID: PMC8012667.
6. Benjamin AR, Ishak AM, Sujata B, David EA, Siddharth S, Jalaj G, et al. Effectiveness and Safety of Direct Oral Anticoagulants Versus Warfarin in Patients With Valvular Atrial Fibrillation. *Annals of internal medicine*. 2021;174(10):1488.
7. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener H-C, Hacke W, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Ep Europace*. 2015;17(10):1467-507.
8. Farmakis D, Davlouros P, Giamouzis G, Giannakoulas G, Pipilis A, Tsivgoulis G, et al. Direct oral anticoagulants in nonvalvular atrial fibrillation: practical considerations on the choice of agent and dosing. *Cardiology*. 2018;140:126-32.
9. Hindricks G, Potpara T, Nikolaos Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2021;42:373–498.
10. Atrial fibrillation: diagnosis and management (2021)  
<https://www.nice.org.uk/guidance/ng196> [accessed 27th August 2021]
11. Minhas AS, Jiang Q, Gu X, Haymart B, Kline-Rogers E, Almany S, et al. Renal function in atrial fibrillation patients switched from warfarin to a direct oral anticoagulant. *J Thromb Thrombolysis*. 2016;42(4):566-72
12. Banerjee A, Benedetto V, Gichuru P, Burnell J, Antoniou S, Schilling RJ, Strain WD, Ryan R, Watkins C, Marshall T, Sutton CJ. Adherence and persistence to direct oral anticoagulants in atrial fibrillation: a population-based study. *Heart*. 2020 Jan;106(2):119-126.

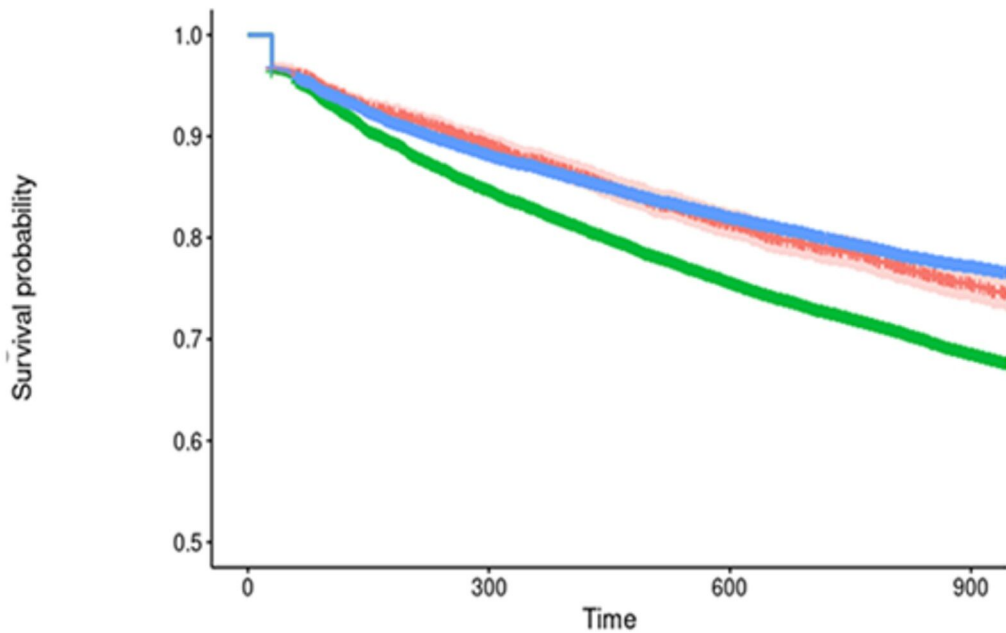
13. Barra ME, Fanikos J, Connors JM, Sylvester KW, Piazza G, Goldhaber SZ. Evaluation of Dose-Reduced Direct Oral Anticoagulant Therapy. *The American Journal of Medicine*. 2016 2016-11-01;129(11):1198-204.
14. de Lusignan S, van Weel C. The use of routinely collected computer data for research in primary care: opportunities and challenges. *Family Practice*. 2006;23(2):253-63.
15. de Lusignan S, Correa A, Smith GE, Yonova I, Pebody R, Ferreira F, et al. RCGP Research and Surveillance Centre: 50 years' surveillance of influenza, infections, and respiratory conditions. *Br J Gen Pract*. 2017;67(663):440-1.
16. de Lusignan S, Van Vlymen J, Hague N, Thana L, Dzregah B, Chan T. Preventing stroke in people with atrial fibrillation: a cross-sectional study. *J Public Health*. 2005;27(1):85-92.
17. Kumar S, de Lusignan S, McGovern A, Correa A, Hriskova M, Gatenby P, et al. Ischaemic stroke, haemorrhage, and mortality in older patients with chronic kidney disease newly started on anticoagulation for atrial fibrillation: A population based study from UK primary care. *BMJ*. 2018;360:k342-k.
18. de Lusignan S, Liyanage H, Sherlock J, Ferreira F, Munro N, Feher M, et al. Atrial fibrillation dashboard evaluation using the think aloud protocol. *BMJ Health & Care Informatics*. 2020 2020-10-01;27(3):e100191.
19. Joy M, Mcgagh D, Jones N, Liyanage H, Sherlock J, Parimalanathan V, et al. Reorganisation of primary care for older adults during COVID-19: a cross-sectional database study in the UK. *British Journal of General Practice*. 2020 2020-08-01;70(697):e540-e7.
20. Tippu Z, Correa A, Liyanage H, Burleigh D, McGovern A, Van Vlymen J, et al. Ethnicity Recording in Primary Care Computerised Medical Record Systems: An Ontological Approach. *J Innov Health Inform*. 2017;23(4):920-806.
21. Jordan H, Roderick P, Martin D. The Index of Multiple Deprivation 2000 and accessibility effects on health. *J Epidemiol Community Health*. 2004;58(3):250-7.
22. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and New CKD-EPI Formulas in Relation to GFR, Age, and Body Size. *Clinical Journal of the American Society of Nephrology*. 2010 2010-06-01;5(6):1003-9.
23. Forbes CA, Deshpande S, Sorio-Vilela F, et al. A systematic literature review comparing methods for the measurement of patient persistence and adherence. *Curr Med Res Opin* 2018;34:1613–25. 10.1080/03007995.2018.1477747
24. McGovern A, Tippu Z, Hinton W, Munro N, Whyte M, de Lusignan S. Comparison of medication adherence and persistence in type 2 diabetes: A systematic review and meta-analysis. *Diabetes Obes Metab*. 2018;20(4):1040-3.
25. Rasmussen L, Pratt N, Hansen MR, Hallas J, Pottegård A. Using the “proportion of patients covered” and the Kaplan-Meier survival analysis to describe treatment persistence. *Pharmacoepidemiology and Drug Safety*. 2018 2018-08-01;27(8):867-71.

26. Afzal S, Zaidi STR, Merchant HA, Babar Z-U-D, Hasan SS. Prescribing trends of oral anticoagulants in England over the last decade: a focus on new and old drugs and adverse events reporting. *J Thromb Thrombolysis*. 2021;52(2):646-653.
27. Mueller T, Alvarez-Madrazo S, Robertson C, Bennie M. Use of direct oral anticoagulants in patients with atrial fibrillation in Scotland: Applying a coherent framework to drug utilisation studies. *Pharmacoepidemiology and Drug Safety*. 2017 2017-11-01;26(11):1378-1386.
28. Perreault S, Denu S, White-Guay B, Côté R, Schnitzer ME, Dubé MP, et al. Oral Anticoagulant Prescription Trends, Profile Use, and Determinants of Adherence in Patients with Atrial Fibrillation. *Pharmacotherapy*. 2020;40(1):40-54.
29. Weernink MGM, Vaanholt MCW, Groothuis-Oudshoorn CGM, von Birgelen C, Ijzerman MJ, van Til JA. Patients' Priorities for Oral Anticoagulation Therapy in Non-valvular Atrial Fibrillation: a Multi-criteria Decision Analysis. *American journal of cardiovascular drugs : drugs, devices, and other interventions*. 2018;18(6):493-502.
30. Wilson LE, Luo X, Li X, Mardekian J, Garcia Reeves AB, Skinner A. Clinical outcomes and treatment patterns among Medicare patients with nonvalvular atrial fibrillation (NVAf) and chronic kidney disease. *PLoS One*. 2019;14(11):e0225052-e

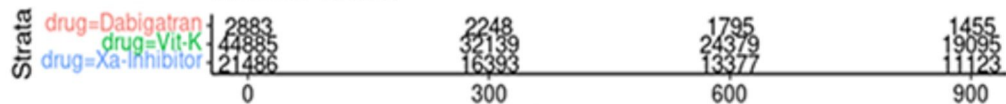




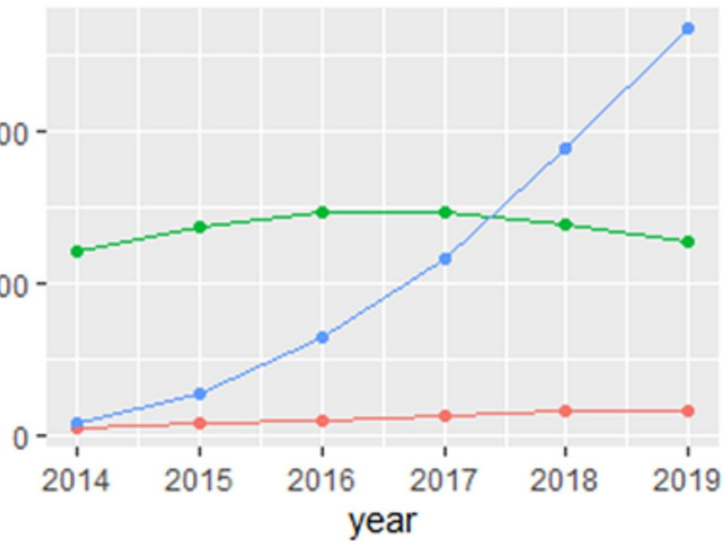
Strata + drug=Dabigatran + drug=Vit-K + drug=Xa-Inhibitor



Number at risk



Number of prescriptions



drug

- Dabigatran
- Vit.K
- Xa.Inhibitor

