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ORIGINAL ARTICLE

Choice of oral anticoagulant prescribed by general practices in Wales: Application of Dirichlet regression and linked data

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Aims: There has been sustained growth in the prescribing of direct oral anticoagulants (OACs) in primary care in the UK. Given the different indications, properties and prices of OACs, variation between prescribers is expected; however, a high level of variation may be evidence of inappropriate or suboptimal prescribing. This study examined the variation in the relative use of OACs in primary care in Wales.

Methods: Data on total defined daily doses of all community-dispensed OACs in 2019 were linked at the GP practice level with disease registers, patient demographic data and GP and patient numbers. The relative use of each OAC, as a fraction of all OACs prescribed, was analysed using Dirichlet regression to quantify the association between prescribing patterns and practice and area-level characteristics.

Results: Across 417 GP practices, the mean (range) in the relative prescribing of warfarin was 37% (6%–64%), apixaban was 32% (2%–65%), rivaroxaban 23% (0%–66%), dabigatran 3% (0%–23%) and edoxaban 6% (0%–59%). Statistical modelling provided strong evidence that prescribing patterns are associated with a GP practice's health board and also their nearest major hospital. Compared to the null model, a model including health board resulted in a 15% fall in Akaike information criterion, increasing to 20% with the addition of nearest major hospital and 27% including further covariates.

Conclusion: Systematic variation in OAC prescribing, by health board and based on nearest hospital, indicates that factors other than patient clinical characteristics and preferences may be influencing prescribing decisions.

KEYWORDS
Dirichlet regression, oral anticoagulants, pharmacoepidemiology, prescribing variation

1 | INTRODUCTION

Oral anticoagulants (OACs) are used predominantly for the prevention of ischaemic stroke in patients with atrial fibrillation (AF) and the treatment and prevention of venous thromboembolisms. Historically, the vitamin K antagonist (VKA) warfarin has been the mainstay of OAC therapy. However, direct oral anticoagulants (DOACs) have become established as alternative treatment options. The sustained growth in the prescribing of DOACs in primary care in the UK has been well documented. For example, DOACs accounted for 56% of all oral anticoagulant prescriptions to patients initiating OACs by 2015[1], and the volume of DOACs prescribed increased from 9% of all OACs

in 2014 to 74% in 2019, while the prescribing of all OACs nearly doubled.[2]

The DOACs differ in many important ways from warfarin and to a lesser extent between themselves. These differences include safety and efficacy profiles, interactions with food and with other drugs, availability of reversal agents, their dosing regimens and routes of elimination.[3–6] The choice of the most appropriate OAC to prescribe is, therefore, a complex decision requiring careful consideration of a range of patient clinical factors and preferences.[4] Various guidance exists in the UK to support prescribers in selecting the appropriate OAC, including national clinical guidance,[7] as well as those developed by countries (e.g. Wales[8]) and regions (e.g. health boards[9]).

Studies conducted in the UK, as well as elsewhere, have found the pattern of use of the available OACs to be highly variable across different segments of the healthcare system. Reports on the use of DOACs by English Clinical Commissioning Groups (CCGs) found that DOACs accounted for between 4% and 70% of all OAC use in 2015,[10] and between 53% to 99.5% in 2018–19.[2] Similar trends have been shown in other countries.[11,12] Although there is a high degree of reported inappropriate prescribing, studies have focused mainly on the dose rather than selection of the appropriate agent.[11,12]

Observational studies can be used to identify those factors associated with OAC choice and provide insights into the possible mechanisms underlying any observed variability. Existing studies have found associations with patients' race and income[13–15]; profession, education and living rurally[16]; and age, stroke or bleeding risk and comorbidities.[17] Across English CCGs, Ho et al. found associations between local policy and the relative use of different DOACs (but not for all DOACs relative to warfarin).[2] Using a sample of the UK population, Loo et al. found higher prescribing in patients with a history of ischaemic stroke, but less with congestive heart failure, coronary artery disease or peripheral vascular disease.[1] Medlinskiene et al. found that the type of prescriber and the sex or age of patients was not associated with the type of OAC initiated.[18] All these studies have been limited by not differentiating between the different DOACs, or by focusing only on a narrow set of explanatory variables.

High levels of variability in the prescribing of OACs, and associations between prescribing patterns and factors that are unlikely to be related to clinical factors and preferences, could signal suboptimal use. However, our understanding of how characteristics at multiple levels (patient, practice, locality or regional) influence the choice of each specific DOAC is limited. This study aimed to assess the extent of variation in OAC prescribing between GP practices in Wales and identify practice or area-level characteristics that may predict prescribing patterns.

What is already known about this subject

- The choice of the most appropriate oral anticoagulant is a complex decision requiring consideration of a range of clinical factors and patient preferences.
- Multiple studies have shown considerable geographical variation in the use of oral anticoagulants and there is concern that this may be evidence of inappropriate or suboptimal prescribing.

What this study adds

- The relative use of the available oral anticoagulants in primary care in Wales is highly variable across GP practices.
- This variation is related to health board and nearest major hospital and to a lesser extent to disease prevalence, general practice workload and dispensing status.

2 | METHODS

2.1 | Setting

The National Health Service (NHS) is the publicly funded healthcare system in the UK, separately administered by each constituent country. NHS Wales provides emergency services and a range of primary, secondary and specialist tertiary care services to its resident population of 3.1 million people. NHS Wales is organised into seven health boards, which are responsible for delivering all NHS healthcare services within geographical areas.

2.2 | Data sources

A list of the GP practices that were operating in Wales in 2019 was obtained from the NHS Wales Shared Services Partnership (SSP) GP Practice Analysis.[19] These data included the practice ID codes, county (unitary authority area), the number of GPs operating at the practice, whether the practice also dispenses prescriptions, and the numbers of prescribing and dispensing patients registered at the practice. Dispensing patients are those patients registered with the GP practice that are able to collect medicines from the practice, an option only available at dispensing practices. Data on prescribing of OACs in primary care were obtained from the NHS Wales SSP General Practice Prescribing Data Extract.[20] These data cover prescriptions issued in Wales by GPs or non-medical prescribers on behalf of the GP practice, that are then dispensed in the community within Wales or England. The data included all prescribed medicines, dressings and appliances dispensed each month. The data did not include any information relating to the patient, such as the indication for which the prescription was issued. Prescriptions that were issued privately (representing 0.01%) or not dispensed are not included in the dataset.

As part of the General Medical Services (GMS) Contract Quality Outcomes Framework (QoF) in Wales, GP practices are incentivised to maintain disease registers.[21] The registers active between 2017 and 2019 included dementia, diabetes, epilepsy, heart failure, hypertension, learning disabilities, mental health, obesity, osteoporosis, palliative care,

rheumatoid arthritis, stroke, atrial fibrillation, asthma, cancer and influenza. These were used to provide an estimate of the prevalence of a disease or health condition amongst patients at a GP practice. Lower super output areas (LSOAs) level indices of multiple deprivation (IMD) for Wales in 2019 were obtained online from the Welsh Government statistics and research portal.[22] The IMD is a metric based on the transformed ranks of geographical areas, weighted and summed across multiple domains of deprivation. This produces an index scaled between 0 and 100, which we rescaled to lie between 0 and 1.

The age and gender breakdown of GP practice registered patients for the years 2017 to 2019 was sourced from the Welsh Government's General Practice Workforce data series.[23] In addition, data on the percentage of registered patients living in a rural area, using the ONS (UK Office for National Statistics) rural/urban classification, were taken from the Public Health Wales Observatory (PHWO) peer group data (2015).[24]

2.3 | Data preparation

The NHS Wales SSP datasets, the disease registers, patient demographic and PHWO data were all linked using the practice ID codes. The GP practice IMD was linked by LSOA codes. The dataset obtained was not complete for all 493 listed GP practices. The NHS SSP GP Practice Analysis, disease register and demographic data series for 2018 and 2017 were used to impute missing data where observations were missing for 2019. Where the number of GPs at a practice was missing, this was obtained through manual searches ($n = 10$). One practice was missing the age and gender breakdown of registered patients and these were estimated based on the age and gender distribution for other practices and the total number of patients. The final dataset included 417 GP practices with complete linked data. The extent of missing data in the remaining 76 practices was considerable, so the data for these practices were discarded. However, there was no evidence of systematic bias in the distribution of these practices among health boards.

In order to investigate the extent to which OACs prescribed in primary care may be a continuation of prescriptions initiated in secondary care, we linked each GP practice to a secondary care unit. To simplify this task, we only considered major hospitals that offer critical care, of which there are 17 in Wales. The easting and northing coordinates were obtained for GP practices and hospitals based on their postcode. We calculated the Euclidean distance between every GP practice and every hospital and then matched each GP practice to their nearest hospital.

Disease register data were included to adjust GP practice prescribing patterns for differences resulting from a different patient case-mix. However, we expect the prevalence of many chronic diseases to be highly correlated and this may result in an ill-conditioned statistical model. To avoid this problem, the complete set of disease registers were mapped onto a set of principal component vectors. This allowed the variation in disease prevalence to be included in statistical modelling without collinearity, which would limit the potential for inference regarding the effects of specific diseases on prescribing. The principal component analysis was perform using the R package *prcomp* and the data were first centred and scaled.

2.4 | Descriptive analyses

The OAC prescriptions of interest were identified by their British National Formulary codes: 0208020Z0 (apixaban), 0208020AA (edoxaban), 0208020Y0 (rivaroxaban), 0208020X0 (dabigatran etexilate) and 0208020 V0 (warfarin sodium). The volume of prescribing was measured using defined daily doses (DDDs), defined by the WHO as the mean maintenance daily dose of a medicine for its principal indication in adults. The DDDs of the five OACs prescribed were summed for each GP practice for all months in 2019. An index of relative prescribing for each GP practice was defined as the number of DDDs of each OAC as a fraction of all OACs prescribed. A proxy measure of a practices' 'workload' was created by taking the ratio of the number of patients and the number of GPs at a practice. This was used to test the hypothesis that busier practices would favour DOACs over warfarin on account of the reduced need for monitoring.

2.5 | Statistical analysis

The aim was to test for systematic differences in patterns of OAC prescribing according to GP practice and area-level differences. The outcome of interest was a vector of five relative prescribing fractions for each OAC which sum to 1 for each practice. An approach was required that can account for the presence of spurious negative correlations between categories of outcome. We assumed that the outcome could be modelled as a Dirichlet random vector and used a generalised linear modelling (GLM)-like framework for estimation of regression coefficients.[25–28] We implemented the Dirichlet regression in the R package *DirichletReg*[25] and R version 3.6.3.

The fraction of the total OAC prescribing volume observed for drug j at the i^{th} GP practice may be written as y_{ij}, where $j = \{1, \ldots, 5\}$ and $i = \{1, \ldots, 417\}$. These are constrained by $\sum_{j=1}^{5} y_{ij} = 1$. The probability density for a Dirichlet random vector $\boldsymbol{y}$ with a corresponding vector of parameters $\boldsymbol{\alpha}$ is given by:

$$\mathcal{D}(\mathbf{y}|\boldsymbol{\alpha}) = \frac{1}{\mathrm{B}(\boldsymbol{\alpha})} \prod_{\mathrm{j}}^{\mathrm{J}} \mathrm{y}_{\mathrm{j}}^{(\alpha_{\mathrm{j}}-1)}$$

The expected values can then be obtained as $E[y_j] = \frac{\alpha_j}{\alpha_0}$ and variance as $Var[y_j] = \frac{\alpha_j(\alpha_0-\alpha_j)}{\alpha_0^2(\alpha_0+1)}$. We used the so-called common parameterisation[25] in which some link function of α is written as a linear combination of predictor variables, as in a GLM. We adopted a log-link and estimation was achieved using maximum-likelihood methods. The Dirichlet distribution cannot accommodate outcome values of zero or one; therefore, where these

occur, the following transformation to the data was applied, to convert an interval of [0,1] to (0,1) where N is the number of observations:

$$y^* = \frac{y(N-1)+1/J}{N}$$

A series of models was estimated of increasing complexity as additional independent variables were added to the five regression equations. The combination of independent variables that best described the observed variation in relative use of OACs was chosen via a process of model selection. Models were compared on the basis of subjective reasoning, fit statistics (Akaike information criterion [AIC] and Bayesian information criterion [BIC]), goodness-of-fit plots, likelihood-ratio tests and prediction error (k-fold cross-validation with $k = 10$). Cross-validation provided a measure of the mean absolute error (MAE) for out-of-sample predictions for each drug, which were then summed to provide a single measure of model prediction accuracy. Model diagnostics also included an assessment of spatial autocorrelation of the residuals using Moran's I-statistic. This was calculated using the residuals from model predictions for each drug and using the R package *ape*.[29]

3 | RESULTS

A summary of the data that was obtained for GP practices operating in Wales in 2019, where data was complete across all linked data sources, is presented in Table 1. The mean number of GPs at a practice was six, but this varied from a minimum of one to a maximum of 17. The location of GP practices ranged from areas of very low deprivation (IMD = 0.02) to areas of high deprivation (IMD = 0.87). The number of patients served by a practice varied considerably: for non-dispensing practices, the number of patients ranged from around 2000 to over 24 000. Practices that dispense served fewer patients on average and dispensing patients typically accounted for just over a

TABLE 1 Summary of the data obtained for GP practices in Wales

	Mean	Minimum	Maximum	St. dev.
All practices				
Number of GPs	6	1	17	3
IMD	0.24	0.02	0.87	0.15
% living rurally	16.97	0.00	99.90	26.06
% patients > 65	20.44	0.24	35.62	5.40
Non-dispensing practices				
Number of prescribing patients	8129	2033	24 863	3888
Dispensing practices				
Number of prescribing patients	4057	117	14 503	3639
Number of dispensing patients	2569	0	9326	1698
Disease register (%)				
Coronary heart disease	3.64	0.04	5.89	0.85
COPD	2.42	0.02	5.57	0.82
Dementia	0.69	0.01	2.94	0.35
Diabetes	6.18	0.59	9.65	1.16
Epilepsy	0.77	0.10	1.59	0.19
Heart failure	1.07	0.02	2.99	0.44
Hypertension	15.98	0.37	25.80	3.36
Learning difficulties	0.48	0.00	3.72	0.28
Mental health	0.98	0.06	2.35	0.32
Obesity	9.84	3.16	20.36	3.26
Osteoporosis	0.25	0.00	2.23	0.27
Palliative care	0.33	0.00	1.86	0.26
Rheumatoid arthritis	0.72	0.02	1.73	0.23
Stroke	2.10	0.03	4.14	0.55
Atrial fibrillation	2.32	0.03	4.47	0.70
Asthma	0.07	0.02	0.12	0.01
Cancer	0.03	0.00	0.06	0.01
Influenza	0.25	0.01	0.39	0.05

IMD: Index of multiple deprivation; COPD: Chronic obstructive pulmonary disease.

third of the total. On average, hypertension and obesity were the most prevalent chronic diseases based on register data; however, there was a wide range in estimates between practices, with diabetes, for example, ranging from 0.59% to 9.65%.

A summary of the relative prescribing for the five OACs by GP practices in 2019 is given in Table 2. On average, warfarin accounted for 37% of DDDs prescribed, while apixaban was the second most commonly prescribed at 32%. The extent to which GP practices had transitioned away from warfarin varied considerably, with the relative use of warfarin ranging from 6% to 64%. There was also a large range in the relative use of each DOAC; use of apixaban, rivaroxaban and edoxaban each ranged from close to zero, up to around 60%. Edoxaban average use was only 6%, but for at least one GP practice edoxaban constituted 59% of all DDDs. The means by health boards indicate greater differences within DOACs than in the use of warfarin. The mean for edoxaban, for example, ranged from 0.1% (Cardiff and Vale University Health Board) to 12.1% (Betsi Cadwaladr University Health Board). The average relative use of edoxaban was higher in dispensing practices at 11.3% of total DDDs, compared with 4.5% for non-dispensing practices.

An exploratory analysis of relationships between variables of interest is summarised in the Pearson correlation matrix in Figure 1. The correlations between relative prescribing of OACs were all negative and of greatest magnitude for warfarin *vs* apixaban, apixaban *vs* rivaroxaban and rivaroxaban *vs* edoxaban. There existed a small positive correlation between the percentage of patients living rurally and the use of rivaroxaban, dabigatran and edoxaban, and only low magnitude correlations for IMD and any relative OAC use. There were small correlations between the percentage of older patients and relative prescribing, this being negative for apixaban and warfarin, and positive for the other DOACs. The months since first use of any DOAC showed only a small negative correlation with apixaban, but moderate positive correlation with the size and percentage of older patients.

Figure 2 presents the Pearson correlation matrix for relative drug use and practice-level disease prevalence. As expected, there is extensive positive correlation between the prevalence of diseases or health conditions. In terms of their correlation with relative drug use, there appears to be a tendency for disease prevalence to be negatively correlated with the relative prescribing of apixaban. Other notable correlations are positive between rheumatoid arthritis and rivaroxaban; diabetes and warfarin; and between COPD and edoxaban.

Complete results of the statistical modelling are provided in the supplementary material, which includes a summary of the main stages of the model development, tables of all regression coefficients and plots of predictions and residuals. The null model, corresponding to the minimal model with each Dirichlet alpha parameter assigned a single value, had a total MAE of 0.294. Health board categories produced a 17.1% fall in total MAE and the addition of nearest major hospital increased this to 26.4%. Although further variables were then included on the basis of other fit statistics (e.g., likelihood ratio tests), these had a negligible impact on the total MAE. Model predictions and residuals for each OAC suggest potential problems for edoxaban and dabigatran components, edoxaban in particular displaying spatial autocorrelated residuals.

The nature of the association between GP practices' prescribing patterns and health boards is difficult to interpret based on the estimated coefficients, as it depends on the values of the coefficients across all alpha parameters. For a visual representation of the association between health boards and prescribing, the marginal effects of predictions are presented in Figure 3. In terms of transitioning to DOACs, this suggests Powys Teaching Health Board is associated with the highest DOAC usage while Aneurin Bevan University Health

TABLE 2 Relative rate of prescribing of each OAC by GP practices in Wales (% of total OAC DDDs in 2019)

	n	Apixaban	Rivaroxaban	Dabigatran	Edoxaban	Warfarin
All Wales GP practices						
Mean	417	31.5	22.9	2.9	5.8	37
Minimum	417	2.1	0.2	0	0	5.8
Maximum	417	64.8	66	22.5	59.4	64.3
Health board						
Betsi Cadwaladr University Health Board	105	31.9	16.2	4.3	12.1	35.5
Powys Teaching Health Board	17	35.9	27.1	2.2	7.4	27.4
Hywel Dda University Health Board	50	29.8	33.5	2.4	1.1	33.2
Aneurin Bevan University Health Board	77	26.3	22.9	1.0	8.7	41.0
Cardiff and Vale University Health Board	62	40.0	22.0	2.6	0.1	35.2
Cwm Taf Morgannwg University Health Board	55	26.1	27.4	3.6	3.8	39.0
Swansea Bay University Health Board	51	34.3	20.6	3.0	1.4	40.7
Dispensing status						
No	341	32.2	23.0	2.7	4.5	37.6
Yes	76	28.6	22.2	3.8	11.3	34.2

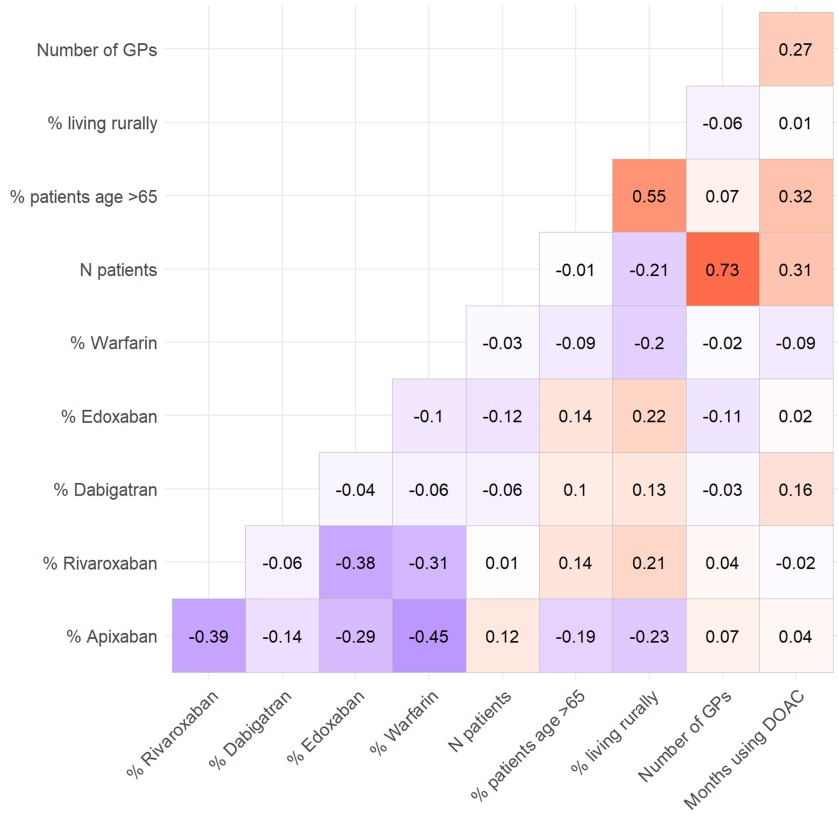

FIGURE 1 Pearson correlation matrix for measures of the relative prescribing proportion of each OAC and GP practice, patient and area-level characteristics. IMD, Welsh index of multiple deprivation

Board the lowest, after adjusting for other variables. We further find evidence for systematic differences between GP practices based on their nearest major hospital, and the corresponding marginal predictions are shown in Figure 4. The nearest hospital associations imply a variation in warfarin use of between 29% and 42% of all DDDs or, for edoxaban, of between 5% and 21% of all DDDs.

The final set of marginal effects, shown in Figure 5, are for a selection of the continuous variables included in the final model. While some evidence of associations was found between these continuous predictors and prescribing patterns after health board and hospitals were included in the model, the improvements this yielded in out-of-sample prediction error were very small. Figure 5 indicates that the magnitude of any effect for an individual variable across its entire range is also small. The results suggest, counterintuitively, that GP practices with a higher ratio of patient numbers to GP number tend to use relatively more warfarin. As expected, the longer the length of time since DOACs were first used, the lower the relative use of warfarin tended to be.

4 | DISCUSSION

In this study we applied novel methodology to examine the variability in the primary care prescribing of OACs in Wales for the year 2019. Considerable variation was observed between GP practices in their use of each of the five OACs as a fraction of their total OAC prescribing. Prescribing behaviours appear to be related to a GP practice's health board and also their nearest major hospital. The differences that these associations imply, based on model predictions with continuous variables fixed at their mean and categorical variables fixed to a reference level, are substantial. For health boards, the marginal predictions for warfarin ranged from 28% to 47%, and for nearest hospital from 27% to 42%. Additional variables were also included in the model, such as the principal components scores from disease register data and the percentage of patients living rurally; however, these led to very limited improvements in model goodness-of-fit metrics.

Systematic differences between health boards were expected since these may issue their own guidance regarding the recommended use of OACs within their jurisdictions. Different policies could result from differing interpretations of the evidence on safety and effectiveness; although national guidance exists with the aim of reducing this variation.[7,8] There could also be local/regional arrangements in relation to pricing, discounts or rebates associated with specific DOACs leading to differences in their usage. Some English CCGs recommend particular DOACs as first-line and this was shown to be associated with the level of prescribing of that DOAC.[2] It is likely that a similar association exists in Wales, but we were not able to identify preferred DOACs for Welsh health boards.

We had hypothesised that there would be an association between OAC prescribing in primary and secondary care within the same locality. To investigate this, major hospitals—defined as those with critical care units—were identified, and matched to GP practices according to the minimum Euclidean distance. The statistical modelling indicated an independent effect based on nearest hospital. Data

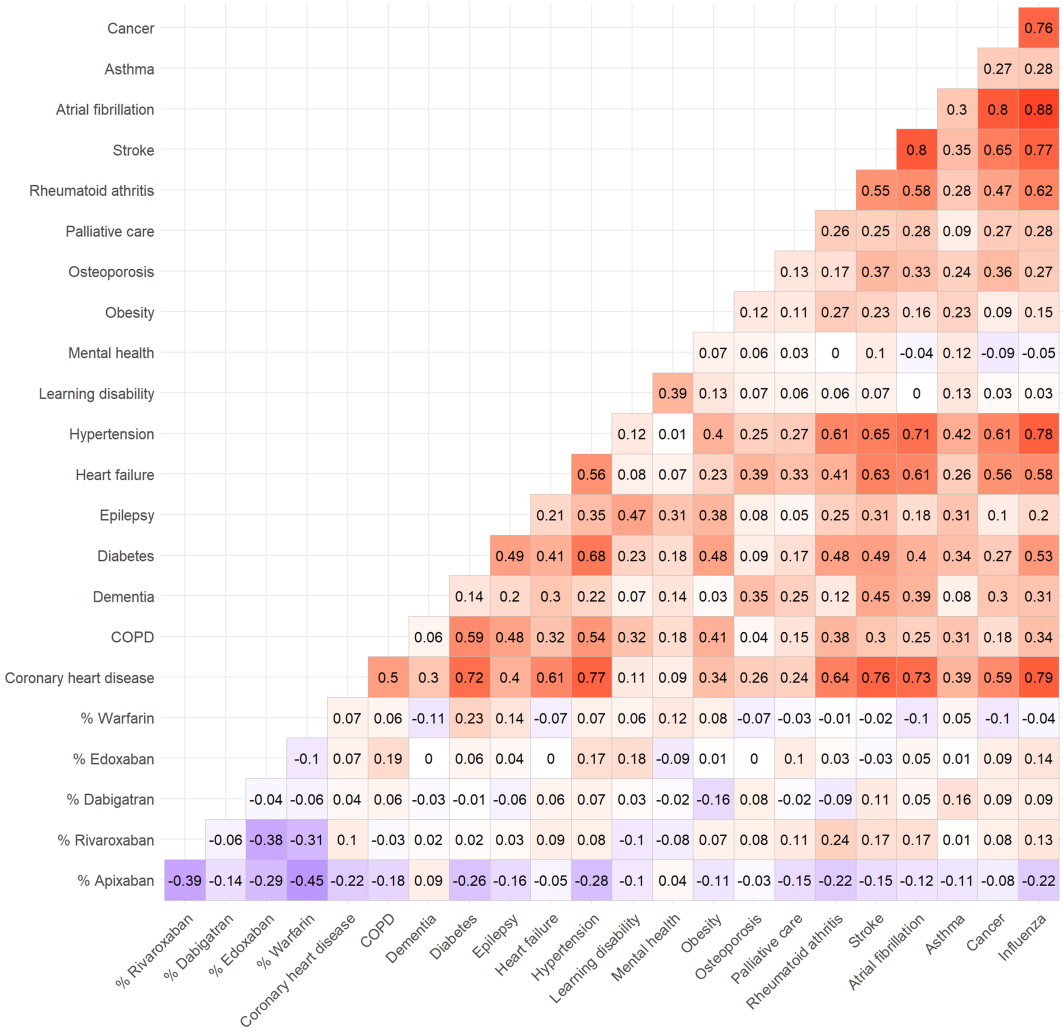

FIGURE 2 Pearson correlation matrix for measures of the relative prescribing proportion of each OAC and disease or health condition prevalence estimated using disease register data

from GP practice disease registers were included in the analyses in order to adjust for patient case-mix when estimating the association with other factors such as health board and nearest major hospital. The use of principal component scores provided advantages in model development but challenges in assessing the associations for specific diseases. It is worth noting, however, that the addition of these principal component scores had a negligible impact on model goodness-of-fit metrics.

Loo et al. investigated the relationship between clinical characteristics and the choice of initial OAC using a large patient dataset for England.[1] They included patient comorbidities and risk factors that overlap considerably with the disease registers used in the current study. Evidence for systematic differences between DOACs *vs* VKAs was found for patients with a history of stroke or cardiovascular conditions (e.g., peripheral vascular disease, congestive heart failure and coronary artery disease), but not for other non-cardiovascular conditions (e.g., diabetes). Since choice of OAC should be based primarily on clinical factors, we might have anticipated that the prevalence of cardiovascular diseases would be related to the relative use of the various drugs. The limited extent of the association between disease register data and OAC choice, suggested by our study, is more likely to be due to limitations in the data than disease not being a major factor in decision-making.

Our study benefited from the application of robust statistical methods, adjusting for known confounders and acknowledgement of regional differences. Decision-makers, pharmaceutical advisors and practice pharmacists rely routinely on analyses of prescription data to inform policy and clinical decisions, but these analyses are largely without consideration of the biases inherent in observational data. We are not aware of Dirichlet regression having been previously used to analyse prescribing data, nor in pharmacoepidemiology research more generally. This approach is well suited to situations where the interest is in the choice prescribers make when there are multiple, clinically comparable treatment options available for given indication(s) and could, therefore, have a wide range of applications. Multivariate statistical analyses that do not account for the

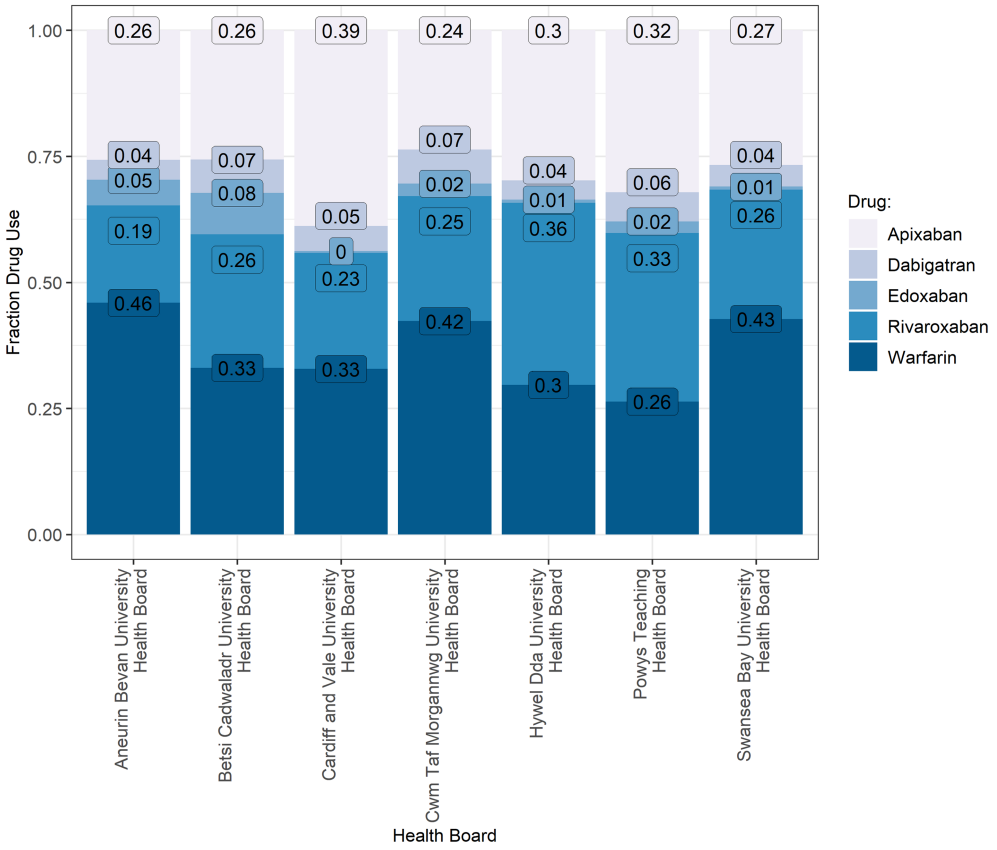

FIGURE 3 Marginal predictions for relative drug use within each health board. These values were obtained from the statistical model using continuous independent variables fixed at their means, with dispensing status set to "not dispensing" and nearest major hospital set to "Princess of Wales Hospital"

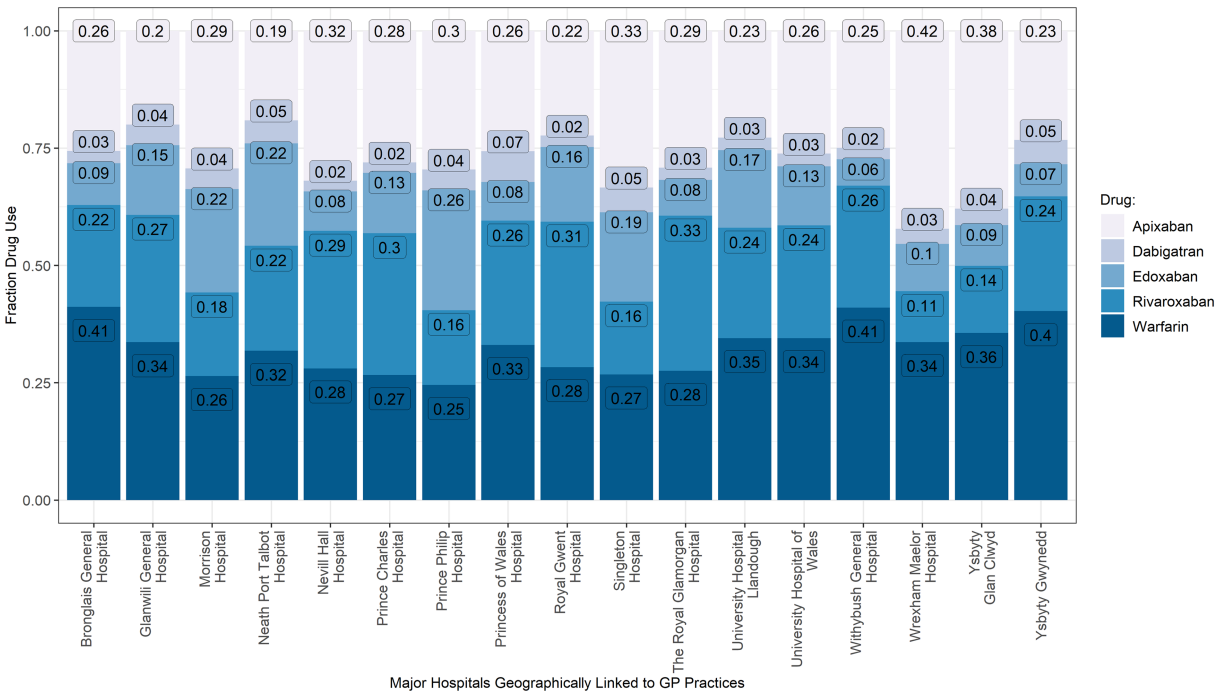

FIGURE 4 Marginal predictions for relative drug use according to nearest major hospital. These values were obtained from the statistical model using continuous independent variables fixed at their means, with dispensing status set to "not dispensing" and health board set to "Betsi Cadwaladr University Health Board"

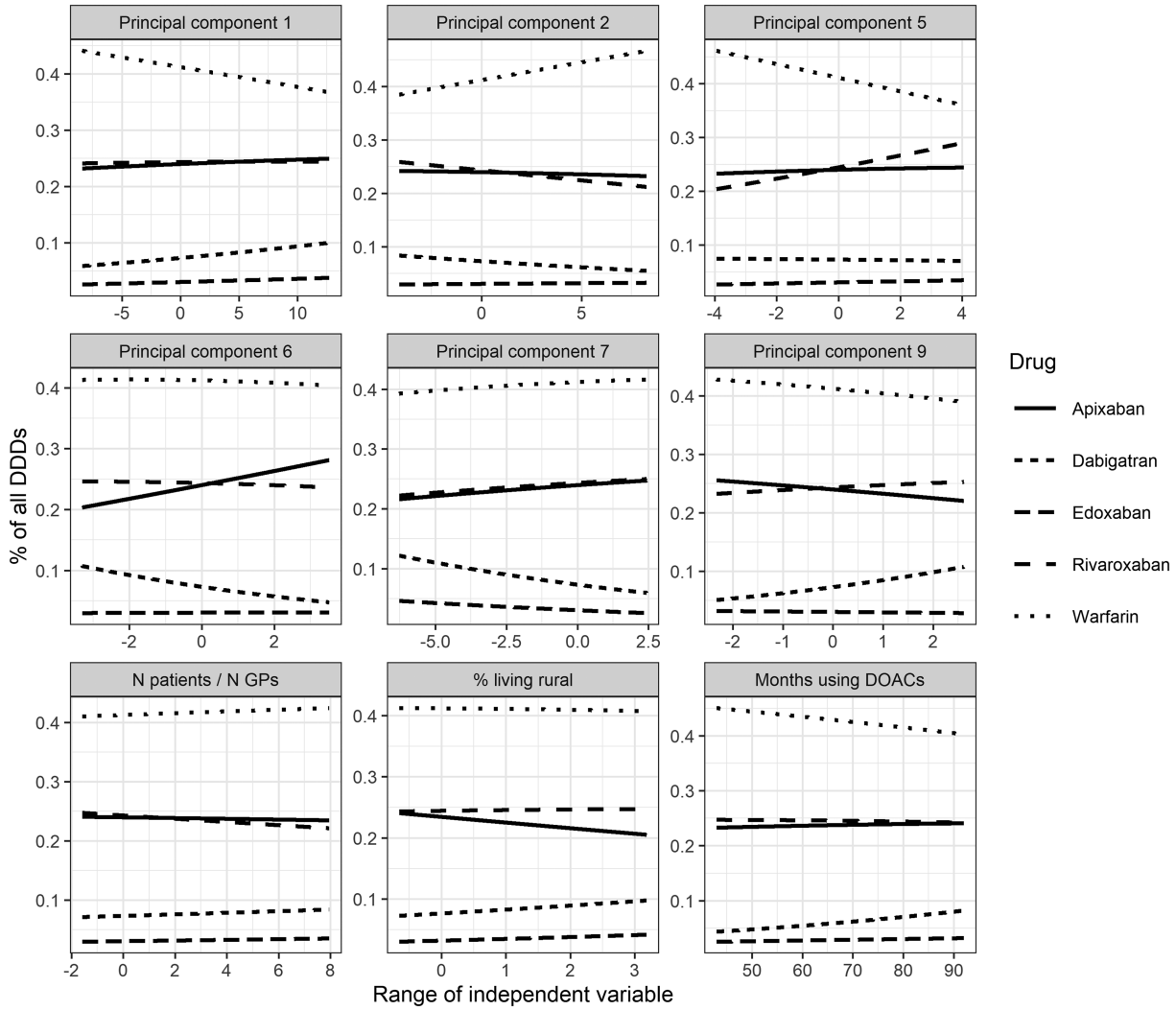

FIGURE 5 Predicted marginal effects for continuous independent variables across the range of each. Categorical independent variables fixed at reference values: health board = "Cwm Taf Morgannwg University Health Board"; Closest major hospital: "Princess of Wales Hospital"; Dispensing status = "no"

constrained nature of such data risk results being affected by the intrinsic spurious negative correlation between outcome categories.[30] The main alternative to Dirichlet regression for compositional data is applying a transformation followed by log-ratio analysis.[31] Drawbacks to this approach include that, owing to the transformation, parameter estimates become difficult to interpret in the original space and are affected by Jensen's inequality when untransformed.

Our research was strengthened by the multiple data sources, which were linked to create a rich dataset containing many features of GP practices that may influence prescribing behaviour. While similar studies have tended to have focused on a specific category of potential predictors such as disease diagnoses,[1] health administrative units[2] or dispensing status,[32] we have been able to combine data on all of these in a single analysis. Thus, we have, to a certain extent, been able to disentangle the various impacts of hospital catchment, health board, dispending status and disease prevalence as well as others, in a single analysis.

There were, however, some limitations to the linked data we obtained. For example, disease registers may not include all eligible patients and the variability in completeness across practices is not known. Moreover, the disease registers do not include all potentially relevant conditions, such as chronic kidney disease. In assessing the relationship between primary and secondary care, we did not include data on hospital prescribing, nor did we include all hospitals where OACs may be initiated, and matching on least Euclidean distance may not accurately reflect hospital catchment areas. We included deprivation in this study via the scaled IMD scores; however, since this is based on ranks and is not itself a measure of deprivation, these results offer limited insights into the relationship between deprivation and prescribing. We have no knowledge of the characteristics of patients receiving OAC prescriptions, including the indication for prescribing, and there are differences in the licensed indications of OACs. The approach we have taken may be better suited to the detection of trends which

require further detailed analysis to elucidate the underlying mechanisms of cause and effect.

In terms of the methods used in the statistical analysis, there may have been advantages in treating health board and nearest critical care unit variables as random effects. We did not use Dirichlet mixed-effects models[27] since these cannot be readily implemented in standard statistical software.[30] Furthermore, the prescribing data contained a fraction of zeros for two drugs and these two categories were the least well described by the statistical model. Zero-adjusted Dirichlet regression[26] may be an option, but again is not readily available in standard statistical software. For variables other than area-level effects, our model assumed a constant effect for all GP practices throughout Wales. This simplifying assumption may not necessarily be valid; for example, there may be an interaction between dispensing status and health board, perhaps reflecting the level of rurality. We did consider separate models by health board or interaction terms, but this would reduce the statistical power considerably. Finally, there are limitations to the conclusions that can be drawn from aggregate data analysis such as this, as opposed to patient-level analyses.[33]

In conclusion, while the differing properties and prices of the OACs means that variation in prescribing patterns between GP practices is to be expected, the extent of the variation observed for practices in Wales leads us to question whether this represents the clinically optimal use in all cases. The evidence this study provides for systematic variation by health board and based on nearest major hospital also raises concern that factors other than patient clinical characteristics and preferences are strongly influencing prescribing decisions. We would consider there to be value in future research, aiming to provide insights into the mechanisms underlying this variation, in order to assess the extent to which this variation is clinically justified.

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COMPETING INTERESTS

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

AUTHOR CONTRIBUTIONS

DHM and DAH made substantial contributions to the conception, design, acquisition of data, analysis and interpretation of data; DHM drafted the manuscript and DAH revised it critically for important intellectual content; DHM and DAH gave final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study were derived from the following resources available in the public domain: https://nwssp.nhs.wales/

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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