A real-world exploration into clinical outcomes of direct oral anticoagulant (DOAC) dosing regimens in morbidly obese patients using data-driven approaches

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Abstract

Introduction

The clinical outcomes of direct oral anticoagulant (DOACs) dosage regimens in morbid obesity are uncertain due to limited clinical evidence. This study seeks to bridge this evidence gap by identifying the factors associated with clinical outcomes following the dosing of DOACs in morbidly obese patients.

Method

A data-driven observational study was carried out using supervised machine learning (ML) models with a dataset extracted from electronic health records and pre-processed. Following 70%:30% partitioning of the overall dataset via stratified sampling, the selected ML classifiers (e.g., random forest, decision trees, bootstrap aggregation) were applied to the training dataset (70%). The outcomes of the models were evaluated against the test dataset (30%). Multivariate regression analysis explored the association between DOAC regimens and clinical outcomes.

Results

A sample of 4,275 morbidly obese patients was extracted and analysed. The decision trees, random forest, and bootstrap aggregation classifiers achieved acceptable (excellent) values of precision, recall, and F1 scores in terms of their contribution to clinical outcomes. The length of stay, treatment days, and age were ranked highest for relevance to mortality and stroke. Among DOACs regimens, apixaban 2.5mg BD ranked highest for its association with mortality, increasing the mortality risk by 43% (OR 1.430, 95% CI: 1.181, 1.732, p=0.001). On the other hand, Apixaban 5mg BD reduced the odds of mortality by 25% (OR 0.751, 95% CI: 0.632, 0.905, p=0.003) but increased the odds of stroke events. No clinically relevant non-major bleeding events occurred in this group.

Conclusion

Data-driven approaches can identify key factors associated with clinical outcomes following the dosing of DOACs in morbidly obese patients. This will help design further studies to explore safe and effective DOAC doses for morbidly obese patients.

Key Points

- Data-driven analysis of electronic health records using machine learning and multivariate regression model provided valuable insights into DOAC dosages in morbidly obese patients
- The decision tree and random forest accurately identified factors contributing to the clinical outcomes in morbidly obese patients receiving DOACs.
- Apixaban 2.5mg BD regimen increased the mortality risk by 43% in morbidly obese patients. Conversely, Apixaban 5mg BD regimen reduced the odds of mortality by 25% but increased the odds of stroke events.

Keywords: Apixaban; direct oral anticoagulants (DOACs); decision trees; electronic health records (EHR); machine learning; artificial intelligence; morbidly obese; mortality; random forest; rivaroxaban; stroke

1.0 Introduction

Apixaban, rivaroxaban, edoxaban, and dabigatran are direct oral anticoagulants (DOACs) currently prescribed in National Health Service (NHS) England following their regulatory and marketing approval. These medicines have recently gained prominence as the preferred agents for stroke prevention in atrial fibrillation (AF) and management of venous thromboembolism, VTE (including deep vein thrombosis (DVT), and pulmonary embolism (PE)). Due to their predictable pharmacokinetic profile, reflected in their convenient fixed dosage regimen, minimal monitoring requirements, fewer interactions, broader therapeutic index, and non-inferior safety and efficacy profile, DOACs have previously gained first-line status occupied by warfarin [1,2].

DOACs are not devoid of limitations [3], including limited dosing options (little room for precise tailoring of doses) for patients with extreme weights [4]. In addition, there is uncertainty about safety and efficacy outcomes for the fixed dosing regimen in special populations due to the poor representation of these groups in landmark clinical trials [2]. Therefore, current guidelines like the *International Society of Thrombosis and Haemostasis Scientific Standardisation Committee ISTH SSC* limit the use of DOAC in patients with a body mass index (BMI) greater than 40 kg/m^2 [5].

Obesity (BMI ≥ 30 kg/m^2) is a massive burden on health systems globally, including in the United Kingdom, and there is a high prevalence rate among adults in England [4]. It is a risk factor for numerous illnesses, notably cardiovascular diseases such as AF and VTE; the population of morbidly obese patients on DOACs therapy is increasing dramatically [6]. For these cohorts, optimising the dosage regimen is a complicated balancing act as clinicians prefer to prescribe DOACs with caution to minimise the risk of strokes or bleeding events [7]. Full consensus on DOAC prescribing for morbidly obese patients has not been reached as yet due to conflicting evidence, as some clinical studies recommend the use of DOACs in morbidly obese patients (citing the obesity paradox) [7,8,9,10,11]. In contrast, others still advocate for alternatives like warfarin [12,13].

Machine learning (ML) is a branch of artificial intelligence that derives rules (functions) from numerous inputs/examples (big data) to identify important features in novel instances accurately. There has recently been increasing popularity in using such data-driven techniques (for example, support vector machines, ensemble learners, and artificial neural networks, among others) in optimising the doses of several medications [14, 15, 16, 17, 18]. Anticoagulants are not an exception to this trend; for instance, the optimisation of warfarin dosing has been explored to demonstrate precision medicine [19, 20, 21, 22]. There is no doubt that there is enormous potential when tailoring the dose of DOAC for special populations—notably morbidly obese patients—using machine learning techniques. Moreover, machine learning is not limited to the prediction of routine diagnosis but also the mapping of factors contributing to optimal clinical outcomes like mortality, cardiovascular events, and hospital readmissions [23, 24, 25].

Given the uncertainty in the dosing requirements of DOACs in morbidly obese populations, this study aims to identify the machine learning algorithm best suited for identifying important features according to their importance in contributing to outcomes (e.g., mortality, stroke) among patients receiving DOAC therapy—based on the analysis of EHR data. This could help in designing further studies to explore safe and effective DOAC doses that can be prescribed to morbidly obese patients.

2.0 Materials and methods

Study design, population, and data collection

This data-driven observational cohort study was carried out in Huddersfield Royal Infirmary (HRI) with data from Calderdale and Huddersfield Foundation NHS Trust (CHFT) Hospitals. From the electronic health records (EHR), we retrospectively identified adult patients (both male and female above 18 years) who were on treatment with DOAC (treatment for one day or less was excluded) for the 1) management or prevention of ischaemic stroke in AF, 2) treatment and prevention of VTE (deep vein thrombosis or pulmonary embolism) between May 1, 2017, and October 2021. In addition, we excluded outpatients and patients admitted to the maternity ward. Patients that met the inclusion criteria were drawn from different wards across the CHFT hospitals (for example, general medicine, elderly, cardiology, respiratory medicine, and stroke wards). They were either admitted to these wards directly or transferred to them.

Given that most patients had several events (treatment episodes), we chose the last treatment (dose of medication) the patient received (last treatment encounter) to reflect the stable or maintenance dose. Also, we only considered patients who received uniform treatment throughout; patients whose treatment was switched were excluded from studying the true association of a particular DOAC therapy with clinical outcomes.

For each patient, demographics (e.g., age, gender, ethnicity), clinical variables (e.g., obesity status, height, weight, chronic kidney disease status, bleeding risk, and VTE risk (using the hospital's local risk assessment tool), comorbidities), and medication (e.g., apixaban, rivaroxaban, edoxaban, and dabigatran), DOAC treatment (in days and years), medication dose, and the indications, respectively, were extracted from the EHR as continuous or categorical features.

The outcomes included all-cause mortality (deceased), length of stay (in days), clinically relevant non-major bleeding (CRNMB) event(s) (in AF and non-surgicanl patients), ischaemic stroke, any thromboembolic events, and the number of emergency admissions (any hospitalisations post-DOAC treatment). We have used International Society on Thrombosis and Haemostasis (ISTH) definition of clinically relevant non-major bleeding that defined CRNMB as 'any sign or symptom of hemorrhage requiring medical intervention by a healthcare professional or leading to hospitilisation or increased level of care or prompting a face to face evaluation [26]. The primary outcomes were CRNMB, all-cause mortality, ischaemic stroke and any thromboembolic events, while secondary outcomes were the length of stay, and the number of emergency visits.

Ethical approval was obtained from the University of Huddersfield Ethics Committee (reference number: SAS-SREIC 21.7.21-7). CHFT granted data access for the study following training and compliance with Information Governance (IG) protocols. A patient consent waiver was applied to the study, given that the data from the electronic health records were deidentified and were used for retrospective analysis (simulated modelling).

Cohort selection and data cleaning

The Hospital's informaticist applied structured queries on the EPR to extract the feature-rich dataset (reports) meeting eligibility criteria for additional data analysis. To guarantee that the extracted data were in an analysis-ready format, they were anonymized and pre-processed (cleaned).

BMI (calculated by dividing weight in kg by the square of height in meters) was the body size descriptor adopted in the study; BMI classification followed the National Institute for Health and Care Excellence (NICE)/ National Health Service (NHS) standard. This was encoded accordingly i.e., less than 18.5

(underweight) = 1; 18.5 – 24.9 (normal) = 2; 25 - 29.9 (overweight) = 3; 30 - 39.9 (obese) = 4; 40 and above (severe/morbid obesity) = 5.

Data pre-processing is the crucial step in the ML pipeline. Irrespective of the power of an ML algorithm, low-quality data would result in unrealistic results. Removing irrelevant and duplicate data, standardised capitalisation of text (either low or upper case), and handling missing values and human errors are the standard data cleaning steps. We encoded long narrative text (e.g., the clinical notes in the *indication* field). Categorical features like gender, race, CRNMB/bleeding risk, and stroke/stroke risk were also encoded via the label encoding method. Feature engineering was guided by domain (clinical) knowledge. The number of features was trimmed from 49 to 26 (redundant or unnecessary features were excluded), and some features were modified, making them more informative.

Missing data of significant count was labelled unknown, while those without significant count (less than 5% of the total sample) were removed. For the (estimated glomerular filtration rate (eGFR) column, missing values were replaced with the average value (imputation of mean); eGFRs *>90* were labelled as *100*); For missing values in the BMI column, we replaced them with their calculated BMI using the height and weight of the patients. Height and weight features contained significant human errors. For instance, in the height column, more than 12,000 values had incorrect decimal points, resulting in many outliers. Therefore, the values were corrected using the weight and BMI feature to recalculate the BMI. Other aspects of data cleaning included normalising and scaling variables.

Statistical analysis

Preliminary statistical techniques were applied to test the normality of the distribution variables extracted for the study. Descriptive statistics were used to summarise the continuous data (e.g., mean, median, mode, standard deviation) and categorical data (frequencies/proportion); carry out the intracohort comparison. Furthermore, a correlation between the variables respectively was assessed using Pearson's test. The significance level was set to $p<0.05$. The analysis was completed in two phases. In the first phase, machine learning algorithms were developed and used to identify important features contributing to a specific outcome. In the next phase, multivariate regression models were conducted to examine the association between DOACs doses and outcomes. The important features identified using ML algorithms were entered as confounders in the multivariate regression models. This step provided a strong rationale for selecting relevant covariates in multivariate regression models to examine the statistical associations.

Machine learning workflow

The experiments were performed on a high-performance computing (HPC) machine with 64 gigabytes (GB) RAM and a Core i5 CPU at 4.10 GHz. The workflow of the experiments is shown in **Figure 1**.

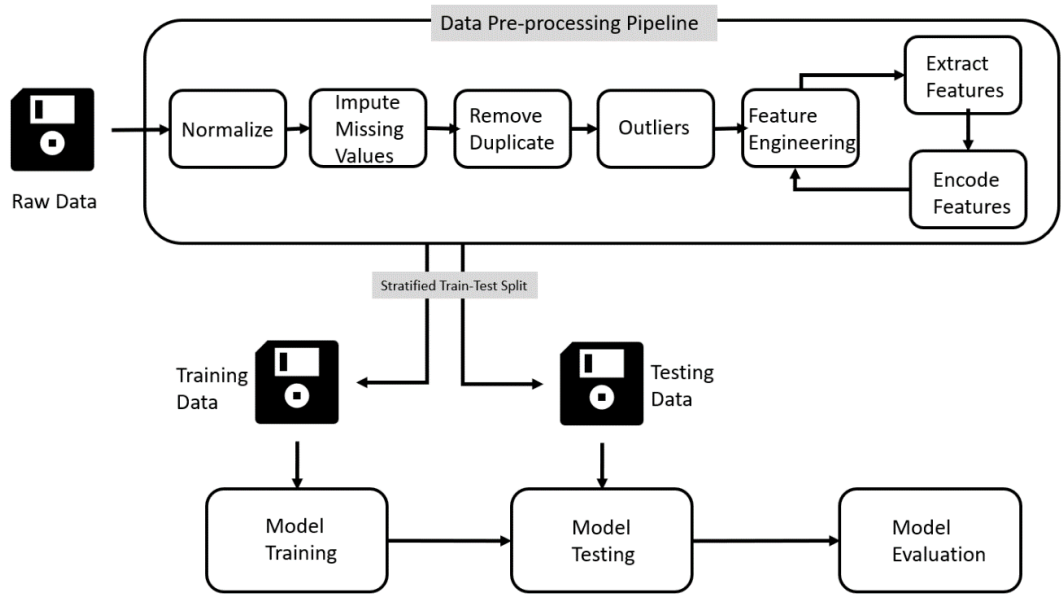

Figure 1. DOACs: Machine learning experimental workflow

The raw data extracted from multiple sources was pre-processed and cleaned at various stages. First, the clean data were split into 70% training and 30% test subsets using stratified sampling to ensure the same target class distribution. Then, classification models were trained using the training data and tested on the held-out unseen testing data. Finally, the models were evaluated on various metrics, including accuracy, precision, recall, F1-score, and confusion matrix. Additionally, various model-specific investigations were employed to understand the model's decision-making process better.

Model development and validation

ML algorithms (Decision trees, Bootstrap Aggregation (Bagging), Random Forest (RF), K-nearest neighbours (KNN), Logistic Regression, Gradient Boosting classifier, and support vector machine (SVM)) were implemented on the curated data set using the open source Scikit-Learn library. Meanwhile, a 70% sample (randomly selected) was assigned as a training cohort for training the ML models; 30% were reserved as a holdout test set for model evaluation. The held-out data remained unseen throughout the model training (i.e., never used for hyperparameter tuning). Finally, the dataset was split into training and test subsets using stratified sampling that ensured the same target class distribution.

The models were trained extensively on various hyper-parameter settings of each model. In addition, various model evaluation criteria such as accuracy, precision, recall, F1-score, and confusion matrix were employed to test the model from different aspects thoroughly. The final trained version of each model was tested on the held-out testing dataset.

Model evaluation metrics

Various classification model evaluation metrics were employed for model testing. A brief description is provided here.

Confusion Matrix

A confusion matrix is a table for test data that compares the actual and predicted values. For example, for a simple binary classification problem, a confusion matrix contains true positive (TP), true negative (TN), false positive (FP), and false-negative (FN). TP and TN are the predictions by the model that matched the actual values (ground truth), whereas FP (type 1 error) and FN (type 2 error) are the wrong predictions by the model.

Accuracy

Accuracy is the measure of all correct predictions of the model. It is given by

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN}$$

Precision

Precision represents how many correctly predicted records by the model are true. It is given by,

$$Precision = \frac{TP}{TP + FP}$$

Recall

Recall refers to how many true positives were predicted by our model. It is given by,

$$Recall = \frac{TP}{TP + FN}$$

F1-score

F1 is the harmonic mean of precision and recall. It is given by,

$$F1 = 2 * \frac{Precision * Recall}{Precision + Recall}$$

3.0 Results

Based on the eligibility criteria, n = 4,275 samples were extracted from the overall dataset (n = 97,413) identified from the EHR. Firstly, the dataset was partitioned into training and test sets (70:30)—2,993 and 1,282, respectively. The features selected were n = 24; six new features were created following the conversion of some continuous features to categorical features to produce more detailed statistical analyses.

Table 1: Characteristics of the study sample

Variable	Total patients (n = 4,275)
Age (yr), mean ± SD	69.25 ± 11.79
Gender (n, % female)	2,432 (56.90)
Ethnicity %	
White	3,915 (91.60)
BAME	166 (3.9)
Other	194 (4.5)
Medication %	
Apixaban	**3,604 (84.3)**
2.5 mg BD	1,193 (27.9)
5 mg BD	2,319 (54.2)
10 mg BD	92 (2.2)
Dabigatran	**4 (0.1)**
110 mg BD	4 (0.1)
Edoxaban	**7 (0.2)**
30 mg OD	6 (0.1)
60 mg OD	1(0.0)
Rivaroxaban	660 (15.4)
10 mg OD	18 (0.4)
15 mg OD	256 (6.0)
20 mg OD	386 (9.0)
***Main Indication(s)**	
Stroke prophylaxis	3,512 (82.2)
Recurrent VTE prophylaxis	18 (0.4)
VTE treatment	348 (8.1)
Unclassified	397 (9.3)
Treatment days, mean ± SD	508.51 ± 460.671
Treatment years	
1 yr.	2,081 (48.70)
2 yrs.	886 (20.70)
3 yrs.	615 (14.40)
4 yrs.	532 (12.40)
5 yrs.	161 (3.80)
CKD (eGFR < 60)	2,103 (49.20)
Comorbidity (yes)	3,425 (80.10)
Bleeding risk (yes)	2,898 (67.80)
VTE risk (yes)	4,220 (98.70)

*NB: The indications Of DOACs overlap across dose regimens

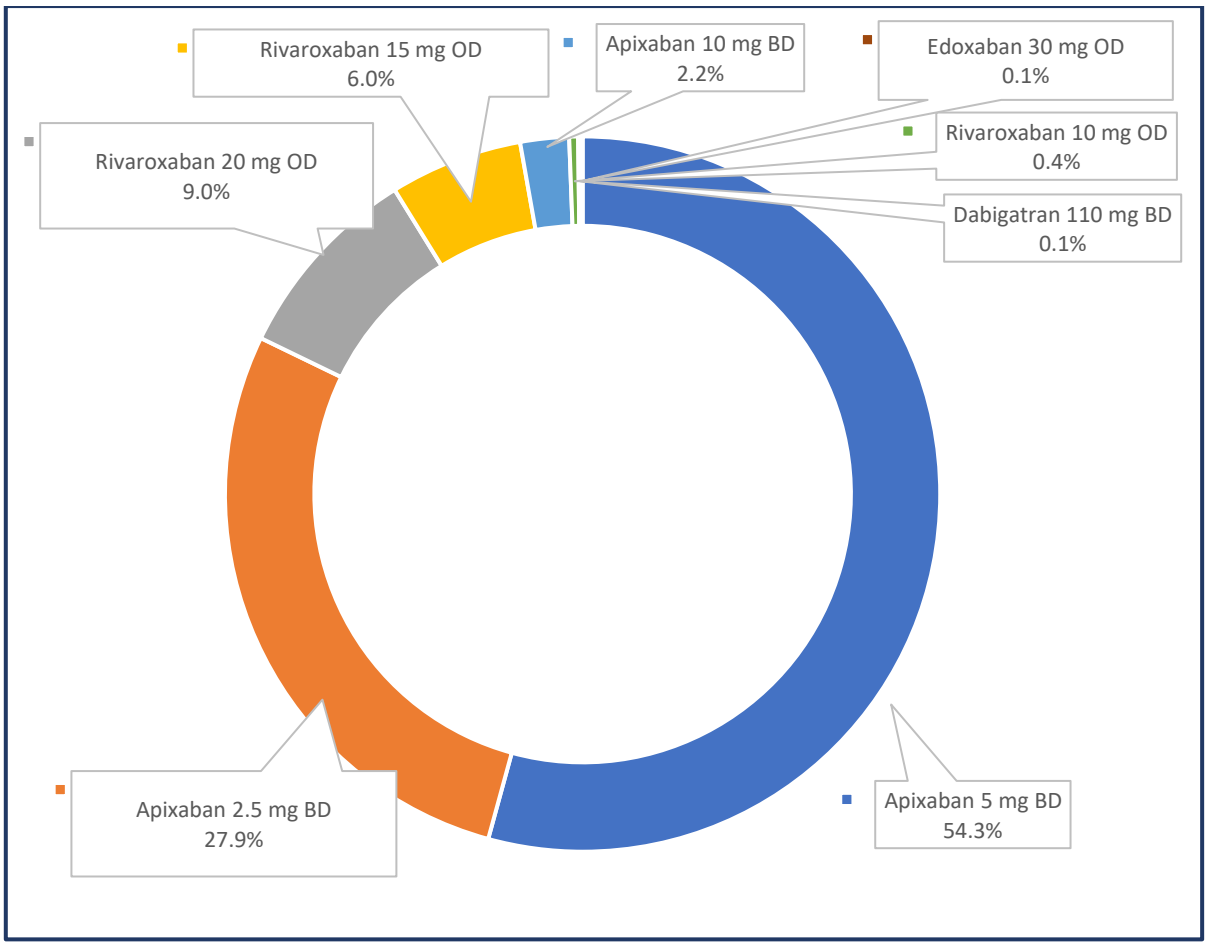

Figure 2: Proportions of morbidly obese patients prescribed various DOACs by a dosage regimen

The exposure variables include patient demographics, direct oral anticoagulant administered, eGFR, bleeding risk and VTE risk, treatment days/years, and comorbidities—these were summarised in **Table 1**; the outcome variables include the length of stay, and the number of emergency admissions, all-cause mortality, CRNMB, and ischaemic stroke. **Figure 2** summarizes the proportions of individual doses of different DOACs prescribed to morbidly obese patients.

Table 2: The overall accuracy of each of the ML classifiers used in the study

Machine learning algorithm	Accuracy
Decision Trees	0.979
k Nearest Neighbour	0.981
Random Forest	0.983
Bootstrap aggregation (bagging)	0.986
Logistic regression	0.707
Gradient Boosting classifier	0.706
Support vector machine	0.706

Training of ML models

The experiments aimed to find the classification model most suitable for our morbidly obese patients dataset. Seven (7) well-known ML classification models were trained on the cleaned dataset. The seven selected models had different classification criteria (hyperparameters). The models were trained on the same dataset under the same training and testing settings. The accuracy of the models on the test dataset is shown in **Table 2**. Apart from the support vector machine, gradient boosting classifier, and logistic regression, the remaining models achieved excellent accuracy of more than 98%. However, using accuracy as the only evaluation metric could be very misleading, especially when the dataset is imbalanced [20]. Precision, recall, and f1 score values present a much better model evaluation. K nearest neighbours, for instance, achieved an excellent accuracy of 98.1%. However, looking at the precision, recall, and f1-score of KNN showed a different picture of the model's learning. The KNN's evaluation metrics are shown in **Table 3**.

The KNN model, like the poorer performers (support vector machine, logistic regression, and gradient boosting classifier), failed to achieve acceptable precision and recall values for most of the target classes, i.e., apixaban 2.5 mg BD, dose regimens of rivaroxaban, edoxaban, and dabigatran respectively. The poor precision, recall, and f1 score by KNN are due to its non-parametric and lazy learning algorithm. It ignores the underlying data patterns and only considers the data proximity for its prediction (16).

On the other hand, decision trees, random forests, and bootstrap aggregation learned the patterns in the data and made accurate predictions. As a result, they achieved higher values of precision, recall, and F1 scores, as shown in **Table 3**.

Table 3: Performance metrics for the DOAC doses based on different ML models

DOACs	**Precision**				**Recall**				**F1-score**				***Support**
	DTA	RFA	BAA	KNN	DTA	RFA	BAA	KNN	DTA	RFA	BAA	KNN	DTA, RFA, BAA & KNN
Apixaban 2.5 mg BD	0.92	0.96	0.99	0.00	0.90	0.91	0.98	0.00	0.91	0.93	0.98	0.00	601
Apixaban 5 mg BD	0.98	0.99	1.00	0.46	0.99	0.99	1.00	0.62	0.99	0.99	1.00	0.53	11,744
Apixaban 10 mg BD	0.99	0.99	1.00	0.43	0.98	0.99	1.00	0.46	0.98	0.99	1.00	0.44	12,277
Rivaroxaban 10 mg OD	1.00	1.00	1.00	0.00	0.98	1.00	1.00	0.00	0.99	1.00	1.00	0.00	242
Rivaroxaban 15 mg OD	0.97	1.00	1.00	0.00	1.00	0.98	1.00	0.00	0.98	0.99	1.00	0.00	85
Rivaroxaban 20 mg OD	0.92	1.00	1.00	0.00	1.00	1.00	1.00	0.00	0.96	1.00	1.00	0.00	11
Edoxaban 30 mg OD	0.99	1.00	1.00	0.00	0.95	0.99	1.00	0.00	0.97	0.99	1.00	0.00	73
Dabigatran 110 mg BD	0.95	0.97	1.00	0.00	0.95	0.96	1.00	0.00	0.95	0.97	1.00	0.00	1,915

DTA = decision tree algorithm, RFA= random forest algorithm, BAA= bootstrap aggregation algorithm, KNN= K nearest neighbours algorithm.

*Support is the number of records against each class

Identification of features contributing to clinical outcomes

Based on the decision trees and random forest algorithms, the features were ranked according to their importance in contributing to clinical outcomes (**Figures 3 & 4**). For example, the LoS, age, and treatment days ranked highest in contributing to stroke and mortality. The supplementary Figure **S1** shows the feature importance for other outcomes like emergency visits, any thromboembolic events, and CRNMB.

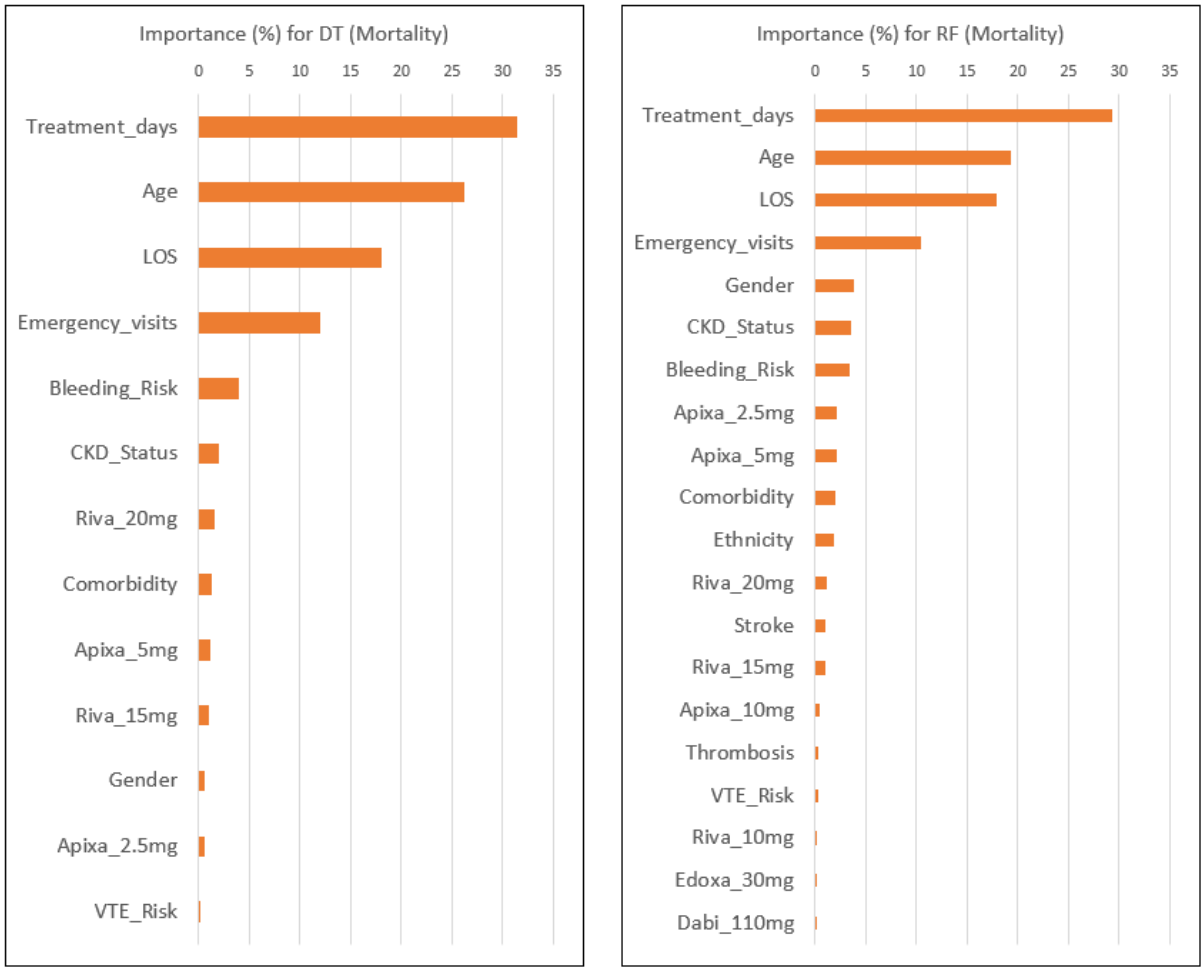

Figure 3: Ranking of features with the morbidly obese patient subgroup according to their importance in contributing to mortality using RF = Random Forest and DT = Decision Trees.

Regarding DOACs dosing regimens, apixaban 5mg BD was the most important DOAC dose feature contributing to stroke with the decision tree and random forest classifier. Apixaban 2.5 mg BD (twice daily) ranked highest with random forest, followed by apixaban 5mg BD and rivaroxaban 20mg OD for their contributions to mortality. With the decision trees classifier, 20 mg OD (once daily) rivaroxaban ranked highest, followed by apixaban 5mg BD and rivaroxaban 15 mg OD. No CRNMB events occurred in the morbidly obese patients.

In the case of any thromboembolic events in morbidly obese patients, edoxaban 30mg OD was the most important feature contributing to any thromboembolic events (with RF), followed by apixaban (2.5mg, 5mg BD respectively) and rivaroxaban (15mg and 20mg OD respectively). Among all DOAC doses, apixaban 5mg BD was the most important feature contributing to emergency visits with the decision tree and random forest classifier.

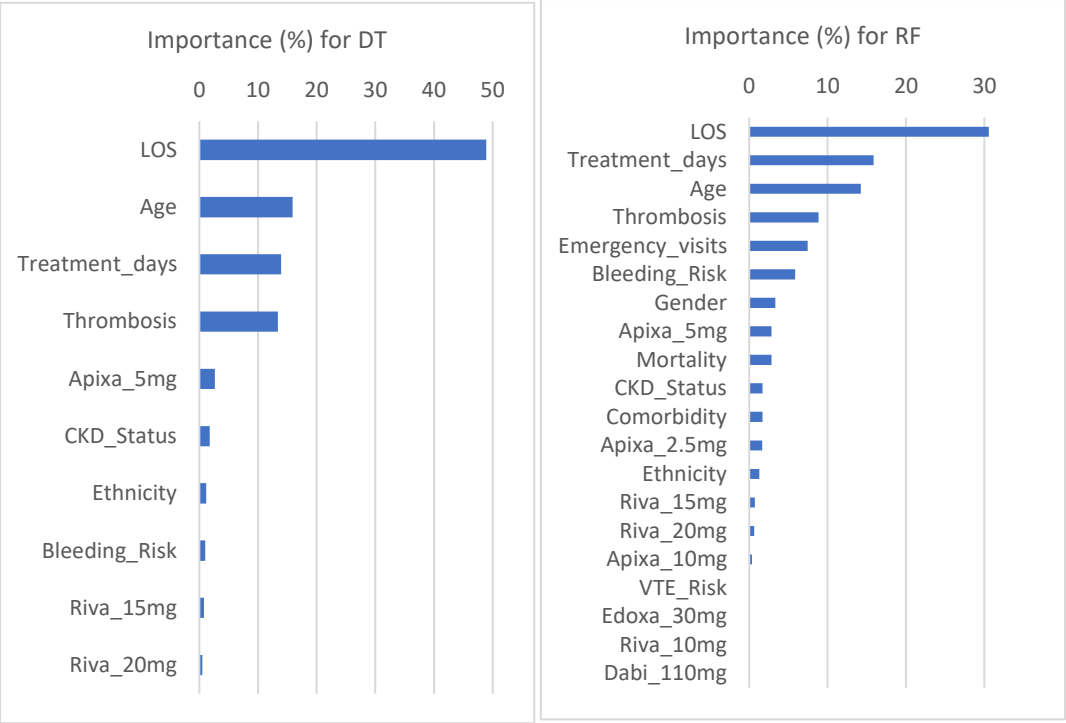

Figure 4: Ranking features with the morbidly obese patient subgroup according to their importance in contributing to stroke using RF = Random Forest and DT = Decision Trees.

The metrics such as accuracy, precision, recall, and F1-score were used to evaluate how well the machine learning models identified important features contributing to a specific outcome. For example, the results for accuracy indicated that the Bootstrap aggregation (bagging) classifier showed the best performance achieving an accuracy score of 98.6% (**Table 2**).

DOACs dosing regimens and clinical outcomes

Tables 4 and 5 present the multivariate regression results. Apixaban 2.5mg BD was associated with increased odds of mortality (OR 1.430, 95% CI: 1.181, 1.1.732, p=0.001), while apixaban 5mg BD was associated with reduced odds of mortality (OR 0.751, 95% CI: 0.632, 0.905, p=0.003). However, the same dose of apixaban (5mg BD) was associated with increased odds of stroke (OR 32.457, 95% CI: 17.083-61.664, p=0.001).

All six patients receiving edoxaban 30mg OD experienced any thromboembolic events; hence regression analysis was not possible. A higher odd of any thromboembolic events in patients taking apixaban 10mg BD (OR 9.108, 95% CI: 3.354 – 24.735, p=0.001) and apixaban 2.5mg BD (OR 2.653, 95% CI: 1.287, 5.468, p=0.008) than patients who were not taking these doses. In multivariate logistic regression, only apixaban 5mg BD and rivaroxaban 20 mg OD significantly reduced the odds of emergency visits (Table 5).

Table 4: Multivariate Logistic regression analysis showing the likelihood of the outcomes (odds ratio) for the morbidly obese patients receiving various DOAC drugs.

Outcome		OR	95% Confidence Interval		*p*-value
			Lower	Upper	
Ischaemic Stroke[a]	Apixaban 2.5mg BD	0.024	0.012	0.046	0.001
	Apixaban 5mg BD	32.457	17.083	61.664	0.001
	Apixaban 10mg BD	2.285	0.495	10.538	0.289
	Rivaroxaban 15mg OD	0.483	0.159	1.468	0.199
	Rivaroxaban 20mg OD	2.122	0.699	6.445	0.184
			95% Confidence Interval		
		OR	Lower	Upper	*p*-value
All-cause Mortality[b]	Apixaban 2.5mg BD	1.430	1.181	1.732	0.001
	Apixaban 5mg BD	0.751	0.623	0.905	0.003
	Apixaban 10mg BD	0.477	0.227	1.001	0.050
	Rivaroxaban 15mg OD	1.097	0.735	1.638	0.651
	Rivaroxaban 20mg OD	1.146	0.771	1.703	0.499
			95% Confidence Interval		
		OR	Lower	Upper	*p*-value
Any thrombo-embolic event[c]	Apixaban 2.5mg BD	2.653	1.287	5.468	0.008
	Apixaban 5mg BD	0.483	0.278	0.840	0.010
	Apixaban 10mg BD	9.108	3.354	24.735	0.001

[a]Stroke variable(s): Length of stay, treatment days, age, thrombosis, bleeding risk, CKD, ethnicity, comorbidity, emergency visits, thrombosis, gender

[b]Mortality variable(s): Treatment days, age, length of stay, emergency admissions, gender, CKD, bleeding risk, comorbidity, VTE risk

[c] Any Thromboembolic event variable(s): length of stay, age, stroke, gender, treatment days, edoxaban 30mg

Table 5: Results of linear regression analysis with DOACs doses as independent variables and length of stay and emergency visits as the dependent variables.

Outcome		Standardised Coefficients	95% Confidence Interval		p-value
			Lower Bound	Upper Bound	
Emergency visits	Apixaban 10mg BD	0.034	0.110	1.249	0.019
	Apixaban 2.5mg BD	0.072	0.274	0.658	0.001
	Apixaban 5mg BD	-0.089	-0.705	-0.331	0.001
	Rivaroxaban 10mg OD	0.024	-0.183	2.330	0.094
	Rivaroxaban 15mg OD	0.046	0.138	0.990	0.009
	Rivaroxaban 20mg OD	-0.065	-1.080	-0.245	0.002
		Standardised Coefficients	95% Confidence Interval		p-value
			Lower Bound	Upper Bound	
Length of stay	Apixaban 10mg BD	-0.004	-3.643	2.668	0.762
	Apixaban 2.5mg BD	-0.031	-2.269	-0.138	0.027
	Apixaban 5mg BD	0.035	0.161	2.243	0.024
	Rivaroxaban 10mg OD	0.031	1.451	15.344	0.018

	Rivaroxaban 15mg OD	-0.008	-2.968	1.751	0.613
	Rivaroxaban 20mg OD	-0.006	-2.663	1.970	0.770

Variable(s) for emergency visits and LoS: Treatment years; age; length of stay or emergency visits; mortality; ethnicity; bleeding risk; stroke; comorbidity; gender; CKD

4.0 Discussion

This was a data-driven observational study in which supervised ML models were used to explore the features contributing to clinical outcomes and the impact of DOAC dosing. Despite slight differences, the results consolidate previous studies, especially on warfarin dosing [27]. Previous studies have shown that clinical and demographic features can be used to optimise medication doses. Our model emphasises the role ML can play in optimising clinical outcomes. Our results showed that it is possible to apply machine learning models to EHR data from real-world patients to optimise clinical outcomes for morbidly obese patients on DOACs

In terms of mapping the dose of DOACs to clinical outcomes in morbidly obese patients, this study is the first of its kind. Furthermore, the study implementation is timely given the rising prevalence of obesity in the UK and associated medication-related problems. Attempts to improve dosing using machine learning have been made in the past, but not for this target patient population, e.g., heart failure patients on digoxin [17].

Use of appropriate ML techniques

The critical clinical features identified in the study are similar to those used to build machine learning models in other studies [28,29]. An example can be found in the ML model adopted by Patel et al. [28] for predicting hospital readmissions for sickle cell patients: length of stay and number of emergency department visits were among the vital outcome features. Likewise, in the model Taylor et al. [29] used to predict mortality in the hospital Emergency Department (ED), in-hospital mortality was a key outcome feature.

Interestingly, the algorithms chosen for the ML study were almost the same as those selected in other ML-based observational studies leveraging EHR: logistic regression, SVM, random forest, KNN, and classification and regression trees (CART). Ensemble methods yielded the highest accuracies, with the bootstrap aggregating (bagging) algorithm giving the best result compared to other models. Essentially bagging is fitting decision trees to the bootstrapped sample (with replacement) of the training data and averaging the predictions. Decision trees have the advantage of minimising the overfitting of the training dataset [30].

Machine learning applications in medical sectors demand fault-free models due to the critical nature of the medical domain. As stated earlier, machine learning models could be misleading if not carefully evaluated and understood, driving the need for further study and sharing of findings. A wrong prediction of clinical outcomes could be misleading, so it is crucial to understand the model's decision-making process. Interpreting the model's decision-making process could increase confidence in ML predictions. Based on the accuracy metric, bootstrap aggregation achieved the highest accuracy of 98.6%, and the random forest was the second best, with a slightly lower accuracy of 98.3%. We selected random forest as the most suitable classifier for estimating the optimal dose. The reason for prioritising random forest over bootstrap aggregation is the model's easy-to-understand internal working. The random forest (RF) consisted of multiple decision trees and made decisions based on the "wisdom of the crowd". RF is more accurate, requires less data scaling, and is better suited to combat overfitting and missing data than decision trees. Though no available studies serve as the point of

reference, our research is a step toward exploring ML-powered clinical decision support systems in the precision dosing of direct oral anticoagulants.

DOACs therapy and clinical outcomes

Figures 2 and 3 ranked the feature's importance in the decision-making process of random forests and decision trees—our model learned the essential underlying features in the dataset, and its results were based on the key factors. Based on the output, the length of stay (LoS), treatment days, and age are the most critical features that need to be incorporated into the model for identifying important features contributing to mortality and stroke in morbidly obese patients. This aligns somewhat with ground truths as age is a risk factor for adverse events (e.g., ischaemic stroke, CRNMB event) due to changes in pharmacokinetics; duration of treatment or hospital admission could improve or worsen clinical outcomes depending on DOAC exposure in the patient.

Cumulatively, the results indicate a positive impact of DOACs on study outcomes in morbidly obese patients. Regression analysis found that the relationship between DOACs and the continuous outcome variables was inconsistent in the morbidly obese cohort. For example, apixaban 2.5mg BD increased the number of emergency visits but decreased the LoS. In contrast, apixaban 5 mg BD increased the LoS but decreased the number of emergency visits. The mean LoS was highest in year 1 for 2.5 mg BD apixaban (30.4 days) and 15 mg OD rivaroxaban (27.4 days) but lowest for 5 mg BD apixaban, 20 mg OD rivaroxaban, and 10 mg BD apixaban (6.6 days, 9 days, and 6 days, respectively) in year 5. The lowest emergency visits occurred in the first year for 15 mg and 20 mg OD rivaroxaban, respectively. The proportion of stroke and any thrombotic events was lower overall for the different doses of apixaban and rivaroxaban, and this could indicate the effectiveness of the doses in the morbidly obese cohort. However, the first two years of treatment with 2.5 mg BD of apixaban were associated with higher mortality, suggesting it may not be safe for complicated cases (e.g., patients with a high risk of stroke or patients requiring long-term DOAC therapy) in the morbidly obese subgroup. Higher mortality was also evidenced for the first year of treatment with 5 mg BD apixaban and 15 mg OD of rivaroxaban, respectively, but they were associated with reduced mortality overall. The individual doses assessed for each DOAC were associated with improvement and deterioration of safety endpoints (e.g., mortality) and effectiveness (e.g., emergency visits and stroke). This is not surprising given the variation between the pharmacokinetics and pharmacodynamics of DOACs across diverse patient groups.

The mixed results from this study reflect previously published evidence by Whittemore et al. [7]. Wu et al. [31] found that a higher BMI was negatively associated with bleeding events and mortality compared to normal BMI for DOACs (i.e., dabigatran and rivaroxaban). This suggests that DOACs were linked to better survival and lower bleeding risk in the morbidly obese (higher BMI) cohort compared to normal BMI patients. This was not the case for thrombosis, as no statistically significant association was reported for the morbidly obese cohort. Furthermore, using a cox proportional hazards model, Weitz et al. [32] reported a lower risk of all-cause mortality in obesity compared to patients with normal BMI. This suggests better safety and effectiveness (obesity paradox). On the other hand, Briasoulis et al. [33] reported an increased risk of all-cause mortality (HR of 1.12, 95% CI: 1.02-1.23) but no significant difference in stroke and bleeding events for morbidly obese patients when apixaban was compared with rivaroxaban. In the morbidly obese cohort, dabigatran was associated with significantly lower all-cause mortality compared to rivaroxaban ($p = 0.001$); apixaban was associated with greater mortality than dabigatran ($p = 0.001$), and rivaroxaban ($p = 0.013$). Lucijanic et al. [13] established that obesity increased the risk (odds) of stroke and bleeding in DOACs overall: dabigatran conferring lower efficacy (higher thrombosis/stroke risk) and Factor Xa inhibitors (rivaroxaban, edoxaban, and apixaban) increasing the odds of bleeding. Potential factors responsible for the

increased risk of bleeding were inappropriate dosage regimens and concomitant interacting medications [34]. It is important to note that a reference to specific DOAC doses was not made in the study (absence of subgroup analysis).

Meanwhile, in the study by Netely et al. [11] and Wang et al. [35], obesity had no significant impact on bleeding or thrombotic events, agreeing with the findings from Aloi et al. [36], Perino et al. [37] and Deitelzweig et al. [38]. However, the authors suggested their findings were due to confounding biases associated with most observational studies. Specifically, other observational studies and RCTs widely suggest that increased BMI in VTE/AF has no significant effect on the safety and efficacy of apixaban. In other words, despite exposure being slightly reduced, no dose adjustment was required [39]. However, this does not rule out that the morbidly obese category had the most incidence of thrombotic events among the BMI classes [8, 9, 40, 41].

In our study, the majority of the patients were on apixaban, similar to the study by Briasoulis et al. [33]. This reinforces the status of apixaban as the most prescribed DOAC in the NHS (between 2017 and October 2022). In addition, the mean age in our study is within the same range as the study by Barakat et al. [1] (74.1 years), which also examined the outcomes of DOACs in patients across different BMI categories—DOACs were linked to a lower risk of bleeding and stroke among the morbidly obese patients. It is worth mentioning that no CRNMB events occurred in the morbidly obese patients.

Interestingly, for the morbidly obese patients who received apixaban, increased odds of mortality were observed for the 2.5mg BD dose. Still, decreased odds were observed for the higher doses (5 mg BD and 10 mg BD) (Table S1). A possible explanation could be the high baseline bleeding risk in the patients receiving lower doses of apixaban (2.5 mg BD), longer duration of treatment (common with prophylactic doses), treatment failure, etc. On the other hand, lower doses of apixaban (2.5mg BD) were associated with increased odds of stroke and any thromboembolic events, while higher doses were associated with higher odds of stroke/any thromboembolic events. Possible reasons for these results could be the severity of the indication, higher risk of stroke/VTE among patients, shorter duration of treatment, insufficient exposure to dose (pharmacokinetic disposition in morbid obesity), etc. Notably, the odds ratio for rivaroxaban and edoxaban were not statistically significant or were omitted altogether. All six patients receiving edoxaban 30mg experienced any thromboembolic events; however, the sample size of patients (on edoxaban) was insufficient in our dataset to draw firm conclusions. It is important to note that more representation is expected in the future due to recent changes in NHS recommendations favouring its use as a first-line (preferred) DOAC for stroke prevention in AF—it has the lowest acquisition cost, and its regimen is once-daily without the need for food. Also, the volume of prescriptions and clinical evidence generated for edoxaban is expected to rise.

Our results add weight to the potential safety and effectiveness of specific doses of DOACs in morbidly obese patients. However, the positive results were inconsistent across all doses and agents of DOACs. Indeed, there is mounting evidence of the safety and effectiveness of DOACs in morbidly obese patients, which is comparable to or even better compared to normal-weight patients [3].

Implications for practice and research

The findings from our study—including conclusions from reviewed literature— suggest that the use of DOACs in morbidly obese patients does not pose significant problems. This gives clinicians some assurance when prescribing medications like apixaban and rivaroxaban. However, there is an urgent need to review the International Society on Thrombosis and Haemostasis Scientific and Standardisation Committee' (ISTH SSC) guidelines on prescribing DOACs for morbidly obese patients

to reflect on current evidence from observational studies. Hopefully, this will be further supported as the evidence from prospective randomised clinical studies becomes available. This implies that more morbidly obese patients in NHS would benefit from DOACs without the constraints of monitoring assays that are in limited supply. In the meantime, morbidly obese patients must still be treated with caution due to the mixed nature of the outcomes from DOACs.

Strengths and limitations of the study

A large sample size rich in relevant predictive features was analysed to improve the generalisability of the model. In addition, real-world data was leveraged in the study. Several limitations could affect the generalizability of the findings. Firstly, this study is largely proof-of-concept and has not been externally validated. We expect that subsequent studies will be refined to ensure external validation and deployment in clinical trials. Secondly, human error in the form of incorrect reporting in EHR by the clinicians/prescribers must not be discounted—as the selection of the wrong indications or incorrect dose from the list of options in the computerised systems undermines the strength of the finding. Periodic crosschecking by humans to ensure accuracy is important. Thirdly, another limitation can arise from potential flaws in the study design. For example, the study was retrospective in design, making it difficult to spot confounders like treatment compliance which may have affected the outcomes—selection bias cannot be ruled out from the method. Fourthly, the input of some variables, such as comorbidity, was not structured or consistent in the EHR to permit exploratory analysis. For those identified, the variety was too wide (for example, diabetes, hypertension, coronary heart disease, cancer, heart failure, CKD, asthma/COPD, osteoarthritis, etc.), making the sample sizes of each comorbidity insignificant. Therefore, we used presence or absence to define it in the curated dataset. Fifthly, regarding the selection of ML models, there are no strict rules for selecting the most suitable machine learning model for a given task. Standard practice is to try all the relevant models and select the most appropriate model that is most accurate by extensive model evaluations. DTs and RFs are preferred over other models, such as SCIGAN (eStimating the effects of Continuous Intervention using GANs), because of their extensive use in relevant medical problems [42]. Next, the study was based on a single trust (CHFT), so there is a need to have EHR data of a wider scale encompassing multiple NHS trusts to obtain findings that are more robust in terms of clinical interpretation. It is also essential to note that the high proportion of the elderly patient group in the dataset—which is not limited to our study—reflects the ageing population in the UK. Lastly, we acknowledge that our statistical associations are liable to inaccuracies due to the small sample sizes of some groups or categories.

5.0 Conclusion

Machine learning techniques can be vital for identifying variables contributing to clinical outcomes for morbidly obese patients receiving direct oral anticoagulants (DOACs). Multiple regression indicated that the apixaban 2.5mg BD regimen increased the mortality risk by 43% in morbidly obese patients. A higher dosage regimen of apixaban (5mg BD) reduced mortality odds by 25% but increased the odds of stroke events. Further studies are needed to explore the safe and effective DOAC doses for morbidly obese cohorts.

AUTHOR CONTRIBUTIONS

SSH and EMN conceptualised the project. EMN completed the data extraction and drafted the manuscript. SSH and EMN conducted the data analysis. MAA undertook the quality assurance of data extractions and helped in ML analysis. EMN, SSH, MAA, HM, and BC contributed to the design of the study, interpretation of results, and preparation and revision of the manuscript. All authors approved the final manuscript.

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CONFLICT OF INTEREST

Ezekwesiri Michael Nwanosike, Hamid Merchant, Wendy Sunter, Muhammad Ayub Ansari, Barbara Conway, and Syed Shahzad Hasan declare that they have no conflicts of interest to declare for this study. Wendy Sunter manages the Anticoagulant services at the Calderdale and Huddersfield NHS Foundation Trust Hospitals, United Kingdom. Hamid Merchant has consulted or worked for pharmaceutical industries in his current and previous employments.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

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