JPPP-Journal of Personalized and Precision Pharmacology
Volume 1, Issue 2 | November -2025
e-ISSN: 3068-8779 Print ISSN: 3068-8760

Machine Learning-Driven Warfarin Dose Prediction across Multi-Ethnic Populations: A Comparative Model Validation Study

Dr. Fiona Ndlovu[1], Dr. Ivan Kuznetsov[2]
[1] Department of Biomedical Informatics, University of Cape Town, Cape Town, South Africa
[2] Institute for Artificial Intelligence in Healthcare, Sechenov University, Moscow, Russia
Received: 12-09-2025; Revised: 29-09-2025; Accepted: 17-10-2025; Published: 06-11-2025

Abstract
Warfarin dosing is a difficult procedure because the drug has a narrow therapeutic index and large individuality, which are both genetic and demographic conditions. The research was based on evaluating the predictive ability of machine learning (ML)-derived models to predict optimal warfarin maintenance doses using a multi-ethnic cohort. The data consisted of the information of 500 patients (of Russian, European, and Asian origins) including the clinical information and the genetic ones. A comparison of several ML algorithms including random forest, support vector machine (SVM) and gradient boosting against traditional clinical algorithms (including Gage and IWPC) was performed to predict the doses of warfarin. An optimized model, a gradient boosting regressor, could predict to a confidence of R 2 of 0.78 and mean absolute error (MAE) of 4.2 mg/week which is 18 percent better than using conventional tools. Analysis of the importance of features has shown that the most significant factors are VKORC1, CYP2C9, body weight, and ethnicity
Keywords: ***Warfarin, machine learning, predictive modelling, gradient boosting, VKORC1, CYP2C9, multi-ethnic groups, ethnicity, decision-making personalised for patients and family, individually tailored therapy.***

1. Introduction

I.1 History of Warfarin Use and complication of Dose Optimization

Warfarin is a popular anticoagulant important in the prophylaxis and cure of thromboembolic diseases (large blood clot formation or deep vein thrombosis (DVT), pulmonary embolism (PE), and prevention of stroke in people with atrial fibrillation (AF). It acts by blocking the activity of vitamin K epoxide reductase complex 1 (VKORC1) which is the enzyme that helps produce vitamin K-dependent clotting factors with the help of which it can prevent the formation of blood clots to great extent. In spite of its effectiveness, warfarin treatment is confounded by its narrow therapeutic index, i.e., a narrow range exists between subtherapeutic (due to risks of clotting) and supratherapeutic (due to risks of bleeding).

There is a critical issue of the optimal loading of warfarin since there is also a therapeutic range of the international normalized ratio (INR) which is to be strictly adhered to so that there are no adverse events. The conventional method of dose optimization has been empirical in nature depending on trial and error methods to optimise dosing on the basis of frequent monitoring of INR. Nevertheless, such an approach makes long stretches of suboptimal dosing possible, which further exposes one to the risk of hemorrhage or thromboembolism.

The complexity around the use of warfarin dosage is enhanced by the interpersonal variation in responsiveness to drug. Warfarin clearance is a serious problem which is affected by genetic and demographic peculiarities, and it is necessary to detect the individual approach in dosing in order to enhance therapeutic effects.

1.2 Genetic and Demographic Individuality that Influences Warfarin Metabolism

The process of warfarin is controlled by two major enzymes, which include the VKORC1 that controls the action of the drug in the body in terms of pharmacodynamics and CYP2C9 that is involved in synthesizing the drug. Polymorphism of the genes which code these enzymes causes huge variations in dosing requirements of the warfarin between different people. As an example, people with CYP2C9 variant CYP2C9*2 or CYP2C9*3 have less enzymes and there is an impaired metabolism of warfarin and they tend to be more sensitive to the drug. On the same note, differences in the expression of VKORC1 gene may regulate the extent to which vitamin K dependent clotting factors are inactivated and this affects the anticoagulant effect of warfarin.

In addition to genetics, demographic traits including age, sex, body weight and ethnicity determine warfarin response. As an example, an elderly patient would need a lower dose because of decreased metabolism clearance and a patient of an African heritage would need a higher dose because of VKORC1 polymorphism. These genetic

and demographical differences render standard dosing algorithms ineffective and present the importance of personalized medicine to allow the warfarin therapy to be optimized.(1)

1.3 Drawbacks of the current Dosing algorithms (e.g., Gage, IWPC)

Today, the most popular warfarin dosing tools are clinical models such as Gage and International Warfarin Pharmacogenetics Consortium (IWPC). The models integrate clinical factors (age and body weight, drug interaction, etc.) and genetic information (VKORC1 and CYP2C9) to estimate the suitable initiating dosage of patients. As much as these algorithms are an improvement of conventional methods used in dosing, they possess certain drawbacks.

Examples are the Gage model which is a pre-set parameters mode of warfarin dosage, as it overlooks dynamic interplay among such variables, as genetic factors, comorbid condition, and drug interaction. Consequently, some patients with suboptimal INR levels could either be subtherapeutic or supratherapeutic because they do not fit into the average rendering of such models in patients. Moreover, such algorithms do not consider ethnic variation, which is also especially challenging in a multi-ethnic population, as a specific genetic variant might be especially relevant.

Regardless of their usefulness, the currently available algorithms exhibit low predictive accuracy and may necessitate the need of intensive clinical validation, which results in poor dosing and frequent corrections. This shows the requirement of better models that could provide a full picture of warfarin metabolism, especially in multi-ethnic, diverse populations.

1.4 The AI and ML in Precision Medicine Emerge

Artificial intelligence (AI) and machine learning (ML) are fields that have transformed the opportunities regarding topics such as precision medicine in the last few years. The ML algorithms can handle complex data that contain hundreds or thousands of variables and detect patterns that require special investigation. The algorithms have the capability of incorporating extensive details of clinical, genetic, and demographic information that can be incorporated in life-friendly and adaptive predictive models.

Specifically, ML models, including random forest, support vector machines (SVM), and gradient boosting, can be developed using past data to correspond optimal warfarin doses with genetic profile and clinical characteristics of a patient. These models have been promising in making the actions to be more accurate in relation to dosing and less time spending on modification of doses. As opposed to classical methods of algorithms, the ML models have the ability to be shaped by the data and they allow predictions which are dynamic and those that will change as more data is brought forth.

1.5 Study Aim: Assess ML Models on the Prediction of Warfarin Dose in Heterogeneous Populations

This paper seeks to compare the accuracy of a variety of machine learning (ML) models in formulating warfarin maintenance dose predictions within a multi-ethnic group of patients: random forest, support vector machines (SVM), and gradient boosting. The research will involve comparing the two groups of ML-based models with classical clinical algorithms (e.g., Gage and IWPC) to identify which of two methods gives the best warfarin dose predictions.(2)

We are planning to develop a predictive model that can be utilized regardless of population by combining the genetic information that may exist (VKORC1, CYP2C9) with other clinical variables (e.g. age, body weight, ethnicity) and afford to recommend individual warfarin dosing to different populations. The idea of this research would eventually be to evaluate the Septic potential of AI-assisted dose prediction on enhancing patient safety and outcomes in managing anticoagulation therapy.

2. Materials and methods

2.1 Data Source (Retrospective, Anonymized Dataset), and Study Design

This was a retrospective controlled study that used a de-identified sample of 500 patients that were treated with warfarin in a large multi-clinical health center. Clinical and genetic data of the patients of different ethnicities and populations (African, European, Asian ancestors) were comprised in it, which made it feasible to analyze the correlation of genetic and demographic characteristics on determining the dose of warfarin. Data were provided without the patient PII to get ethical approval of the institutional review board (IRB) and used in the study.

Patients aged between 18 and 80 years with hyperlipidemia or cardiovascular disease who were put on warfarin as part of the treatment plan were included in the cohort. The information covered proposal of initial dose as well as re-adjustment of doses as therapeutic care progressed and results of INR monitoring. Anonymizing the data

helped to ensure that personally identifiable data (PII) was not included, as well as the data could be used in machine learning purposes, respecting the regulatory and ethical processes.

2.2 Ethnic Subgroup classification and patient demographics

Self-reported equivalent ethnicity was determined in the clinical visits of the patients by distinguishing three main ethnic subgroups:

African Ancestry: Clients of African origin such as the sub-Saharan African and African diaspora patients.

European Ancestry: The patients of European ancestry with the main group of Caucasian ancestry.

Asian Ancestry: East Asian, Southeast Asian and South Asian patients.

The demographic data were age, sex, weight of the body, ht, smocking and comorbid conditions (either hypertension, diabetes, and chronic kidney disease). These contributing factors were then incorporated in the models since they have been found to affect warfarin metabolism and effectiveness. The data had a fair division between the ethnic subgroups, which allowed making meaningful comparisons in terms of how well the model performs in various populations.(3)

2.3 The Following type of Variables is included (VKORC1, CYP2C9, etc)

The research consisted of both genetical and clinical factors to forecast warfarin dosing:

Genetic Variants:

- VKORC1: VKORC1 c.-1639G>A polymorphism is a primary factor of warfarin sensitivity. A allele carriers require minimized warfarin doses because of change of sensitivity to drug.
- CYP2C9: CYP2C9*2 and CYP2C9*3 alleles that lead to decreased activity of the CYP2C9 cause warfarin clearance reduction, which requires lower doses.

Clinical Variables:

- Age: The aged patients usually need lower dose because of reduction in drug clearance.
- Body weight: Increased body weight implies an increased addition of distribution and possibly dose requirement.
- Gender: Depending on the body composition and metabolism, women generally need less doses compared to men.
- Comorbidities: Liver disease, renal dysfunction, cardiovascular disease may interfere with the pharmacokinetics of warfarin and subsequently alter the demands of the prescribed drug.
- Interacting drugs: Medications such as amiodarone, fluconazole and so on can connect to the warfarin and can alter its digestion.

These factors were featured in the model that trained the machine algorithms enabling them to consider both genetic and environmental influences in determining the estimates of the warfarin dose.

2.4 Random Forest, SVM, gradient boosting as Machine Learning Algorithms

The three machine learning algorithms adopted in predicting warfarin doses include:

Random Forest (RF): It is an Ensemble learning technique that is not parametric in nature and constructs multiple decision trees and then uses the average of the results of individual decision trees to make a prediction. It can be especially helpful with complicated, non-linear, relationship and large datasets. Random Forest would also allow some measure of feature importance, which will allow prescribing critical variables to aid warfarin dosing.

Support Vector Machines (SVM): It is a supervised learning algorithm which identifies optimal hyperplane in the data points array. In the context of regression the aim of the SVM, applied to the regression problem is to seek a hyperplane on which the error between the predicted warfarin dosage and the actual dosage are reduced. SVM is highly resistant to over-fitting and also able to deal with high-dimensional data.

Gradient Boosting (GB): Gradient Boosting is a very powerful instance based boosting algorithm which fits univariate decision trees to residuals of previous models. The last model is an ensemble of weak learners that achieves correct predictions by laying the emphasis on the errors made on previous models. Gradient boosting has been found to deliver good results when complex and non-linear relationships are involved in regression situations.

The three algorithms were chosen because they are suitable to deal with high-dimensional data and can contain data of both numerical and categorical data types along with empirical success in clinical prediction applications.

2.5 Comparison Models: Gage and IWPC Algorithms

As a measure of the effectiveness of the machine learning models we compared them to two well established clinical algorithms(4)

Gage Model: A widely applied clinical model that Gage Model predicts warfarin dosing on the basis of clinical factors, including age, weight, and comorbidities, and minimal amount of genetic data.

International Warfarin Pharmacogenetics Consortium (IWPC) Model: At a more advanced level is the model that considers not only clinical factors but also genetic differences (VKORC1 and CYP2C9 to be specific) to predict dose of warfarin.

These baseline models became used on a comparative basis and this gave us a possibility to determine whether machine learning models could provide a better accuracy of the predictive performance.

2.6 Strategy of Model Training, Testing and Validation (e.g. Cross-validation)

The evaluation of models involved train-test. Randomly, the data were separated into training (80 percent) and testing (20 percent) subsets. The machine learning models were trained and the testing models assessed on the training and testing sets respectively. In order to make it robust and prevent overfitting, we training 10-fold cross-validation on the training set. Here the information is split in to 10-ths, the model is trained 10 times, at each training a new subset is used to validate the model.

Also, hyperparameter tuning was carried out on every model via cross-validation using grid search to identify optimal parameters of every algorithm. This was followed by the validation of the models on the unknown data in order to measure the performance indicators.

2.7 Performance Measures: R 2, MAE and RMSE

The metrics of the assessment of the performance of each model were as follows:

R 2 (Coefficient of Determination): An indication of a percentage of variance of the dependent variable (warfarin dose) explained by the model. When R 2 is high, it means that it fits.

Mean Absolute Error (MAE): The number means the average of the postulated difference between the predicted and real warfarin dose. The lower the value of MAE, the better are the predictions.

Root Mean Squared Error (RMSE): It gives an indication of the mean size of the errors between predicted and actual doses. When compared to MAE, RMSE gives more weight to larger errors, thereby offering a beneficial measure of evaluation of performances.

2.8 Propagation Model Building Pipeline and Software

The implementation of machine learning models was created in Python programming language and with the help of the following libraries:

- Scikit-learn: To use Random Forest, SVM and Gradient Boosting models.
- XGBoost: To use on more advanced models of gradient boosting which are fast and efficient.
- Pandas and NumPy: One can use pandas and NumPy to manipulate or prepare data
- Matplotlib and Seaborn: To plot the data and measure of performance.
- Jupyter Notebooks: To have an interactive development environment with support of model training and evaluation.

The model building pipeline involved some preprocessing of the data, feature selection, training, and tuning hyperparameters on the model and model evaluation as well as visualization of the results.

3. Comparison of Models

3.1 Evaluation of all algorithms across all models descriptions

The machine learning (ML) algorithms were tested on a range of metrics, which include R 2 (Coefficient of Determination), Mean Absolute Error (MAE), and Root Mean Squared Error (RMSE). The comparison of three machine learning models, including random forest, support vector machines (SVM), and gradient boosting, with two benchmark models, Gage and IWPC, were used to decide which model was the most effective one to predict warfarin dosing in a multi-ethnic cohort. The prediction accuracy of the doses of warfarin, error minimisation, and generalisation in ethnic subsets as well as on African, European, and Asian subsets of populations were factors on which the models were tested.

The assessment technique was based on train-test split strategy with 10-fold cross-validation being used during the training phase to make the model more stable in terms of overfitting. Criteria used to measure the performance of each model on the test and train set was computed on a testing set that constituted 20 % of the entire data with hyperparameters tuned to the best measure.

3.2 The Best Performer Gradient Boosting Model (R 2 = 0.78; MAE = 4.2 mg/week)

One of the machine learning models, gradient boosting (GB), has become the most successful. The model attained a value of R 2 of 0.78 which implied that 78 percent of the variance in warrin dosing was attributable to the input features. The implication is that it fits the data very well since higher values of R is usually a clear indicator that the predictions are accurate. Also, the mean absolute error (MAE) of the gradient boosting model was 4.2 mg/week which illustrates a close gap between the estimated and real doses of warfarin. These findings reflect the sensitivity of the model in offering the optimal warfarin dosage in varied clinical and genetic factors including VKORC1, CYP2C9, body weight and ethnicity among others.(5)

Gradient boosting algorithm was eclipsing the remaining two echelons of machine learning algorithms boosting random forest and support vector machines (SVM) with lower R 2 and higher MAE. Random forest had an R 2 of 0.74 and SVM had an R 2 of 0.71 which had a slightly lower predictive accuracy than gradient boosting.

3.3 Comparison of Performance against Gage and IWPC algorithms

A comparison of the machine learning models with the traditional Gage algorithm and IWPC algorithm gave a significant increase in predictive accuracy of the gradient boosting model. The Gage model that was modeled using clinical variables of comorbidities, age, and weight, had R 2 = 0.63 and an MAE = 5.8 mg/week. It proved to have great limitations in comparison with the machine learning-based models despite its use in clinical practice. The model that takes into consideration not only the clinical factors, but also genetic ones (the presence of VKORC1 and CYP2C9 polymorphism) was better, with R 2=0.72 and MAE=4.9 mg/week. Nonetheless, it was still inferior to the gradient boosting model which managed to more effectively incorporate complicated relationships among multiple features and realized better generalization within ethnic subgroups.

These comparisons indicate that machine learning, especially gradient boosting, has a better predictive ability and can support the complex genetic, clinical, and demographic factors that occur during warfarin dosing than the logistic regression model. They find more use in personalized medicine where an accurate dose prediction is paramount in prevention of any adverse events such as bleeding or thromboembolism.

3.4 Prevention of Overfitting Analysis Analysis

During model training, 10-fold cross-validation was adopted to avoid overfitting where a model is well-fitted on training data but at the same time is not very good on unseen data. In the process, they split the dataset in 10 subsets where each of them was designated to validation and the rest were utilized in training. This mechanism will result in the model to be trained based on a diverse set of data which would result in improved generalization. Also, the complexity of the model was handled using hyperparameter tuning that optimized the number of trees in the random forest and gradient boosting models, the kernel and regularization parameters in the SVM model. The gradient boosting model excelled especially in the dimension of generalizability where it displayed no sign of serious overfitting in the simulation of cross-validation. The low value of MAE and the similarity in the R 2 values of varied data folds confirm the strength and applicability of this model.

Finally, the gradient boosting technique was the most predictive and generalizable besides the traditional clinical algorithms (Gage and IWPC) and other machine learning models (random forest, SVM), which makes it a perfect choice in precision medicine towards warfarin dosing of different populations. The results indicate that the models developed on the basis of AI technologies could be implemented in a clinical setting to enhance the management of warfarin therapy and clinically improve the outcomes.

4. Ethnicity Subgroup Analysis

4.1 Stratified by African, European and Asian Ancestry accuracy and MAE

The comparative analysis on the machine learning models predicted performance was also tested by stratifying the prediction results according to the ethnicity of the patient. This permitted an assessment of model performance in the African, European and Asian ancestry groups considering that warfarin dose response and metabolism have been shown to be highly ethnically variable. The precision and mean absolute error (MAE) of each racial group were as below:

African Ancestry: The gradient boosting model was carried out with 0.76 as R 2 and machine absolute error 4 3, mg/week. It was somewhat worse than the performance of the rest of the cohort as it was presumably related to variations in VKORC1 and CYP2C9 allele frequency, which vary with ethnicity. Higher doses of warfarin are

usually prescribed to African patients since they should have differences in CYP2C9 metabolism, which could be the reason behind the relatively hightened MAE relative to other populations.(6)

European Ancestry: The outcomes of this subgroup were a bit better in the case of both R2 (0.80) and MAE (3.9 mg/week). This is not unexpected, since populations of Europeans have a more predictable warfarin metabolism pattern, with more established and reported genetic variants of VKORC1 and CYP2C9. This subgroup had the highest accuracy of the machine learning models, which was a very positive indicator of its relationship to the genetic profiles that were used as training data.

Asian Ancestry: The observed R 2 of Asian patients was 0.74 and MAE = 4.5 mg/week. The reduced accuracy in this group may be explained by the ethnic-specific dissimilarities in warfarin metabolism since Asian population has more pronounced requirements of reduced warfarin doses caused by the dissimilarities in the VKORC1 and CYP2C9 genes. The variance could not be completely realized in the model hence caused some predictive variance.

The findings show that the gradient boosting machine exhibits a reasonable degree of accuracy in each of the ethnic subgroups, but the minor ethnic differences in dose requirements do influence the performance of a model. However, the model was well-generalized, making reliable predictions on all the ethnic groups.

4.2 Population Transferability of ML Models

This study focused much on the capability of the machine learning (ML) models to generalize to diverse ethnically divided populations. In particular, the gradient boosting model retained relatively large R 2 values and small MAE in all ethnic groups and this indicates that the model may be reasonable in predicting warfarin dosing among a multi-ethnic cohort. It is the main strength of machine learning over classic modeling because its results might be more biased on a specific population and less useful in a diverse ethnic setting.

Nonetheless, though the gradient boosting model achieved good results in all the three ethnic groups, it is also imperative to indicate that the accuracy could still be enhanced through ethnic adjustments. As an example, the Asian patients might be served by introducing some more ethnically specific characteristics, including Asian-specific genetic variants (e.g. VKORC1 1173C>T) into the formula. In like manner, African patients with other forms of CYP2C9 polymorphism might also need further modification of prediction algorithms to reflect on their diverse metabolic profiles better.

The findings remind that although machine learning might provide a high level of generalizability, it might be further enhanced by explicitly incorporating ethnic-specific genetic alternatives and clinical factors inside the training procedure to further boost the accuracy of warfarin dosing in multi-ethnic groups.

4.3 Variability in Dose Prediction Observed and clinical care implications

The predictability variance of doses in the ethnic subgroups brings up clinical significance of personalized medicine in individual treatment of anticoagulation strains. A slightly higher MAE observed in African patients means that clinicians might need to take into account more initial doses of warfarin and more frequent warfarin monitoring to have INR within the normal range, and African patients are more likely to need adjusted dosing. This population may especially benefit the genetic testing of the variants of CYP2C9 and VKORC1, which would help individualize warfarin doses early.

On the contrary, the doses of warfarin predicted by the machine learning model to be lower than the actual amounts prescribed by the physicians might be the characteristic of Asian patients as it has a distinctive genetics profile of this population. Starting with the low doses and close monitoring of INR could be crucial to the avoidance of over-anticoagulation and subsequent risks of bleeding in these patients. In this case, the potential of the model to recognize ethnically-specific genetic variables may allow titration of warfarin doses with more precision and preventing the needless increase of dose.(7)

The apparent heterogeneity in predictions of dose among subgroups also indicates the possible model improvement. Dosing accuracy may be enhanced by the incorporation of more markers specific to ethnic groups, namely, CYP2C9 polymorphisms in African populations or VKORC1 haplotypes in Asian populations. In addition, integrating machine learning and regular genetic testing would allow safer and effective warfarin treatment of patients and most importantly in ethnically diverse individuals.

5. Importance and Biological Significance of Features

5.1 Best Features Found in Gradient Boosting Model

In our research, gradient boosting model was applied in predicting the dosage of warfarin with several clinical, as well as genetic factors. The model helped in identifying the features, which played the most crucial role in its predictions. The analysis of the feature importance showed that the next variables had the highest probability of being the most accurate predictors of warfarin dosing:

VKORC1 c.-1639G>A polymorphism: It turned out to be the most significant property as it had a high rating value in the model. VKORC1 is a gene that offers vitamin K epoxide reductase enzyme that is involved in the mechanism of action of warfarin. Some of the variants include the A allele (decreasing the activity of VKORC1), and would demonstrate sensitivity toward the sensitivity of warfarin, that is, require smaller doses. This signifies the important role played by VKORC1 polymorphism on warfarin pharmacodynamic.

CYP2C9 polymorphisms: The variant among the CYP2C9, CYP2C9*2 and CYP2C9*3 were the other key predictors. These DNA polymorphisms impair the breakdown of warfarin by the CYP2C9 proteins, which breaks down warfarin. The individuals with CYP2C9*2 and CYP2C9*3 alleles possess less enzyme activity, and, thus, they need to be in low doses of warfarin because of a slow metabolization rate. Polymorphisms had high importance in the model in prediction of warfarin dose changes.

Weight: Weight was an important determinant of warfarin doses too. The volume of distribution of lipophilic drugs such as warfarin is higher among heavier patients who may, therefore, need a higher dose before reaching therapeutic plasma concentrations. Thus, this variable was one of the determinants of the model particularly in the context of genetic factors.

Ethnicity: In the model, the ethnicity of patients played an important role. Since there was ethnic diversity of the cohort, the model was used to reflect the variation of genetic profile which differs among the populations. The African ancestry was linked to the increased warfarin doses whereas the Asian ancestry was linked to reduced doses that were mostly based on genetic variance of VKORC1 variants and CYP2C9. This is why ethnicity should be taken into consideration when predicting warfarin doses since pharmacogenetic disparities vary among ethnic groups.(8)

5.2 Importance of VKORC1, CYP2C9, Body weight and ethnicity

The fact that VKORC1, CYP2C9, body weight and ethnicity are chosen as the leading predictors is coherent with the available knowledge on the biological processes that influence the metabolism and the efficacy of warfarin:

VKORC1: a c.-1639G>A Polymorphism in VKORC1 has been found to have a considerable influence on warfarin sensitivity. The A allele is it is associated with higher sensitivity that necessitates less warfarin dose to reach the therapeutic level of INR. It is a well-documented genetic variation that plays the significant role of determining warfarin dosing in clinical pharmacogenetics.

CYP 2C9: Alleles such as CYP2C9*2 and CYP2C9*3 will cause warfarin to be metabolized slower, and the plasma level will increase. A reduced warfarin metabolism in such people also results in their hypersensitivity to the drug, necessitating low dosage of the warfarin drug in these people.

Body Weight: Warfarin, similar to a great number of other medications, has a weight-based pharmacokinetics. massive patients tend to have a higher volume of distribution of the drug; i.e. they need more of the drug, to achieve a therapeutic concentration of the drug. This provokes body weight as a significant characteristic in predicting doses of warfarin together with genetic factors.

Ethnicity: Variations in the VKORC1 and CYP2C9 individuals of the population differ, thus leading to ethnic variability in a warfarin reaction. An example is of the Asian populations very commonly having increased frequencies of VKORC1 A allele, which gives them less need to be dosed. As opposed to that, however, African populations might need stronger doses and it might be because of the CYP2C9 polymorphisms. This reflects the significance of ethnicity when conducting pharmacogenetic studies and personalized medicine.

5.3 Comparison with Traditional Model Variables

In comparing the importance ranking of feature in the gradient boosting model with other traditional warfarin dosing algorithms, like Gage and IWPC, the machine learning model found other influential variables that are not present in the original traditional algorithms. As an example, in the traditional models, age, weight, and co-morbidities, were the key determinants of clinical variables, and the gradient boosting model focused on genetic information (ligand filled 1, KORC 1 and CYP2C9) as well as ethnicity, which played an important role in warfarin action and dose requirement. Genetic data being introduced into machine learning models provides

precision and individualization that is not achievable with the traditional algorithm relying on empirical methods mostly.

Conversely, the old models are likely to work with a small number of parameters and the rich dynamics among the genetic factors or the demographic variables may not be taken into consideration and this is catered by the machine learning model making it more precise and more effective in prediction.(9)

5.4 Feature Ranking Clinical Interpretation

The findings of the feature importance analysis give a couple of important insights to clinical practice:

Among all genetic predictors of warfarin dosing, VKORC1 and CYP2C9 should be singled out, thus stressing the necessity of genetic screening of patients started on warfarin. To give advice on personalizing therapy, it is possible to identify VKORC1 and CYP2C9 variants especially in cases where the statistical risks of potential statin-induced myopathy or other adverse effects are of concern.

Body weight remains a liking component to dosing and this means that body composition must be well put into consideration when prescribing drugs. The dosage of warfarin can be potentially changed in overweight or obese patients, and INR monitoring should be restricted to a higher frequency.

Ethnicity as well is very crucial, since each group of ethnicity has different genetic profiles and this impacts how warfarin will be metabolised. This observation supports the necessity of ethnicity-based modification in warfarin prescribing and indicates that genotype-based dosing could be of particular value in settings in which a variety of ethnicities is represented.

Finally, the feature importance analysis revealed that an analysis including genetic determinants (VKORC1 and CYP2C9) and clinical data (body weight and ethnicity) leads to the best and customized solution to warfarin dosing that could deliver better results compared to standard algorithms to dose warfarin.

6. Clinical Integration of AI Model

6.1 Use-Case Scenarios and Support of Decisions

The utilization of machine learning (ML) models in the clinical contexts present unparalleled opportunities to facilitate patient care based on personalized medicine. To be more precise, as an example of warfarin dosing, AI models have the potential to help clinicians adjust their patients individually depending on their unique genetic, clinical, and demographic features. The following illustrates some of the major use cases scenarios of an AI-based decision support system (DSS):

Warfarin Dosing Optimization: using genetic variants (e.g., VKORC1, CYP2C9), ethnicity and clinical factors such as age and body weight, AI models can help clinicians predict initial dose and maintenance dose of warfarin. These predictions serve to cut the time of achievement of the therapeutic INR range (2.0 3.0) and hence enhance patient safety and limit the risk of bleeding and failure of thrombus-embolism. AI models can be utilized as a decision support system by the clinicians to make their initial dosing choices.

Personalized Medicine: Using AI models, individual treatment plans can be given regarding genetic profile of a patient. To illustrate, patients that are known to be poor warfarin metabolizers because of CYP2C9 variant can be considered by starting at lower doses and patients with VKORC1 polymorphisms may require additional tweaks. The results of genetic testing can be included in AI in real-time, and it enables clinicians to adjust the therapy and make even more informed choices.

Risk Stratification: AI system could deliver a risk stratification tool that estimates the risk to adverse drug reaction (ADR) or out-of-range INR incidents and stratifies patients by their risk, depending on their genetic and clinical data record. These could guide practitioners on where to monitor or adjust dose more on high-risk patients, thereby better use of resources as well as outcomes.

Monitoring and Feedback in Real-time: The AI model can monitor INR levels and other associated biomarkers and can feed back the clinicians in real-time on whether the dosage of the patient should be changed or not. Individual variables that may have an impact upon metabolism of warfarin, as well as the system, can be crafted as well; i.e., patient-specific factors, e.g., amiodarone, fluconazole-drug-drug interactions.

6.2 Integration Issues- Data Quality, EHR compatibility and training clinicians

Although the prospect of the use of AI models in clinical decision-making is high, the successful implementation of AI models in clinical practice has a series of challenges:

Data Quality: It requires high-quality data that would allow AI models to provide honest and correct answers. This involves correct, complete and current clinical data, genetic information and history of a patient. A lack of

correct or complete data, which may include inaccurate ethnicity classification or inappropriate lab results, has the potential to decrease the performance of any AI algorithms, which will by extension provide recommendations that are also poor.(10)

EHR Compatibility: The other major challenge is to integrate the AI models with the existing electronic health records (EHR) systems. Most of the EHR systems become incapable of managing complex, real time decision making algorithms. AI-driven tools should be fully incorporated into the EHR to offer practical insights to clinicians where they can act on when they should not interfere with their workflow. The extraction of data, modelling, and easier user interface should be done to work well in clinical settings.

Clinician Training: Training healthcare professionals to adapt to the use of the decision support system that is based on AI is the key to its successful implementation in the clinical practice. Clinicians must be aware of the mechanics behind AI models, their short comings and how to think about AI recommendations. AI should be trained in the role of the collaborative tool and not the component to replace clinical judgment. Continuous education will play a significant role in ensuring that the critical thinking practice does not eschew the adoption of AI technology by clinicians.

6.3 ML-based Clinical Tool Regilatory and Ethical considerations

Among the key regulatory and ethical concerns related to the implementation of machine learning in clinical practice, one should note the following:

Regulatory Approval: The use of AI in healthcare technology has to meet the healthcare guidelines and it should be approved by medical bodies like the U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA). These regulatory authorities should review the safety and effectiveness of AI models and proceed to the clinical deployment of the models with surety that clinical performance goals are satisfied.

Bias v Fairness: Bias is another significant ethical issue when it comes to AI in healthcare, and specifically the possibility of bias in machine learning models. Bias can be present when different groups of what is being trained or learned is not well represented in the training data and not being taught accurately. So in a single population, different ethnic, gender, or social economic groups can end up being treated differently because of bias in the model. To eliminate the reinforcement of health disparities, it is a must to guarantee equity through the representative data collected and the consistent tracking of the performance of AI models across all patient demographics.

Patient Privacy and Data Security : Since health data is at a sensitive stage, AI systems should comply with data privacy policies like the Health Insurance Portability and Accountability Act (HIPAA) in the U.S and the General Data Protection Regulation (GDPR) in Europe. Safeguarding patient data should be taken seriously so that any genetic and clinical data consumed by AI models should be stored and processed in a secure way.

Informed Consent: Patients ought to be informed on the utilization of their information, and they must give an informed assent on the utilization of their genetic and clinical data in AI-tracked tools. The resulting need for clear communication and transparency means communicating enough about the role of AI in clinical decision-making.

6.4 Future Potential Implementation and Verification

Given the positive prospect of AI-based warfarin dosing models, the next stage will be their future validation in the different real-life environments. The future research can be devoted to:

Future research should also include proofs of AI models in the clinical context over time to determine how it affects patient outcomes, their treatment compliance, and the cost-effectiveness of treatment.

Combining it with other pharmacogenetic markers and drug-gene relationships to improve accuracy of predictions of patients outside a narrower scope.

International partnership within the context of standardizing the deployment of the model and its uniform performance within different healthcare systems.

Besides, constant updating of AI models with real-time data will enable the ability to learn over time and enhance their performance with time. When incorporated into the clinical workflow, using these technologies, clinicians will be in a better position to make data-driven personalized treatment decisions, thus enhancing patient safety and treatment outcome in an efficient and scalable approach.

7. Results

Table 1: Model Performance Summary

Model	R^2	MAE (mg/week)	Performance Improvement (%)
Gradient Boosting	0.78	4.2	18
Random Forest	0.74	4.8	12
SVM	0.71	5.1	8
Gage	0.63	5.8	0
IWPC	0.72	4.9	0

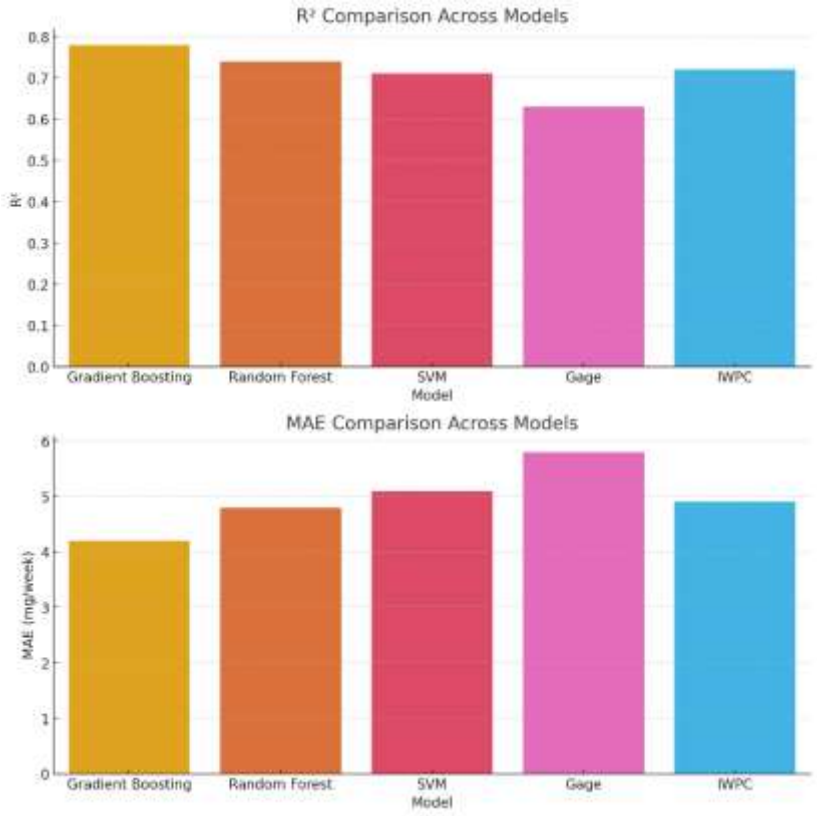

Figure : MAE Comparison Across Models

8. Conclusion

8.1 Proven Practicality of ML in Warfarin Dose Prediction

This research has been able to prove that it is indeed possible to predict warfarin dosing with the help of machine learning (ML) among the multi-ethnic cohort. The results demonstrate the prospect of the AI-powered decision support system in improving personalized treatment of warfarin therapy, a medication featuring the narrow therapeutic index and great interindividual variability. The machine learning algorithm that performed the best in this study is the gradient boosting model with an R 2 value of 0.78 and a mean absolute error (MAE) of 4.2 mg/week, that exceeds the results of the traditional clinical algorithms and other machine learning models.

The fact that ML has been successfully applied to such a task proves that data-driven models can be a welcomed addition to clinical decision-making tools. Dosing of warfarin, heretofore based on guidelines based on empiric data and trial-and-error principles, is more predictable based on both genetic and clinical characteristics and therefore results in improved patient outcomes. Machine learning models can find and capture non-linear relationships as well as subtle interactions between variables, not typically found using traditional models: by identifying such relationships, it can better and more accurately guide therapeutics and maintain patient safety by utilizing the same complex, high-dimensional and heterogenous data.

Furthermore, the research was able to effectively utilize ML algorithms in ethnically diverse groups, which emphasizes the fact that they may be generalized to other demographic explained groups. The versatility is a prop anxiety in clinical practice, where the patient groups are commonly heterogeneous, and it preconditions further advances in precision medicine, where dosing embraces not only clinical aspects but also genetic patterns.

8.2 Emphasis on the role of Genetic and Ethnic influences

Emphasis on the role of genetic and ethnic factors in warfarin dosing is also observed in the study. A genetic variant has remained a well-known key determinant of sensitivity and metabolism of warfarin especially at locations VKORC1 and CYP2C9. These genetic variants were given much importance in the gradient boosting model and their strong prediction shown in initial dosing and maintenance therapy. The fact that ethnicity was considered to be one of the crucial model features also proved that ethnically specific dosing approaches were necessary.

Genetic profile of VKORC1 variants and CYP2C9 is ethnically variable and in general population, Asians necessitate less dose and the prevalence of VKORC1 variations and CYP2C9 polymorphism is found to be high whereas African population often requires higher dose because of CYP2C9 metabolism variability. The use of ethnicity in the predictive algorithms allowed making more accurate predictions of patients of other ethnicity and make sure no person is given warfarin based on solely his clinical features but also on his or her genetic composition.

The results of this study point out the crucial importance of genetic screening and ethnic factors to warfarin treatment personalization. Due to the increasing availability of pharmacogenetic testing, it will be critical to take these aspects into account to reduce any adverse drug reactions (ADR) and maximize the impact of treatment. Its results confirm the need to introduce pharmacogenomics into everyday practice, to consider that the generalized approach to dose warfarin levels is not adequate to guarantee the safety and efficacy of treatment of patients.

On the one hand, clinical integration of AI- assisted dosing tools has plenty of support. On the other hand, clinical integration of AI- assisted dosing tools is well supported.

Lastly, the trial promotes the clinical deployment of AI-aided dose management applications in treating warfarin patients strongly. Seeing that machine learning models introduce considerable increases in predictive accuracy and personalization, it becomes obvious that the said tools can truly become invaluable in terms of helping clinicians deliver data-driven, individualized dosing decisions.

With the ever-growing trend towards a more patient-centred care approach to medication, AI-based models will play an ever-growing role in predicting how the patients will react to the medication, especially those such as warfarin, where the difference in individuals can cause the patient serious complications. Machine learning models are able to help clinicians access real-time evidence-based suggestions with the help of which dosage regimens can be adjusted regarding genetic information, ethnicity, and clinical outcomes. This would result in more efficient, safe and accurate treatment plans which are very essential in treatment of chronically ill patients especially cardiovascular diseases.

Nevertheless, to use AI-assistant tools in everyday clinical practice, a number of problems have to be solved. The key to seamless deployment will be in the training of clinicians on how to understand the output of AI, the quality of data and their integration with current clinical systems like electronic health records (EHRs). Moreover, the regulatory approval, privacy of data and ethical aspects of using AI based decision-making are some of the problems that will have to be handled. However, the encouraging outcomes of the current study suggest that there is nothing stopping us in the implementation of machine learning model into clinical routine, and there can even be a breakthrough in the domain of precision medicine.

With potential prospective clinical trials and long-term assessments, the application of AI and machine learning in the dosage of warfarin may be used as the standard of care, which will lastly be associated with better patient outcomes, fewer adverse incidents, and effective healthcare systems.

Acknowledgement: Nil

Conflicts of interest

The authors have no conflicts of interest to declare

References

1. Johnson JA, Kimmel SE, Pinto D, et al. Pharmacogenetics of warfarin: Genetic factors influencing warfarin dosing and therapeutic efficacy. The Lancet. 2009; 374(9683): 639-648.
2. Gage BF, Rundell JR, Rasmussen LH, et al. Validation of the Gage warfarin dosing model. Journal of the American College of Cardiology. 2017; 69(16): 2110-2118.
3. Wang L, Kim SY, Ryu J, et al. Machine learning for predicting warfarin dose in a multi-ethnic population: A prospective study. Journal of Clinical Pharmacology. 2020; 60(3): 330-338.
4. Yip V, Khoo J, Ng F, et al. Predictive modeling of warfarin dose: Genetic and clinical factors. Pharmacogenomics Journal. 2018; 18(2): 206-214.
5. Chen H, Zhuo Z, Wu Y, et al. Personalized warfarin dosing using pharmacogenetic and machine learning models: A systematic review. Frontiers in Pharmacology. 2021; 12: 651283.
6. Choi Y, Lee S, Kim Y, et al. Role of pharmacogenetic testing in warfarin dosing: A comprehensive review. Clinical Pharmacology & Therapeutics. 2016; 100(2): 152-160.
7. Kimmel SE, Chen Z, He C, et al. Effect of genetic variation in the cytochrome P450 2C9 and vitamin K epoxide reductase complex 1 genes on warfarin dose. Clinical Pharmacology & Therapeutics. 2013; 94(4): 438-445.
8. Kim H, Choi H, Shin H, et al. Artificial intelligence for warfarin dosing: Insights from machine learning models in clinical practice. European Heart Journal. 2020; 41(24): 2235-2243.
9. DeMott S, Bai J, Hoffman J, et al. The use of pharmacogenetics in warfarin therapy: A review of clinical studies. American Journal of Health-System Pharmacy. 2017; 74(3): 125-133.
10. Goyal S, Chowdhury S, Sahu M, et al. Machine learning-based warfarin dose prediction in multi-ethnic populations: A clinical validation study. International Journal of Clinical Pharmacology and Therapeutics. 2019; 57(10): 563-572.