Elnour AA, Ahmed IM, Khalid AA, Elmustafa M. Validation and comparison between two warfarin dosing clinical algorithms and warfarin fixed dosing in specialized heart center: cross-sectional study. Pharmacy Practice 2022 Jul-Sep;20(3):2722.
https://doi.org/10.18549/PharmPract.2022.3.2722

Original Research

Validation and comparison between two warfarin dosing clinical algorithms and warfarin fixed dosing in specialized heart center: cross-sectional study

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Received (first version): 04-Jul-2022 Accepted: 05-Aug-2022 Published online: 14-Sep-2022

Abstract

Background: Warfarin is well known as a narrow therapeutic index that has prodigious variability in response which challenges dosing adjustment for the maintenance of therapeutic international normalized ratio. However, an appreciated population not on new oral anticoagulants may still need to be stabilized with warfarin dosing. **Objective:** The current study's main objective was to validate and compare two models of warfarin clinical algorithm models namely the Gage and the International Warfarin Pharmacogenetics Consortium (IWPC) with warfarin 5 mg fixed standard dosing strategy in a sample of Sudanese subjects. **Method:** We have conducted a cross-sectional study recruited from the out-patient clinic at a tertiary specialized heart center. We included subjects with unchanged warfarin dose (stabilized), and with therapeutic international normalized ratio. The predicted doses of warfarin in the two models were calculated by three different methods (accuracy, clinical practicality, and the clinical safety of the clinical algorithms). **Main outcome measure:** The primary outcomes were the measurements of the clinical (accuracy, practicality, and safety) in each of the two clinical algorithms models compared to warfarin 5 mg fixed standard dose strategy. **Results:** We have enrolled 71 Sudanese subjects with mean age (51.7 ± 14 years), of which (49, 69.0%) were females. There was no significant difference between the warfarin 5 mg fixed standard dose strategy and the predicted doses of the two clinical algorithm models (MAE 1.44, 1.45, and 1.49 mg/day [P =0.4]) respectively. In the clinical practicality, all of the three models had a high percent of subjects (95.0%, 51.9%, and 66.7%) in the ideal dose range in middle dose group (3-7 mg/ day) for warfarin 5 mg fixed standard dosing strategy, Gage, and IWPC clinical algorithm models respectively. However, a small percent of subjects was exhibited in the warfarin low dose group ≤ 3 mg/day (0.0%, 15.0%, and 10.0%) and warfarin high dose group ≥ 7 mg/day (0.0%, 33.3%, and 33.3%) for warfarin 5 mg fixed standard dosing strategy, Gage, and IWPC clinical algorithms respectively. In terms of clinical safety, the percent of subjects with severely over-prediction were 28.2%, 22.5%, and 22.5% for warfarin 5 mg fixed standard dosing, Gage, and IWPC, respectively. While the percent of severely under-prediction was 12.7%, 7.0%, and 5.6% for the warfarin 5 mg fixed standard dosing, Gage, and IWPC, respectively. **Conclusion:** The Gage and IWPC clinical algorithm models were accurate, more clinically practical, and clinically safe than warfarin 5 mg standard dosing in the study population. The cardiologist can use either models (Gage and IWPC) to stratify subjects for accurate, practical, and clinically safe warfarin dosing..

Keywords: accuracy; clinical safety; over-prediction; practicality; warfarin clinical algorithms; warfarin fixed standard dosing strategy; under-prediction

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BACKGROUND

Warfarin is a widely prescribed anticoagulant for various thromboembolic disorders, such as pulmonary embolism and atrial fibrillation (AF). Besides its narrow therapeutic index, it has great variation in dose requirements for individual subjects making the selection of the right dose challenging.[1] Many strategies have been developed to estimate the appropriate dose for specific subjects including, warfarin tables,[2] dosing algorithms,[3] and Bayesian decision support tools.[4] The warfarin dosing clinical algorithms models developed for an exact population by; firstly, identifying variables that affect dose requirements like age, gender, genotype, and weight. Thereafter exploring and identifying the relationship between each variable and warfarin dose, and finally developing of the equation.[5-7]

Those warfarin clinical algorithms models can be divided into two types based on the type of data they utilize: clinical algorithms (non-pharmacogenetic algorithms) which are based on clinical data only and pharmacogenetic algorithms which are based on both clinical and pharmacogenetic/ pharmacogenomics data.[3,8] Many warfarin clinical algorithms

www.pharmacypractice.org (eISSN: 1886-3655 ISSN: 1885-642X)

have been developed for particular populations such as Omani,[6] Chinese[9] and Indian.[10] Others were built on multiethnic populations such as International Warfarin Pharmacogenetics Consortium (IWPC) algorithm which was developed from white, Asian, black and mixed races.[11] The Gage clinical algorithm was developed from Caucasian, African American, Hispanic, and mixed race.[7] In order to apply a developed clinical algorithm in practice, the algorithm must first be validated in terms of accuracy, practicality and safety.[1,12]

The rationale of the current study, relies on the fact that warfarin is used widely in our population despite the known pharmacokinetic and pharmacodynamics problems including adverse effects and hospitalization due to bleeding. There is a growing trend for using the direct oral anticoagulants (DOAC), nevertheless the cost resembles a major barrier for their continued use. Therefore, warfarin remains an inevitable choice for most subjects in low-income countries (provided cost-effectiveness models in place). In such a population the need for more accurate, safe, and practical clinical algorithm models resembles fundamental to appropriate clinical utility of warfarin.

The current study embraces the clinical pharmacist's knowledge, skills and competencies to validate and compare between two known non-pharmacogenetic warfarin dosing clinical algorithms with the conventional warfarin 5 mg fixed standard dosing in a sample of Sudanese subjects with valvular and non-valvular AF. The collaborative anticoagulation clinic in our heart center (cardiologists and clinical pharmacists) provides a great opportunity to successful management of subjects on warfarin.

Objective

The main objective was to validate and compare two non-pharmacogenetic models of warfarin clinical algorithms namely the Gage and the IWPC with warfarin 5 mg fixed standard dosing strategy in a sample of Sudanese subjects receiving warfarin for indicated anticoagulation treatment.

METHODS

Study setting

We have conducted a cross-sectional study of subjects attending the out-patient anticoagulation clinic receiving warfarin for valvular and non-valvular AF. The study was conducted at Medani Heart Centre (MHC) in Wad Medani city, the capital of Gezira State-Sudan. It serves subjects from different localities in Gezira State as well as other neighboring states. The outpatient anticoagulant clinic is held twice a week by two attending cardiologist (including the clinical pharmacist) who follow up subjects and modify the dose of warfarin according to their international normalized ratio (INR) and current medical status. The study was conducted in accordance with the Declaration of Helsinki and informed consent forms were signed by eligible subjects prior to participation. The subjects have received detailed information sheet about the purposes of the study. We have followed the STROBE checklist for reporting cross-sectional studies [Appendix 1].

Study population

Our population was comprised of Sudanese adult subjects mainly with valvular and non-valvular AF who were invited to participate in the current study. The subjects were selected based on specific inclusion criteria.

Eligibility criteria

The inclusion criteria included Sudanese subjects aged 18 years old or above who were receiving warfarin for anticoagulation treatment (stabilized on warfarin). Subjects were considered stabilized if they have taken the same maintenance dose without change in the last three months, and the last three consecutive INR measurements were in the therapeutic target range.[8,13] The subjects did not receive medications (e.g. acarbose, acetaminophen, allopurinol, azole Antifungals) that affect the metabolism of warfarin (except for amiodarone and statin). While the exclusion criteria included subjects with any blood disorders that need special consideration such as hemophilia, pregnancy, subjects with liver disease and those with cancer.

Data variables

The variables collected included age, body surface area (BSA), gender, height, weight, smoking status, and concomitant medications such as statin and amiodarone. In addition to INR values and the warfarin fixed dose. The warfarin fixed dose was defined as the average daily dose of warfarin (mg/day, weekly dose/7 days) when the INR was in the target range (2.0 to 3.0) for at least 3 consecutives (at least 7 to 14 days) days after warfarin treatment.[14] Subjects were matched at baseline for the stabilized warfarin fixed dose to reduce the effect of bias.

Sample size calculation

We have used convenient sample size calculation. However, we confirmed the sampling technique with the Z score sample calculation to drive the needed number that will suit the study design. This validation study requires a smaller sample size (one tailed statistics) for detection of the minimum difference. We used 50.0% confidence level (50.0% actual mean falls within our confidence interval [CI]), 0.5 standard deviation (the expected variance), and a margin of error (CI) of ± 5% (much higher or lower than the population mean to let our sample mean falls). The needed sample was calculated as: 50.0% - Z score= 0.674, $(0.674)^2$ X 0.5(0.5) / $(0.05)^2$, (0.454X 0.25) / 0.0025 = 45. Therefore, we recruited more than 45 subjects (71 recruited) to allow for any dropouts or withdrawal.

Validation of the warfarin dosing models

The predicted dose for each patient was calculated by the three different models. The Gage clinical algorithm model,[7] in which dose (mg/day) = Exp. [0.613+ (0.425*BSA) - (0.0075*age) +(0.156*African American race) + (0.216*target INR) – (0.257*amiodarone) + (0.108* smokes) + (0.0784*DVT/PE)]. Where, Exp. is exponent, BSA is body surface area, DVT is deep

vein thrombosis, and PE is pulmonary embolism. The IWPC clinical algorithm model,[11] in which the predicted dose was calculated based on their website http://www.warfarindosing.org. The warfarin 5 mg standard dosing model, in which all subjects were given a 5 mg dose /day. The clinical algorithm models' validation method was performed based on the Bazan's study[8] and consisted of three methods: -

The first method was the accuracy of the warfarin clinical algorithm which means to how much extent the model is accurate in predicting the warfarin dose. It is measured by mean absolute error (MAE) which is the average of absolute errors. Where, MAE is equal to predicted dose minus the actual dose. The predicted dose is the dose calculated by the clinical algorithm. The actual warfarin dose is the maintenance dose the subject was taking at the time of recruitment to the study. This the interpreted in the way that the smaller the resultant difference between the predicted and the actual dose, the more accurate will be the predicted warfarin dose of the clinical algorithm model.

The coefficient of determination (R2) is an analysis of the relationship between the actual dose and the dose predicted by applying linear regression. This is interpreted in the way that the higher in the R2 the more is the stronger the association between the predicted dose and the actual dose of warfarin.

The second method was the clinical practicality means to how much extent the model is accurate in subjects with different warfarin dose requirement, which was measured by categorizing the subjects into three warfarin dosing groups: low dose group (≤ 3 mg /day), middle dose group (3 - 7 mg /day), and high dose group (≥ 7 mg/day). The proportion of subjects in each group was categorized according to the MAE value to ideal range as: those with MAE (-1 mg/day to +1 mg/day) were considered in ideal range, MAE (> 1 mg/ day) were considered over-prediction, and MAE (< -1 mg/day) was considered under-prediction.[11]

The third method was the clinical safety of the clinical algorithm models which was estimated based on the proportion of subjects with severely over-prediction warfarin dose (MAE >2 mg/day) or severely under- prediction of the actual warfarin dose (MAE <-2 mg/day). This interpreted in the way that considered severely over-prediction when MAE > 2 and severely under-prediction when the MAE (< - 2). The clinical safety was measured by determining the percent of subjects with severely over-prediction or severely under-prediction of the actual dose for each model. The smaller the percentage of severely over-prediction or severely under-prediction the safer the clinical algorithm model in the population.[15] The MAEs of the two clinical algorithms were comparable to the validation of the sub-group in the Gage,[7] and IWPC[11] validation studies.

Main outcome measure

The primary outcome measures were the measurements of the clinical accuracy by MAE, clinical practicality (percentage of subjects in ideal, severely over-prediction, and severely under-predicted dose range), and the clinical safety (percentage of subjects with severely over-prediction/severely under-prediction) in each of the two clinical algorithms models compared to warfarin 5 mg fixed standard dose.

Statistical analysis

The data were cleaned, reviewed and processed using the Statistical Package for Social Sciences version 24 (SPSS 24), SPSS, Inc., Chicago, Illinois, United States of America (USA). We did not encounter any missing data. We have used descriptive and normality tests. The non-parametric test was used to compare the differences between the warfarin doses in the clinical algorithms (range as data was not normally distributed). The correlation between the warfarin fixed standard dose and different variables was conducted by Pearson correlation analysis. Linear regression was performed on the correlation between the predicted and actual doses of both mentioned clinical algorithms (Gage and IWPC). A statistical difference of <0.05 was considered significant.

Operational definitions (adapted from references).[7,8,11,12,14,15]

Actual warfarin dose: is the maintenance dosing that is taken by the patient.[11,12,14]

Warfarin 5 mg fixed standard dose: it is the strategy to initiate warfarin therapy by given 5 mg dose then after 3 days can be adjusted according to INR. The warfarin fixed dose was defined as the average daily dose of warfarin (mg/day, weekly dose/7 days) when the INR was in the target range (2.0 to 3.0) for at least 3 consecutives (at least 7 to 14 days) days after warfarin treatment.[8]

Low warfarin dose: when the patient actual dose is 3 mg/day or less.[15]

Moderate warfarin dose: when the patient actual dose is more than 3 mg/day and less than 7 mg/day.[15]

High warfarin dose: when the patient actual dose is more than 7 mg/day.[15]

Predicted warfarin dose: is the dose that is calculated by the clinical algorithm.[7,15]

Severely over-predicted warfarin dose: when the predicted dose is more than 2 mg/day from the actual dose.[15]

Severely under-predicted warfarin dose: when the predicted dose is less than 2 mg/day from the actual dose.[15]

Mean absolute error [MAE]: is equal to the warfarin predicted dose minus the actual dose.[8,12]

RESULTS

The current study has enrolled 71 eligible Sudanese subjects of which (49, 69.0%) were females. The mean age was (51.7 ±14 years, 95% CI 48.2 – 55.3). The mean age based on gender was 50.1 ±14.3 for females, and 55.6 ±16.2 for males. The indications for warfarin were either heart valve replacement (HVR, 38 [53.5%]), and/or atrial fibrillation (AF, 33 [46.5%]). The most common co-morbidity in the study population

was hypertension either with or without diabetes and/or dyslipidemia (31, 43.8%), [Table 1].

Table 1. The characteristics of the study population N=71

Variables	Value
Gender (F, %)	Female 49 (69.0%)
Age in years (mean ±SD)	51.7 ±14
Weight in kg (median, range)	70 (50 - 100)
Height in cm (median ,range)	168 (155 - 190)
BMI kg/m^2	25.7 ±3.45 (95% CI 24.9 – 26.5)
Warfarin maintenance dose in mg/day (median, range)	4 (1.5 - 12)
Indication for taking warfarin F, (%)	
HVR	38 (53.5)
AF	23 (32.4)
AF with IHD	6 (8.5)
AF with HVR	4 (5.6)
Total in rows	71 (100.0)
Co- morbidity F, (%)	
Hypertension	11 (15.5)
Hyperlipidemia	8 (11.3)
Hypertension and Hyperlipidemia	7 (10.0)
Hypertension and diabetes mellitus	5 (7.0)
CAD	3 (4.2)
No co-morbidity	37 (52.0)

Keys: AF: atrial fibrillation; BMI/kg2: Body Mass Index; CI: confidence interval; CAD: Coronary artery disease; F: frequency; IHD: ischemic heart disease; HVR: heart valve replacement; SD: standard deviation; %: percent

The accuracy of the two clinical algorithm models

The mean ±standard deviation (SD) warfarin's actual dose was (4.5 ±1.8, range 1.5 – 12 mg/day; 95% CI 4.1 – 4.9), and the MAE ±SD for the warfarin 5 mg fixed dose was 1.44 ±0.1. The mean ±SD warfarin dose calculated based on Gage clinical algorithm model was (5.3 ±1 0.9, range 3.7 – 9 mg/day; 95% CI 5.1 – 5.5, MAE ±SE 1.49 ±0.136; R2 0.121). While the mean ±SD warfarin dose calculated based on IWPC clinical algorithm model was (5.3 ±0.7, range 3.7 – 7 mg/day; 95% CI 5.1 – 5.5, MAE ±SE 1.45 ±0.129; R2 0.195) [Table 2]. The difference in MAE between the warfarin fixed standard dose and the two models (Gage and IWPC) was not significant (MAE 1.44, 1.49, 1.45; P= 0.4) respectively.

The R2 for Gage and IWPC was 12.1% and 19.5% (variations of the difference between the actual dose and the predicted dose) respectively. Needless to say that there was no MAE for the warfarin fixed standard dose as the line is straight. The linear regression correlation between the predicted and actual doses of both clinical algorithm models was significant (P 0.003, <0.0001) for Gage and IWPC respectively.

Clinical practicality of the two clinical algorithm models

In the clinical practicality, all of the three models had high or relatively high percent of subjects (95.0%, 51.9%, and 66.7%) in the middle dose group (3 mg/day - 7 mg/day) for warfarin 5 mg fixed standard dosing strategy, Gage, and IWPC clinical algorithm models respectively. Therefore, warfarin 5 mg fixed standard dosing was more practical than both Gage and IWPC clinical algorithms. However, a small percent of subjects was in the low dose group ≤ 3 mg/day (0.0%, 15.0%, and 10.0%) and high dose group ≥ 7 mg/day (0.0%, 33.3%, and 33.3%) for warfarin 5 mg fixed standard dosing strategy, Gage, and IWPC clinical algorithm models respectively. This indicated clearly that, in the low dose and high dose groups, both Gage and IWPC had high prediction [Figure 1].

Table 2. The warfarin mean doses for the actual, fixed, and the two clinical algorithm models (Gage and 015 participants, the independent predictors of therapeutic dose were: VKORC1 polymorphism −1639/3673 g>a (−28% per alleleIWPC clinical algorithm)

Model	Mean dose ± SD	Range	MAE ±SE	R^2
Actual dose (mg/day)	4.5 ±1.8	1.5 - 12	NA	NA
Warfarin 5 mg fixed standard Dosing	5.0 ±0	NA	1.44 ±0.1	NA
Gage (mg/day)	5.4 ±1	3.7 - 9	1.49 ±0.136	0.121
IWPC (mg/day)	5.4 ±0.7	3.7 - 7	1.45 ±0.129	0.195

Keys: Gage: Gage clinical algorithm; 015 participants, the independent predictors of therapeutic dose were: VKORC1 polymorphism −1639/3673 g>a (−28% per alleleIWPC: international warfarin pharmacogenetic consortium clinical algorithm; MAE: mean absolute error, NA: not applicable; R^2: Co-efficient determination; SD: standard deviation; SE: standard error

Clinical safety of the two clinical algorithm models

In terms of clinical safety, the percent of all subjects (disregarding the dose categories) with severely over-prediction was 28.2%, 22.5%, and 22.5% for warfarin 5 mg fixed standard dosing, Gage, and IWPC respectively. Indicating clearly that the Gage and IWPC clinical algorithms had less severely over prediction compared to warfarin 5 mg fixed standard dosing.

While the percent of severely under-prediction were 12.7%, 7.0%, and 5.6% for the warfarin 5 mg fixed standard dosing, Gage, and IWPC respectively. Indicating clearly that the Gage and IWPC clinical algorithms had less severely under prediction compared to warfarin 5 mg fixed standard dosing [Figure 2].

However, with dose categorization (high and low dose groups) the warfarin 5 mg fixed standard dosing had 100.0% severely

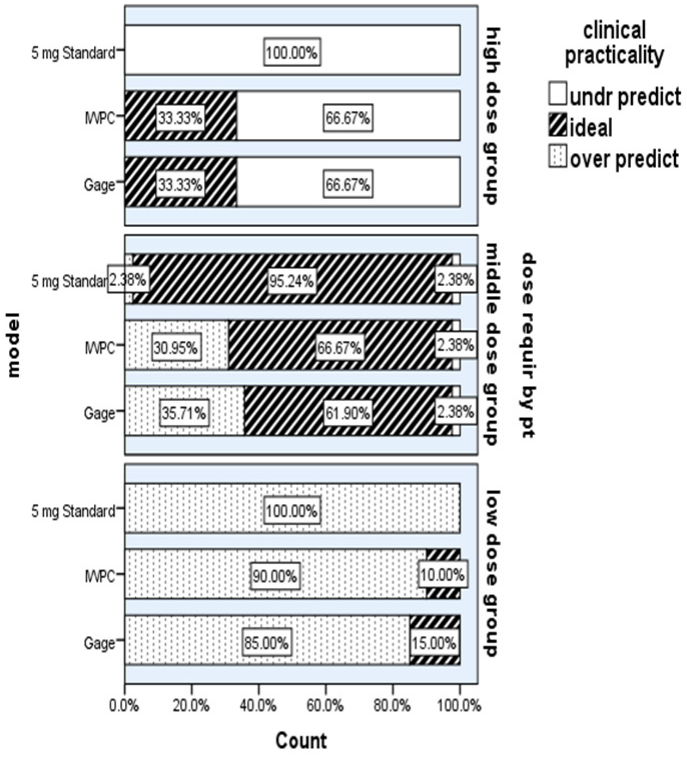

Figure 1. The prediction of clinical practicality in the two clinical algorithms models (Gage and IWPC) compared to warfarin 5 mg fixed standard dosing strategy
Keys: Gage: Gage clinical algorithm; IWPC: international warfarin pharmacogenetic consortium clinical algorithm; in the low dose and high dose groups, both Gage and IWPC had high prediction.

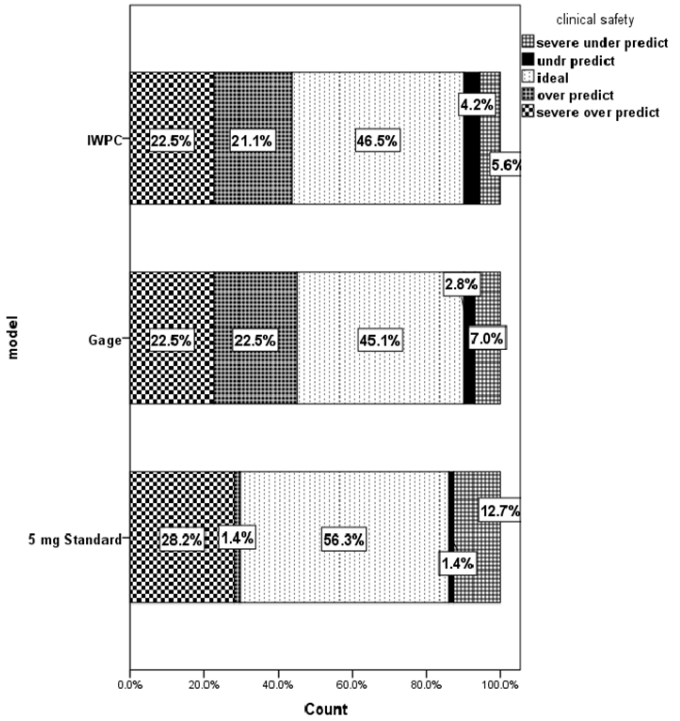

Figure 2. The clinical safety of the two clinical algorithms models (Gage and IWPC) compared to warfarin 5 mg fixed standard dosing strategy
Keys: Gage: Gage clinical algorithm; IWPC: international warfarin pharmacogenetic consortium clinical algorithm. The Gage and IWPC clinical algorithms had less severely under prediction compared to warfarin 5 mg fixed standard dosing.

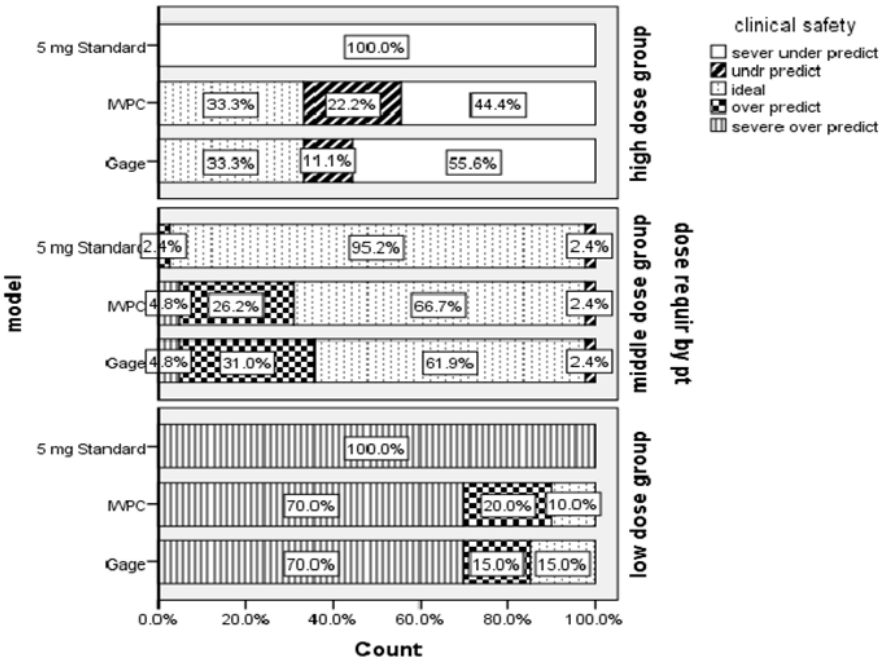

Figure 3. The clinical safety in their different dose ranges comparing the two clinical algorithms models (Gage and IWPC) to warfarin 5 mg fixed standard dosing strategy
Keys: Gage: Gage clinical algorithm; IWPC: international warfarin pharmacogenetic consortium clinical algorithm. The Gage and IWPC had better performance in severely under-prediction and severely over-prediction.

under-prediction in high dose group, while for Gage and IWPC was 55.6%, and 44.4% respectively. Similarly, warfarin 5 mg standard dosing had 100.0% severely over-prediction in low dose group, while for Gage and IWPC was 70.0%, and 70.0% respectively that falls in severely over-prediction [Figure 3].

DISCUSSIONS

There are enormous published studies that have compared the warfarin dosing services delivered by the clinical pharmacist led anticoagulation clinic versus the conventional physician's care that proved the role of the clinical pharmacist with improved clinical outcomes. However, to the best of our knowledge, the current study is the first of its kind that attempted to validate multiethnic warfarin dosing clinical algorithms in Sudanese subjects. Currently there are three models that attempted to guide warfarin anticoagulation. The first model is the warfarin clinical dosing, which report the significance impact of different clinical variables affecting warfarin dosing such as gender, age, BSA, diet and certain medications. The second model is the warfarin 5 mg fixed standard dosing strategy, which compares different warfarin loading doses or warfarin Nomogram at the start of treatment. The last recent model is the pharmacogenetic-guided warfarin dosing, which compares different warfarin pharmacogenetic dosing algorithms to each other or derived their own algorithm.

In our study we have validated and compared the two warfarin clinical algorithms non-pharmacogenetic models namely Gage and IWPC with the warfarin 5 mg fixed standard dosing strategy in a sample of Sudanese subjects. The comparison was based on three methods of accuracy, practicality, and clinical safety as mentioned earlier in the methods section.

The main findings of the current study were that, the MAE of the two clinical algorithms (Gage and IWPC) were comparable to the validation of the sub-group in the original Gage,[7] and IWPC[11] validation studies. In the clinical accuracy, the Gage and IWPC clinical algorithms were as accurate as warfarin 5 mg standard dosing strategy in the study population (accuracy) as there was no significant difference between the fixed and the predicted doses of the two models. The R^2 for Gage and IWPC clinical algorithms was 12.1% and 19.5% (variations of the difference between the actual dose and the predicted dose) respectively. The R^2 indicated that both clinical algorithm models were within the 20% of the difference between the actual and the predicted dose. There was a significant correlation between the predicted and actual doses of both clinical algorithm models. Furthermore, in the clinical practicality, the Gage and IWPC clinical algorithms are more clinically practical than warfarin 5 mg standard dosing strategy in low dose (3 mg/day) and high dose (7 mg/day) groups. Warfarin 5 mg fixed standard dosing is more clinically practical than Gage and IWPC clinical algorithms in the middle dose (3 mg/day – 7 mg/day) group. The main finding in the clinical safety, the Gage and IWPC clinical algorithms have less severely over-prediction (in low dose group) and less severely under- prediction (in high dose group) than warfarin 5 mg fixed standard dosing strategy.

In our study we have higher female's subjects (69.0%) compared to males which was depicted as gender distribution skewed from normal. This finding was similar to other earlier studies conducted in Sudan 56.0% and 73.3%[16,17] respectively. Although the international prevalence of cardiovascular diseases is higher in males compared to females, this study has higher percent of female's participants, as there is no large study in Sudan about the prevalence of cardiovascular diseases among Sudanese. One should consider variations in gender for the generalizability of the study findings.

An earlier Sudanese study conducted by Shrif and his co-workers to investigate the effect of genetic variants on warfarin response, the main dose of warfarin taken by subjects was 5.58 ±2.48 mg/day (203 subjects) compared to actual dose of warfarin 4.5 ±1.8 mg/day in our study (71 subjects). It should be born in mind that initiation of warfarin at a dose near to fixed dosing of 5 mg permits cardiologists to titrate the dose in upward directions rather than the opposite.

The mean age in the current study was (51.7 ±14.9 years) which was higher than Shrif's (39 ±13.9 years) and Ahmed's (41.8 ± 13.0 years) studies.[16,17] It has been known that increasing age is a predictor of warfarin dose nonetheless, it is a non-modifiable risk factor for bleeding (particularly hemorrhage). Therefore, age has great implications on the warfarin dosing in a clinical algorithm model. The current study exhibited increased percent of co-morbidities as compared with Shrif's (47.0% versus 15.3%).[16] However, it was less than Ahmed's study (64.4%).[17] It was anticipated that the increased age of our sample, and the subsequent increased comorbidities impact the warfarin dosing. Consequently, effective and safe warfarin dosing is of at most importance in clinical algorithm model.

The clinical accuracy

In our study, the two clinical algorithm models were comparable in accuracy to the warfarin 5 mg fixed standard dosing strategy. This was different from the finding of Bazan[8] in which clinical algorithms were more accurate than the warfarin 5 mg fixed standard dosing strategy. This may be due to the wide range of doses in our sample and the small sample size. However, the determination coefficient (R^2) of the two clinical algorithms in our study was comparable to the two Bazan and Selim Egyptian's studies.[8,16] Furthermore, the percent of subjects within 20.0% of the actual dose was more than that found in other studies.[2,8,18,19] From a real clinical perspective warfarin 5 mg fixed standard dosing strategy enable gradual titration of anticoagulation in setting with scarcy resources which was the case in low in come country like our setting.

Similar to Bazan and co-workers; all models worked better in the middle dose group, however, in the current study the high dose group and low dose group had better accuracy than that found by Bazan.[8] Our study performed better than Selim's study which exhibited a higher percentage of subjects in the ideal dosage range in the middle dose group and in the high dose group but a lower percentage in the low dose group.[18] Finkelman had comparable results in the percentage of the

subjects in the ideal dose range in the middle dose group, but in the low dose group and high dose group, our study performed better.[2] In high dose group and low dose group, our study and Finkelman study had zero percentage for warfarin 5 mg fixed standard dosing.[2] A Japanese study that validated the IWPC clinical algorithm had comparable results with our findings in the middle dose group but not with the low dose and high dose groups.[19] All those findings from different studies when taken together support our current study finding that the Gage and IWPC clinical algorithm models worked better in low and high dose groups than the fixed dosing strategy.

In the current study when comparing severely over-prediction for Gage and IWPC clinical algorithms with 5 mg standard dosing strategy, the results were comparable with that of Bazan study.[8] However, when comparing severely under-prediction for the two models with 5 mg dosing, this study had less percentage compared to Bazan's study.[8] When looking at the overall over-prediction it is appearent that warfarin 5 mg standard dosing had less percentage of over-prediction than the two clinical algorithm models. However, upon breaking down the over-prediction range, it appears that the majority of subjects of the warfarin 5 mg fixed standard dosing strategy fall in severely over prediction dosage range and the percentage of severely over-prediction was higher than the two clinical algorithms. The same was true for severely under-prediction.

When comparing clinical safety of warfarin 5 mg fixed standard dosing and the two clinical algorithm models in the three dose range groups, these two clinical algorithms were far safer than warfarin 5 mg fixed standard dosing in low dose and high dose groups.

Future prospects

It has been reported that the computer assisted clinical algorithms improves the time in the therapeutic INR target range compared with the clinician's empiric dosing attempts to adjust warfarin dose.[20,21] Other studies have incorporated clinical factors to select the initial warfarin dose.[7,22] One recent study[23] on sub-Saharan Black-African patients (364) has evaluated and compared the performance of 21 machine-learning techniques (MLTs) in predicting stable warfarin dose. The study externally validated (270 subjects) a previously developed[24] Warfarin Anticoagulation in Patients in Sub-Saharan Africa (War-PATH) clinical dose–initiation algorithm based the MAE (differences between the actual and predicted doses). The random forest regression (12.07 mg/week; 95% CI, 10.39–13.76) was the best performing machine-learning technique in the external validation cohort. However, the worst performing technique was model trees (17.59 mg/week; 95% CI, 15.75–19.43). The authors reported that simpler regression techniques perform similarly (MAE of 13.01 mg/week; 95% CI, 11.45–14.58) to more complex supervised MLTs.[23] Furthermore, the use of computer-assisted warfarin clinical algorithms dosing programs by the clinical pharmacist can improve warfarin dosing.[25,26] Combined genetic and clinical factors have proved to predict an algorithm for adjusting individual dosing of warfarin.[27] Some recent African studies have found other diverse variants relevant to predicting pharmacogenetics-based warfarin dosing additionally to those known in CYP2C9 and VKORC1 which indicate the necessity to conduct more pharmacogenomics studies on African population for other potential predictors for warfarin variability in response.[28]

Finally, there were numerous studies that support the effectiveness of pharmacist-led anticoagulation monitoring services in improving INR, stabilize warfarin dose, reduced adverse effects, lower bleeding and thromboembolic events, better quality, lower health care utilization, better patient's satisfaction, and minimizes hospitalization.[29-32]

Current study strength and weakness

Strength the strength of our study relies on the steps followed for the validation process of the two warfarin clinical algorithm models. Furthermore, the included eligible subjects were stable on warfarin fixed standard dose prior to their involvement in the study which permit more accuracy in findings and generalizability.

Weakness the main weakness of the current study was the lack of customized pharmacogenetic algorithm in clinical practice in Sudan. Therefore, there is a need to compare the pharmacogentic guided warfarin dosing with clinical algorithm models, in order to establish more accurate and robust prediction of warfarin dosing.

Current study limitations

Our study has included a small sample size due to the small number of subjects who met the inclusion criteria and were adherent and stabilized to their warfarin dosing. This was mainly a result of unavailability and shortage of brands and the different strengths of warfarin tablets which forced many subjects to change from one brand to another before and during the study period. Also, doses that require multiple warfarin tablets (6 mg need to combine 5 mg with 1 mg) caused confusion in dosing which might have had an impact on anticoagulation status. The study didn't incorporate a pharmacogenetic version of Gage and IWPC due to lack of financial support, and technical constraints. The cross-sectional nature of the study design didn't allow measuring the effect of taking the predicted warfarin dose calculated by the clinical algorithm.

CONCLUSIONS

Both Gage and IWPC clinical algorithms were as accurate as warfarin 5 mg fixed standard dosing with no significant difference between the fixed and the predicted doses of the two models. However, the two models were more clinically practical and safe than warfarin 5 mg standard dosing in low and high dose groups, but not in the middle dose group. The cardiologist can use either models (Gage and IWPC) and stratify subjects to accurate, practical, and clinically safe warfarin dosing. Further research with a larger sample size is needed to assess outcomes based on predictions made by the clinical algorithm models.

Impact of the study

Application of the warfarin clinical algorithms can improve dosing among subjects with heart diseases, particularly in scarce resources.

The warfarin dosing clinical algorithms models were more accurate than the conventional warfarin 5 mg fixed standard dosing.

The clinical pharmacist should provide the cardiologist with the best method that stabilizes warfarin dosing.

The cardiologist can use either models (Gage and IWPC) to improve the warfarin dosing rather than to use the conventional warfarin fixed standard dosing method.

Stratification of subjects based on warfarin clinical algorithms provides accurate, practical, and clinically safe warfarin dosing.

What is known on the topic?

It is known that numerous clinical algorithms have been developed using a number of techniques to improve warfarin dose prediction.

What is not known on the topic?

Do Gage and IPWC clinical algorithm models perform similarly to warfarin fixed standard dose, and what is their validity?

What the current study add?

We have shown that both Gag and IPWC clinical algorithm models performed similarly to warfarin fixed standard dosing strategy, and we have validated the two clinical dose–initiation algorithms in our population.

AUTHORS' CONTRIBUTIONS

We declare that A A Elnour, Islam Mohammed Ahmed, Al-Kubaissi, Khalid A and Mohamed Elmustafa, have made substantial contributions to the conception, design of the work; the acquisition, analysis, interpretation of data, drafted the work, and revised it critically for important intellectual content. In addition to approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DECLARATIONS

Funding

No research funding was received for this study.

Conflicts of interest/Competing interests

No conflicts of interest or competing interests.

Ethics approval

Ethics approval (A/T/KH 444) was obtained from the general department of planning and development, State Ministry of Health in Wad Medani, Gezira State, Medani-Sudan.

Consent to participate

Yes, participant consented.

Consent for publication

We declare consent for the publication of our study.

Availability of data and material

Data transparency associated data available.

ACKNOWLEDGEMENTS

We would like to thank the medical staff and the administration at Medani Heart Centre, Wad Medani-Sudan for their assistance.

ABBREVIATIONS

AF	Atrial Fibrillation
BSA	Body Surface Area
CI	Confidence Interval
CYP2C9	Cytochrome P-450 2C9 enzyme
DOAC	Direct Oral Anticoagulants
DVT	Deep Vein Thrombosis
Exp.	Exponent
HVR	Heart Valve Replacement
INR	International Normalized Ratio
IWPC	International Warfarin Pharmacogenetics Consortium
MHC	Madani Heart Centre
MAE	Mean Absolute Error
MLTs	Machine Learning Techniques
PE	Pulmonary Embolism
R2	Coefficient of determination
SD	Standard Deviation
SE	Standard Error
SPSS	Statistical Package for Social Sciences
USA	United States of America
VKORC1	Vitamin K epoxide reductase enzyme
War-PATH	Warfarin Anticoagulation in Patients in Sub-Saharan Africa

http://www.warfarindosing.org free Web site to help doctors and other clinicians initiate warfarin therapy by estimating the therapeutic dose in patients new to warfarin.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***			
	Item No	**Recommendation**	**Page No**
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4,5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6,7
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8,9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9*
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	12
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	13
		(c) Consider use of a flow diagram	-

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13
		(b) Indicate number of participants with missing data for each variable of interest	13
Outcome data	15*	Report numbers of outcome events or summary measures	12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13-15
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20-21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	-

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.