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Accuracy of an internationally validated genetic-guided warfarin dosing algorithm compared to a clinical algorithm in an Arab population

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ABSTRACT

Purpose: To identify the impact of *CYP2C9*2, *3, VKORC1−1639 G>A* and *CYP4F2*3* on warfarin dose in an Arab population. To compare the accuracy of a clinical warfarin dosing (CWD) versus genetic warfarin dosing algorithms (GWD) during warfarin initiation.
Methods: A cohort of Arab patients newly starting on warfarin had their dose calculated using CWD published in www.warfarindosing.org and were followed for 1 month. Each patient provided a saliva sample. DNA was extracted, purified and genotyped for *VKORC−1639 G>A, CYP2C9*2, CYP2C9*3* and *CYP4F2*3*. After reaching warfarin maintenance dose, the dose was recalculated using the GWD and median absolute error (MAE) and the percentage of warfarin doses within 20% of the actual dose were calculated and compared for the two algorithms.
Results: The study enrolled 130 patients from 12 Arabian countries. Compared to those with wild type, carriers of reduced function alleles in *CYP2C9* required significantly lower median (IQR) warfarin weekly dose [24.5 (15.3) vs. 35 (29.8) mg/week, p=0.006]. With regards to *VKORC*, patients with AA genotype had a significantly lower median (IQR) weekly warfarin dose compared to AG and GG [21(10.5) vs 29.4 (21), p<0.001 for AA vs AG, p<0.001 for AA vs GG]. The MAE (IQR) for the weekly dose of the GWD was significantly lower compared to CWD [8.1 (10.5) vs 12.4 (12.6) (p<0.001)].
Conclusion: CYP2C9 and *VKORC1* variants are important determinants of warfarin dose in the Arab population. The use of the genetic and clinical factors led to better warfarin dose estimation when compared to clinical factors alone.

Introduction

Oral anticoagulants are the cornerstone for management and prevention of thromboembolism. Warfarin, a mainstay oral

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anticoagulant works by inhibiting the vitamin K coagulation factors II, VII, IX and X [1]. A major challenge when using warfarin is the interindividual variability during therapy initiation. This led to either delay in reaching therapeutic range, which increased the risk of thromboembolism, or increased risk of bleeding due to excessive anticoagulation.[1] Although Direct oral anticoagulants are widely used and have overcome many of warfarin drawbacks, there are still indications where vitamin K antagonists are used exclusively and make warfarin irreplaceable.[2] Some examples may include mechanical heart valves,[3] atrial fibrillation with moderate to severe mitral stenosis[4] and antiphospholipid syndrome with venous thromboembolism.[5]

Various methods can be used for warfarin initiation. Fixed (empirical) warfarin dosing, which is most widely used, uses a preset dose of warfarin for one or two days and the international normalized ratio (INR) should be checked on day three or four with the warfarin dose adjusted accordingly. In addition to fixed dosing, other methods were developed aiming for accurate prediction. Clinical warfarin dosing (CWD) uses patients' clinical factors which are incorporated into an algorithm and are used to predict a maintenance dose. Genetic guided warfarin dosing (GWD) uses genetic and clinical factors together to predict a maintenance dose using a validated warfarin algorithm.

It has been estimated that clinical factors alone contribute to nearly 10% of warfarin maintenance dose.[6] However, when genetic factors are added, which is the case in most genetic-guided warfarin dosing algorithms, this value exceeds 50%. A number of GWD algorithms that uses clinical and genetic factors exist. Some are validated in specific races while others are validated in diverse populations.[7,8] Gage et al. and the International Warfarin Pharmacogenetics Consortium (IWPC) algorithms were both used in landmark trials comparing genetic-guided warfarin dosing to conventional warfarin dosing.[9,10] Both algorithms are available online and were validated in diverse populations with better results compared to clinical warfarin dosing or fixed warfarin dosing. Previous studies validated GWD algorithm for patients from the Gulf council countries (GCC). The results of these studies although satisfactory, do not have the ease of use or accessibility of Gage et al. algorithm which is available online at www.warfarindosing.org. One drawback of genetic guided warfarin dosing is the need for genetic testing/ genotyping of the variants which are associated with the warfarin dose in the studied population. This could be problematic if logistics, funds or insurance are not available. The best second option could be clinical warfarin dosing, which is available as an online algorithm and uses variables that are readily available such as weight, height, age, indication, etc….

In this study we aim to identify the impact of *CYP2C9*2, *3, VKORC1−1639 G>A* and *CYP4F2*3* on warfarin dose and describe the Minor Allele Frequency (MAF) for these genetic variants in an Arab population residing in Qatar. Thereafter, we aim to utilize Gage et al. algorithm to calculate the warfarin dose using clinical factors alone (CWD) and using both clinical+ genetic factors (GWD) and compare the accuracy of the 2 algorithms using the median absolute error (MAE) and percentage within 20% of actual dose of both models. This will help in the validation of the Gage et al. algorithm in the Arab population residing in Qatar.

Materials and methods

Study design and settings

This is a cross-sectional study from a previously published trial by our group (Clin-Fix study).[11] We included all patients in the prospective arm of the Clin-Fix study who were recently started on warfarin. Patients were recruited from three centres in Qatar: Al-Wakra Hospital, Hamad General Hospital and Heart Hospital. These three centres are part of the largest health institution in Qatar; Hamad Medical Corporation.

Participants and inclusion criteria

Warfarin patients who were of an Arab descent (those holding a passport with an Arab nationality) between October 2020 and August 2023 were screened for inclusion in the study. To meet inclusion criteria, patients should be newly starting on warfarin, should have at least two International Normalized Ratio (INR) readings in the first week and a weekly INR reading thereafter for four weeks, and have reached a stable warfarin dose (defined as having three subsequent INR readings at least 48 h apart within therapeutic range. Patients were excluded from the study if they were <18 years of age, have a life expectancy <6 months, have severe liver diseases defined as ALT, AST or total bilirubin> 2 times the upper limit of normal, INR> 1.45 at baseline and if non-adherent to warfarin dosing protocol as suggested by warfarin prescriber.

Data collection, and genotyping

Patients were asked to provide a saliva sample using the Oragene-DNA ® (OG-500) self-collection kit (DNA genotek™, Canada) as instructed by manufacturer. This sample was sent to the pharmacogenomics lab at the College of Pharmacy, Qatar University for DNA extraction, quantification and genotyping.

DNA extraction was performed using the prepIT®•L2P manual protocol using a 0.5 ml sample. DNA quantification was carried on using The Nanodrop 2000c Spectrophotometer (Thermo Fisher Scientific™). DNA genotyping and Single Nucleotide Polymorphism (SNP) detection was performed using the real-time polymerase chain reaction (RT-PCR) 7500 Fast System with the TaqMan drug metabolizing enzyme genotyping assay, Applied Biosystems™, Life Technologies. The following genotypes were tested: *CYP2C9*2* (rs1799853), *CYP2C9*3* (rs1057910), *VKORC1-1639G>A* (rs9934438) and *CYP4F2*3* (rs2108622).

Study outcomes

After being recruited and signing the informed consent, patients' warfarin dose was calculated using their clinical parameters as guided by Gage et al. algorithm (available on www.warfarindosing.org). Genetic parameters were not included in the calculation of the warfarin dose initiation. Post week 1, INR results were used to guide the warfarin dosing as per the anticoagulation protocols followed at Hamad Medical Corporation. At the end of the 4 weeks and after reaching stable warfarin dose, warfarin dose was recalculated using both clinical and genetic variables.

To validate the contribution of the genetic factors to warfarin dosing in Arabs, we compared warfarin dose between *VKORC1-1639G>A* (rs9934438) genotypes, *CYP2C9* phenotypes (reduced function versus normal function) and *CYP4F2* (reduced function versus normal function)

We finally compared between the accuracy of the dose predicted using the algorithm clinical component (CWD) and the algorithm clinical + genetic component (GWD).

The primary outcome of the study was to compare the MAE of the genetic-guided warfarin dosing (GWD) algorithm and the clinical warfarin dosing (CWD) algorithm. MAE is defined as the difference between the predicted warfarin dose and the actual warfarin dose. We also evaluated the percentage of predicted warfarin doses within 20% of the actual warfarin dose between the two methods.

Statistical analysis

www.danielsoper.com was used to calculate the sample size. For an effect size of 0.4, a power of 80% and an alpha error of 0.05, at least 100 patients should be included per group.

IBM SPSS 25 ® was used for statistical analysis. Continuous data were described using mean and standard deviation where as categorical data were described as frequencies and percentages. Hardy-Weinberg Equilibrium (HWE) was checked for the various alleles using Chi-Square-Goodness of fit and any allele frequency with a P value> 0.05 was consistent with HWE. Since weekly warfarin dose was not normally distributed, Kruskal-Wallis test was used to compare the median weekly warfarin dose of patients with *VKORC1-1639G>A*: AA, AG and GG genotypes and. We used pairwise comparisons to test for differences between the median of each group

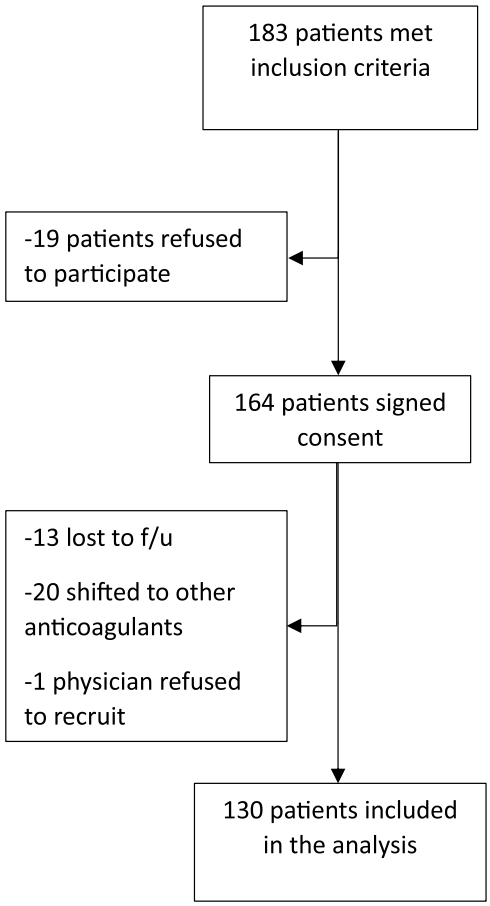

Fig. 1. Patients' flow chart.

compared to the other two groups. Since multiple pairwise comparisons increase the type 1 error, a Bonferroni correction was applied to the p-value and therefore a p-value < 0.0167 (0.05/3) was considered significant. Mann-Whitney U test was used to compare the median weekly warfarin dose of patients with or without CYP2C9 reduced function. Comparing CYP2C9, and VKORC1 multiple groups was performed using Kruskal-Wallis Test. CYP2C9 reduced function was defined as carrying one or two alleles in the CYP2C9*2 and/or *3 genotypes. Similarly, warfarin dose was compared between CYP4F2 reduced function (carrier of one or two copies of *3) and CYP4F2 normal function (*1/*1). Since the same population was used to compare the accuracy of the CWD and GWD algorithms, Wilcoxon Signed rank test (continuous paired data, non-parametric) was used to compare the MAE of both algorithms. McNemar test (nominal data, paired) was used to compare the percentage of predicted warfarin doses within 20% of the actual warfarin dose between the two arms.

Table 1
Baseline characteristics.

Baseline characteristics	(N=130)
Age (years)- mean ± SD	52.6 ± 14.4
Weight (kg)- mean ± SD	92.3 ± 25
Height (cm)-mean ± SD	168.4 ± 8.9
Body mass index (kg/m^2)-mean ±SD	32.5 ± 8.1
Male (%)	85 (65.4)
Blacks (West Africa) (%)	0 (0)
Origin (%)	
GCC & Yemen	43 (33.1)
Levant	42 (32.3)
Egypt	29 (22.3)
Sudan	12 (9.2)
North Africa (Excluding Egypt)	2 (1.5)
Other [a]	2 (1.5)
Indication for anticoagulation (%)	
AF	23 (17.7)
DVT	28 (21.5)
PE	22 (16.9)
Prosthetic valves	7 (5.4)
LVT	19 (15.6)
Other [b]	31 (23.8)
Diabetes (%)	53 (40.8)
Hypertension (%)	64 (49.2)
Heart failure (%)	19 (14.6)
Coronary artery diseases (%)	19 (14.6)
Liver diseases (%)	3 (2.3)
Patients who smoke (%)	32 (24.6)
Patients who drink alcohol (%)	2 (1.5)
Interacting medications (%) [c]	15 (11.5)
Target INR other than 2-3 (%)	1 (0.8)
Anticoagulation duration (%)	
3 months	25 (19.2)
6 months	27 (20.8)
Undefined	17 (13.1)
Life long	61 (46.9)
Baseline INR-mean ±SD	1.1 ± 0.1
Received loading dose (%)	44 (33.8)
Weekly warfarin dose (mg)-median (IQR)	31.5 (26.1)

AF: atrial fibrillation, DVT: Deep vein thrombosis, GCC: Gulf council countries, IQR: Interquartile range, INR: International normalized ratio, PE: Pulmonary embolism, LV: Left ventricular thrombus, SD: Standard deviation, TTR: Time in therapeutic range

[a] Other: Iraq, India

[b] Other: Cerebral vein thrombosis, portal vein thrombosis, mesenteric vein thrombosis, hepatic vein thrombosis, jugular vein thrombosis, renal vein thrombosis, peripheral vascular disease, LV non-compaction, arterio-venous fistula thrombosis, and atrial thrombosis)

[c] Interacting medications: Any medication that interacts with warfarin and has a category higher than category C according to Lexicomp® interaction checker.

Results

Recruitment of patients

183 patients met the inclusion criteria and 130 patients were included in the analysis as indicated in the patient's flow chart (Fig. 1). Table 1 shows the baseline characteristics of the studied population. Median weekly warfarin dose was 31.5 mg and the doses ranged from 9 mg/ week to 110 mg/week with >10 times variation.

Prevalence and MAF of the genetic variants of the study population

All tested genotypes were observed for HWE. Results (Table 2) showed that all genotypes did not show any deviation from HWE. MAF of different Arab nationalities is shown in Table 2. Overall, the MAF for the tested genetic variants were as follows: *VKORC1-1639G>A*=0.47, *CYP2C9*2*=0.1, *CYP2C9*3*= 0.07 and *CYP4F2*3*=0.35. The genotype frequencies are shown in Table 3.

The effect of variant genotypes on warfarin dose

An association between weekly warfarin dose and all tested genetic variants was observed except for *CYP4F2*3*. With regards to *CYP2C9* reduced function alleles, those with at least one reduced function allele required a significantly lower median (IQR) weekly dose compared to the normal function allele [24.5 (15.3) mg/week vs. 35 (29.8) mg/ week, p=0.006] (Fig. 2).

Additionally, carrying an extra copy of reduced function CYP2C9 allele reduced warfarin dose as follows in median (IQR): 35 (29.8) mg/ week for non-carriers, 24.5 (16.5) mg/ week for carriers of one copy, and 16.6 (15.5) mg/week for carriers of 2 copies. (p=0.001 for WT vs carriers of 1 copy variant and p=0.012 for WT vs carriers of two copy variants)

Similar findings were seen in carriers of reduced function alleles of *VKORC1-1639G>A* (rs9934438) (Fig. 3). Those with AA genotype had a significantly lower median (IQR) weekly warfarin dose compared to AG and GG [21 (10.5) vs 29.4 (21) vs 45.5 (30.6) mg/ week, p<0.001 for AA vs AG, p<0.001 for AA vs GG and p=0.001 for AG vs GG]. With respect to *CYP4F2*3* genetic variants, there was no association between the weekly warfarin dose of reduced function and normal function allele (p=0.97).

Comparing the accuracy of CWD and GWD

The MAE (IQR) for the weekly dose of the GWD was significantly lower compared to CWD [8.1 (10.5) vs 12.4 (12.6) (Wilcoxon signed rank test p<0.001)] (Fig. 4a). Similarly, percentage of patients within 20% of warfarin actual dose, were significantly higher in the GWD compared to the CWD [58 (45%) vs. 39 (30%) p=0.013] (Fig. 4b)

Discussion

Our results revalidated the significant association between warfarin dosing and *VKORC1-1639G>A* and *CYP2C9* genetic variants in this Arab cohort. Warfarin dose was 30% lower in patients who had at least one reduced function allele compared to wild type in the *CYP2C9* gene. Furthermore, *VKORC1*- AA or AG genotypes had over 50% and 30% reduction in warfarin dose, respectively compared to wild type. The results clearly indicate the higher accuracy of GWD using Gage et al algorithm to predict warfarin dose compared to CWD. This is evident with >30% lower MAE and 50% increase in warfarin doses within 20% of the actual dose compared to CWD.

Previous studies in the middle east and GCC area have shown similar results with regards to the MAF and the association of warfarin dose with VKORC and CYP2C9 genetic variants.[12] Similar to our study, CYP4F2 was not associated with warfarin dose variability. A systematic review that included articles addressing the MAF of genotypes and factors associated with warfarin dose showed that the mean MAF of VKORC for different populations in the middle east was 46% (MAF in our population was 47%). Similarly, the mean MAF for CYP2C9*2 and CYP2C9*3 were 11.6% and 9.5% respectively (MAF in our population was 10% and 7%).[13] With the exception of CYP4F2, all the mentioned variants were associated with warfarin dose and were included in most of the derived genetic algorithm to predict a warfarin dose in their respective populations. In comparison to regions outside the MENA, the MAF for *VKORC1-1639G>A* and *CYP2C9*2* and **3* resemble those of the European decent (0.41,0.12 and 0.07) rather than those with African American decent (0.1, 0.02 and 0.01) or East Asian decent (0.86, 0.002 and 0.03).[14,15]

The clinical utility of the GWD compared to conventional warfarin dosing with fixed warfarin dosing (FWD) or CWD was previously established.[9,16] The European Pharmacogenetics of Anticoagulant Therapy trial (EUPACT) compared GWD to FWD and showed better

Table 2
Minor Allele frequencies for overall population and most prominent nationalities in the Arab population.

	GCC and Yemen (n=43)	Levant (n=43)	Egypt (n=29)	Sudan (n=12)	Overall* (n=130)
VKORC1 -1639G>A	0.38	0.58	0.48	0.38	0.47
*CYP2C9*2*	0.07	0.1	0.14	0.13	0.1
*CYP2C9*3*	0.06	0.08	0.09	0.04	0.07
*CYP4F2*3*	0.28	0.37	0.45	0.33	0.35

* Including other nationalities not mentioned in the table

Table 3
Genotype frequency for overall population.

Genotype Frequency no (%)	Cohort (N=130)	P-Value
VKORC1(-1639G>A)		0.89
GG	37 (28.5)	
AG	64 (49.2)	
AA	29 (22.3)	
CYP2C9 *2 & *3		0.83 & 0.39
****1*1***	91 (70)	
****1*2/*2*2***	24 (18.5)	
****1*3/*3*3***	18 (13.8)	
CYP4F2*3 (C>T)		0.38
CC	52 (40)	
CT	64 (49.2)	
TT	14 (10.8)	

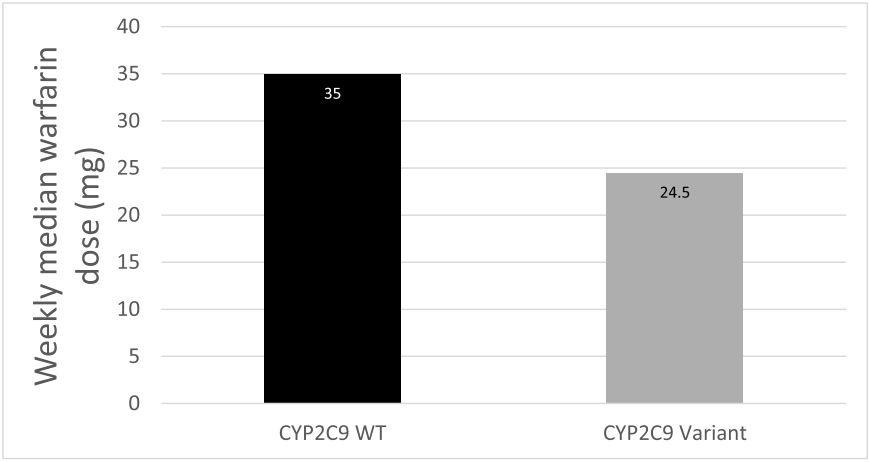

Fig. 2. Effect of *CYP2C9* loss of function genotypes on weekly warfarin dose (n=130). WT: Wild Type.

percentage time in therapeutic range (PTTR) compared to GWD [67.4 vs 60.3%, adjusted difference= 7 percentage points; (95% CI, 3.3 to 10.6)].[9] Similarly, when compared to the CWD, the GWD in the Genetic Informatics Trial (GIFT) was associated with a lower primary outcome [10.8 vs 14.7%, relative risk= 0.73 (95% CI, 0.56-0.95)], which was a composite of major bleeding, INR of 4 or greater, venous thromboembolism, or death.[16] The exception was the Clarification of Optimal Anticoagulation through Genetics trial (COAG), which showed no difference in the PTTR between GWD and CWD [45.2 vs 45.4, adjusted difference= −0.2 (95% CI, −3.4 to 3.1)].[10] Nearly a third of the patients recruited in the COAG trial were of African American decent and were tested for variants in the *CYP2C9*2* and *CYP2C9*3*. The prevalence of these variants is low in the African American population compared to the European white population.[17] Also, these patients have other genetic variants associated with the warfarin dose like *CYP2C9*5, CYP2C9*6, CYP2C9*8, CYP2C9*11* and The *CYP2C* (rs12777823) cluster.[17] Additionally, post-hoc analysis of the COAG trial in the GWD group showed that the PTTR of the African American patients was significantly lower compared to their European counterparts (35.2% vs. 43.5%; mean difference, −8.3%; P = 0.01).[10]

Findings of our research help to confirm the importance of GWD in predicting warfarin dose more accurately compared to CWD in the Arab population. Although non-homogenous, no large differences were observed in the results between different nationalities of the Arab population. In addition to better accuracy, previous landmark trials comparing GWD to conventional dosing in homogenous populations showed better clinical outcomes, this is especially important during warfarin initiation when the warfarin requirement is not known.[9,16] The uniqueness of this study stemmed from the fact that it looked at warfarin associated genotypes in an Arab population with different nationalities rather than concentrating on one nationality. In addition, this approach helped in validating Gage et al. algorithm in the Arab population.

Among the limitations in the study is that other genotypes associated with warfarin dose were not tested E.g. *CYP2C9*5,*6,*8, *11* and the *CYP2C* (rs12777823) cluster. These variants, although important, were not shown to be consistently associated with warfarin dosing in previous studies in Arabs.[13] Although we tried our best to include various nationalities from different Arab countries, some regions like North Africa (excluding Egypt) were under represented which may affect the generalizability of our study to this population.

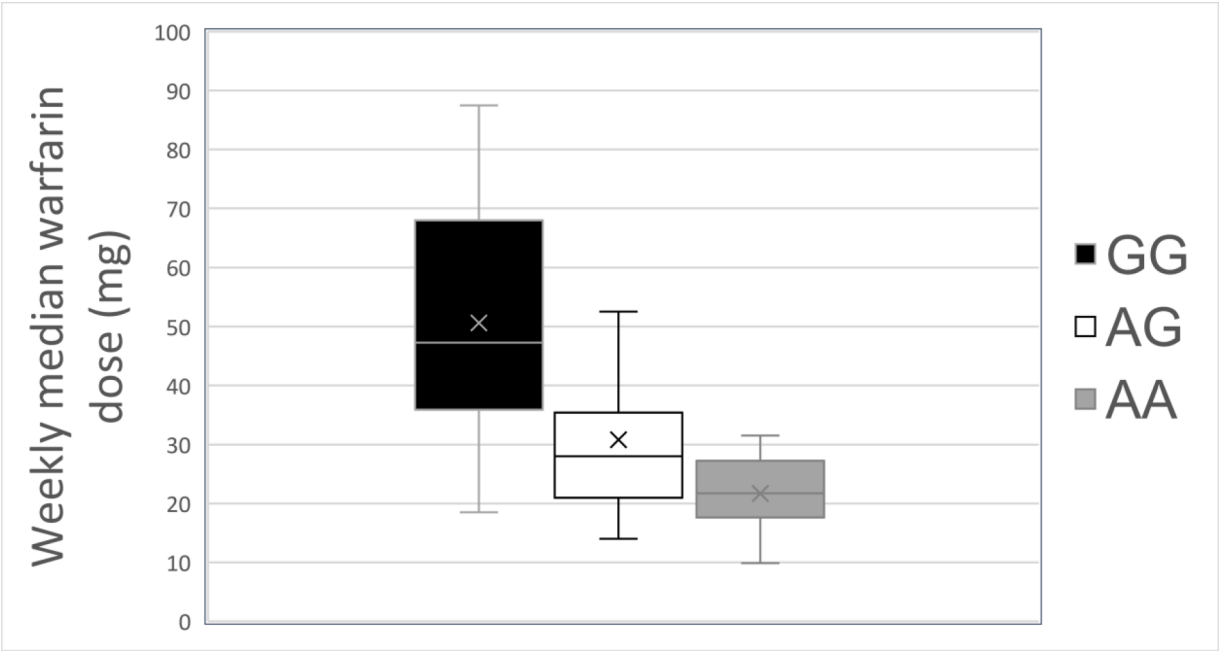

Fig. 3. Effect *VKORC1c.-1639G≥A* genotypes on weekly warfarin dose (n=130).
Weekly warfarin dose median and interquartile range represented in box and whiskers plot. Maximum and minimum values are represented by the lines above and below the boxes.

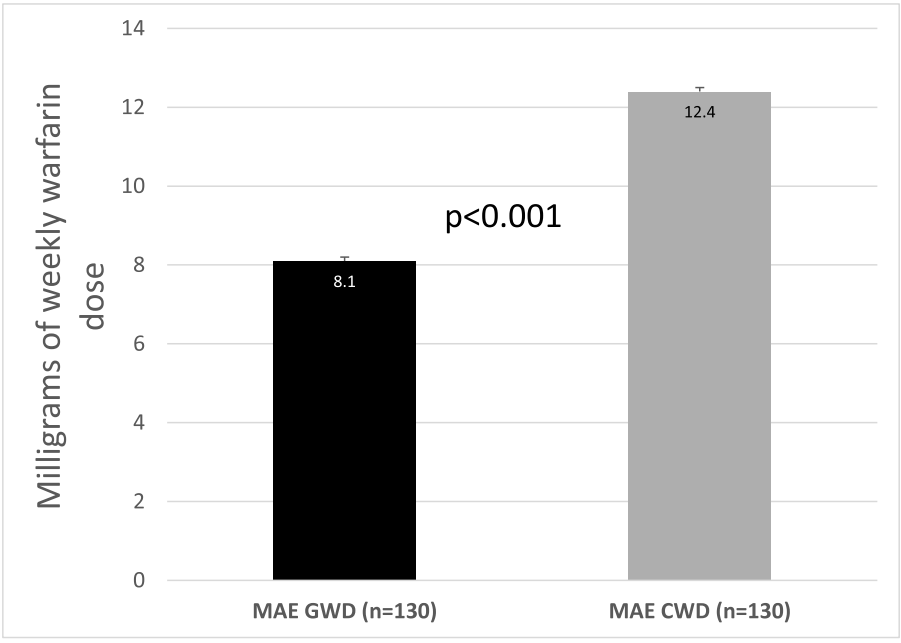

Fig. 4a. Median absolute error (MAE) of predicted warfarin dose using GWD compared to CWD (mg/week).
MAE: The median difference between the predicted warfarin dose and the actual warfarin maintenance dose, CWD: Clinical Warfarin Dosing, GWD: Genetic guided warfarin dosing.

Conclusion and future directions

CYP2C9 and *VKORC1-1639G>A* variants are important determinants of warfarin dose in the Arab population. The use of the genetic and clinical factors led to better dose estimation when compared to the clinical factors alone. Future studies should explore a

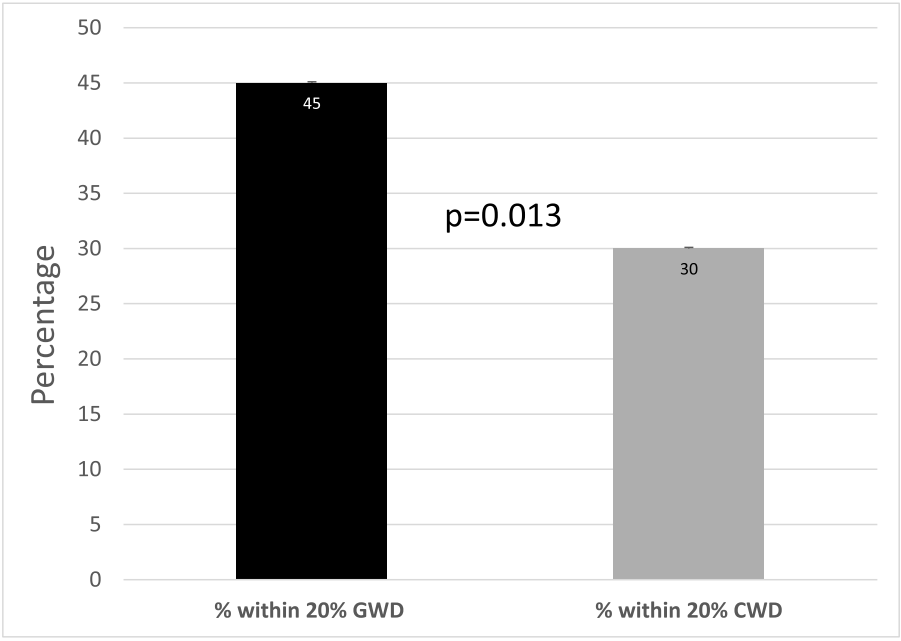

Fig. 4b. Percentage of predicted warfarin doses within 20% of the actual maintenance dose of GWD compared to CWD. CWD: Clinical Warfarin Dosing, GWD: Genetic guided warfarin dosing.

unique GWD algorithm in the Arab population and compare its results to Gage et al. or other universal algorithms.

Authors' Declarations:

1. Funding: The study was funded by a grant from Hamad Medical Corporation (IRGC-06-JI-19-205)
2. Conflict of interest: The authors have no financial/ non-financial disclosures to report.
3. Data availability: Available on reasonable request from corresponding author.
4. Code availability: Not applicable
5. Authors' contributions: Amr M. Fahmi and Ahmed El Bardissy are equal contributors as first author. Hazem Elewa is the corresponding author. Amr M. Fahmi, Ahmed El Bardissy, Hazem Elewa and Mohamed Omar Saad helped in all study roles and reviewed the manuscript. Amr Fares, Ahmed Sadek, Mohamed Nabil Elshafei, Asma Eltahir and Asmaa Mohamed helped in patient screening and reviewing the manuscript.
6. Ethical approval: The study was approved by Hamad Medical Corporation Medical Research Centre (HMC/MRC).
7. Informed consent: Recruited subjects signed an informed consent to participate in this research.
8. Consent for publication: Approved from HMC/MRC

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Hazem Elewa reports financial support was provided by Hamad Medical Corporation. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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