Review Article

# Warfarin Therapy and Pharmacogenetics: A Narrative Review of Regional and Iraqi Studies

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## Abstract

The aim of this work was to review several studies investigating the effects of genetic polymorphisms on warfarin dosing in regional and Iraqi studies and to report any consistent pattern of relevant findings. Despite the growing use of the recently introduced direct oral anticoagulants, warfarin is still the mainstay agent for oral anticoagulation because of its cost-effectiveness. However, a difficulty to establish a stable warfarin dose is frequently encountered. In addition to the warfarin narrow window of efficacy and safety, the main contributor to the challenging dosing is the wide range of variability in warfarin pharmacokinetics and pharmacodynamics among different patients as well as within the single patient context. A link between nonappropriateness of warfarin doses and dramatically increased risk of thromboembolic and hemorrhagic events has been well documented. Several single nucleotide polymorphisms (SNPs) in the genes implicated in warfarin pharmacokinetic and pharmacodynamic processes have been highlighted as possible contributors to warfarin dosing instability. Vitamin K epoxide reductase complex 1 gene SNPs have consistently been found to be the predominant genetic factor contributing the dosing variations. The SNP rs9923231 was significantly associated with the greatest predicting capability of warfarin dosage. However, a range of about 30%–50% of the variances in warfarin dosing was explained by the combined contribution effect of several genetic and nongenetic (clinical) factors in the regional and Iraqi studies.

**Keywords:** Iraq, Middle East, pharmacogenetics, warfarin

## Introduction

Warfarin is the commonest oral agent used for anticoagulation purposes. Warfarin's indications include the therapeutic and prophylactic management of thromboembolic conditions associated with postoperative patients of orthopedic and cardiac valves surgeries, atrial fibrillation, and vascular thrombosis.[1] Despite the growing use of the recently introduced direct oral anticoagulants, warfarin is still the mainstay agent for oral anticoagulation.[2]

Warfarin anticoagulant effects were thought to be mediated by the inhibition of vitamin K epoxide reductase complex 1 (VKORC1), which is encoded by the *VKORC1* gene. Such inhibition causes a reduction in vitamin K that acts as a cofactor involved in the synthesis of pro-thrombotic factors.[3]

Despite effectiveness, a difficulty to establish a stable warfarin dose is frequently encountered. In addition to the warfarin narrow window of efficacy and safety, the main contributor to the challenging dosing is the wide range of variability in warfarin pharmacokinetics (PxK) and pharmacodynamics (PxD) among different patients as well as within the single patient context. Consequently, a broad range of warfarin doses has been used in different clinical situations as low as 0.5 mg/day and as high as 20 mg/day.[4-7]

A link between nonappropriateness of warfarin doses and dramatically increased risk of thromboembolic and hemorrhagic events has been well documented.[7-9]

In terms of PxD, there are two racemization forms of warfarin (R and S isomers) with different inhibitory

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activity on VKORC1 (S > R).[10] Warfarin-mediated inhibition to VKORC1 diminishes the amount of vitamin K available in the reduced form (see [Figure 1]).[3]

VKORC1 is essential in the production of the biologically active vitamin K (in the reduced form) in proper quantities, the function of which is complementary to a carboxylase enzyme (γ-glutamyl carboxylase [GGC]) involved in the activation of a variety of pro-thrombotic factors such as II, VII, IX, and X.[9,11,12] The effects of vitamin K are also regulated through another governing factor, the calumenin (CALU) protein.[13]

In terms of PxK, cytochrome P450 enzymes (CYP) were found to be involved in warfarin phase-1 metabolism. The main metabolizing enzyme of the S-warfarin is CYP2C9 subtype, whereas R-warfarin is predominantly metabolized through CYP3A4 subtype with a partial enzymatic participation of several CYP1A and CYP2C isoenzymes.[14-17]

Several sulfate and glucuronide metabolites of warfarin have been identified; however, the metabolic pathways of warfarin in phase-2 reactions have not been appropriately investigated.[18]

The role of pharmacogenetics in the drug therapy is often illustrated by the exemplar consideration of warfarin pharmacogenetics. Genetic factors affecting PxK and PxD processes of warfarin have been explored in several pharmacogenetic investigations to interpret the variability in response to warfarin therapy.[8,19,20]

## *VKORC1* and *CYP2C9*

The single nucleotide polymorphisms (SNPs) rs9923231 in the *VKORC1* gene as well as rs1799853 (*2 mutated allele) and rs1057910 (*3 mutated allele) in the *CYP2C9* gene were of characteristic significance in determining the dose and risk of clinical complications of warfarin therapy.

A significantly reduced warfarin dose was required in patients carrying the A allele of the SNP-1639 G > A in *VKORC1* gene in several different populations.[20-27]

Individuals carrying the CYP2C9*2 and *3 allele genotype are phenotypically known as poor metabolizers. These phenotypes were significantly associated with a lower warfarin dose requirement, a longer delay to achieve the desired international normalized ratio (INR) range after the warfarin initiation, and a higher hemorrhage risk.[4,28]

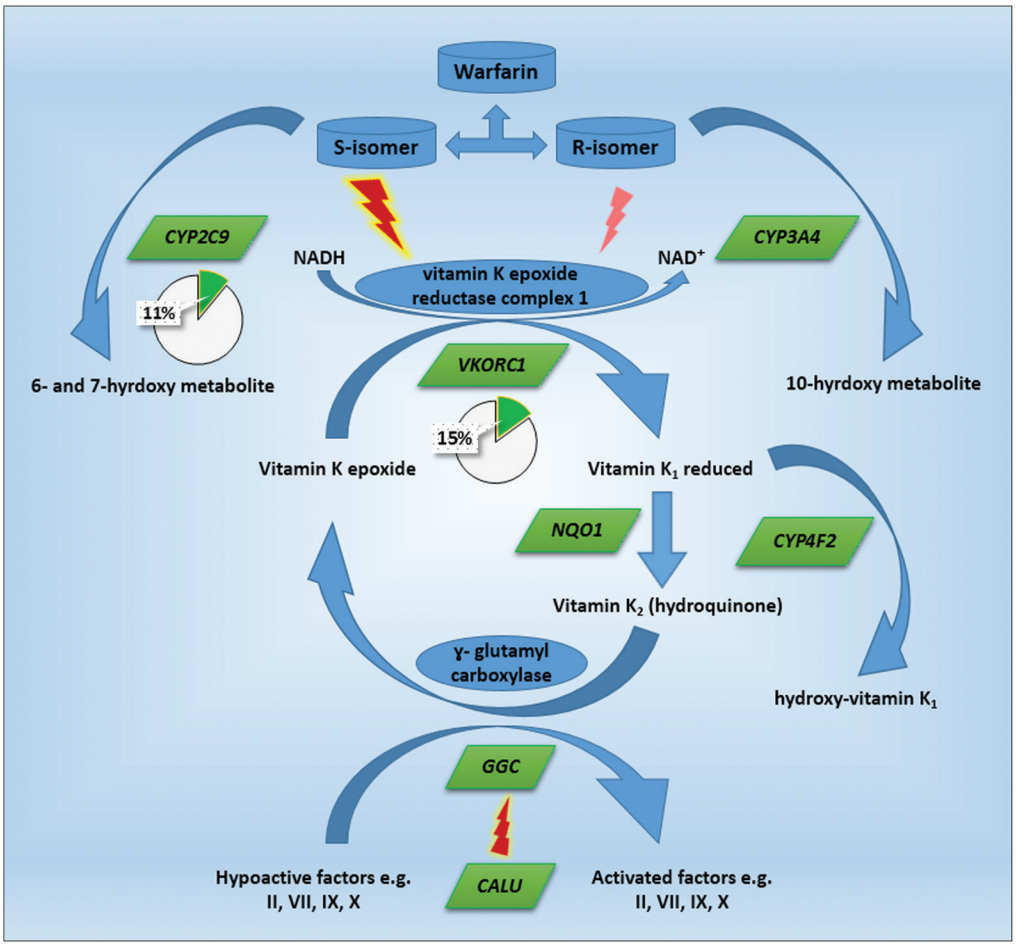


**Figure 1:** The genes involved in the PxK and PxD of warfain and the approximated percentage of warfain dose variability explained by the main pharmacogenes reported as a regression coefficient in a Qatari study

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Different *CYP2C9* SNPs have been investigated in warfarin-treated patients, and a significant impact on the metabolism has been revealed in a number of them (e.g., the mutated alleles *4, *5, and *11).[29-31]

## CYP4F

Many studies examined the effect of *CYP4F* genetic polymorphism on warfarin dosing. Warfarin stable dose was significantly different (about 1 mg per day variance) among different genotypes for the SNP rs2108622 in the *CYP4F2* gene.[32] In contrast, such significant association was not found in Qatari or Egyptian patients.[33,34]

## CALU

To our knowledge, five studies have investigated the effect of the SNP rs339097 in the *CALU* gene on warfarin dose. A significant association of the mutated allele "G" with increased warfarin dose was noted in different populations except in two studies (in Asian and Egyptian populations).[35]

## APOE

Several attempts studied the effect of the SNP rs429358 (T > C) in *apolipoprotein E* (*APOE*) gene on the dose ($n$ = 3), efficacy ($n$ = 1), and safety ($n$ = 2) of warfarin therapy.[33,36-40]

The studies investigating the effect on warfarin dose underlined a significant association of the "T" allele for the SNP rs429358 (T > C) in *APOE* gene with a lower dose requirement in Europeans and Egyptians but not in African-Americans.[33,38,39]

The homozygous "TT" genotype for the SNP rs429358 in *APOE* gene was significantly associated with a longer duration to attain stable warfarin dosing.[37]

The "C" allele association with a risk of bleeding due to warfarin therapy was found to be statistically significant in a study (European venous thromboembolism patients) and insignificant in another (prosthetic cardiac valve patients).[36,40]

Another SNP (rs7412 T > C) in the *APOE* gene was also studied for an effect on dose and clinical outcomes of warfarin therapy.[33,36-38,40-42] A significantly higher dose was associated with the "CC" genotype, and a lower dose was associated with the "T" allele.[33,42] However, the two allele were insignificantly affecting the dose in two studies.[36,38] A significantly longer period to attain stable dosing was found in the "CC" genotype for the SNP rs7412 in comparison to the other genotypes.[37] No significant difference in the bleeding risk was found among the different genotypes.[40]

## GGC

Several pharmacogenetic studies involved the *GGC* gene variant (rs11676382 C > G). Some of these studies reported that a lower warfarin dose requirement was associated with the mutated allele as compared to the C allele, and this association was statistically significant.[43-47] However, no such significance was found in other studies.[36,48-50]

## NQO1

The *NQO1* gene encodes reduced nicotinamide adenine dinucleotide phosphate dehydrogenase quinone 1. This enzyme functions to reduce vitamin K (one of the quinone substrates of the enzyme) into a hydroquinone compound as a part of a recycling process (see [Figure 1]).[51]

The effect of the SNPs *NQO1* rs1800566 (G > A) and rs10517 (A > G) on warfarin dose was studied, and the "AA" genotypes for both SNPs (rs1800566 in Hispanic population and rs10517 in Asians) required a significantly higher warfarin dose.[52-55]

At the same time, the risk of bleeding was significantly higher in the individuals carrying the "A" allele for the SNP rs1800566 in comparison to the noncarriers.[56]

It has been shown that individuals carrying the "G" allele for the SNP *NQO1* rs10517 had about 50% increase in warfarin dosage in comparison to the reference genotype "AA."[51]

The SNP rs1800566 was relevant to the therapeutic warfarin dosing requirement. Bress *et al.* (2012)[52] highlighted that allele A required an additional 34% of warfarin dose to maintain the therapeutic range in Hispanic population (after the adjustment of remaining predictor factors).

Duconge *et al.* (2016) underlined a similar finding.[53] A significantly higher warfarin dose was noted in AA and AG genotypes as compared to GG genotype in Caribbean Hispanics from Puerto Rico.[53]

The most consistent finding among the studies was that the SNPs in the *VKORC1* gene were the predominant genetic contributor to about a third of variability in warfarin doses. The VKORC1 genotype is considered the genetic factor with the greatest predicting capability of warfarin dose.[20-25]

Furthermore, several investigations studied the possibility of constructing an optimized dosing model by considering several contributing factors (genetic and otherwise) to warfarin dose variability.[22,26,57] The regression analysis revealed that the patient's genotype for SNPs in VKORC1 and CYP2C9 and clinical parameters such as body mass index, age, and the underlying condition interpreted more than 50% of the dose variances.[57]

The Food and Drug Administration agreed in 2007 to incorporate an advisory statement to the warfarin products supporting the usefulness of screening for the VKORC1 and CYP2C9 SNPs to optimize the estimation of warfarin starting dose.[58]

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Although its importance has been well documented, there is still a limited effort to review the available literature about warfarin pharmacogenetics in the regional populations.

Moreover, studies reviewing the available investigations on the pharmacogenetics of warfarin in the Iraqi population were not conducted.

Multiple searches for the relevant articles were performed in Google search engine by typing "warfarin and" or "warfarin therapy and" and the genes of interest "CYP2C9," "CYP3A4," "CYP4F2," "VKORC1," "NQO1," "GGC," "CALU," or "APOE" followed by the words "genetic polymorphisms." The pharmacogenetics studies conducted in Iraq and the Middle East region were considered for the purpose of this review. Otherwise, the studies that were carried out in regions other than Iraq and the Middle East were excluded. Several findings were reported.

## Regional Pharmacogenetic Studies

In 207 Egyptian patients, Shahin *et al.* (2011) studied *VKORC1* (3673 G > A), *CYP2C9* *2*3*4*5*8, *CYP4F2* (V33M; rs2108622), *APOE* (rs429358, rs7412), and *CALU* (rs339097) gene polymorphisms.[33]

The mutated genotypes for the SNPs *VKORC1* rs9923231, *CYP2C9* gene, and *APOE* ε2 haplotype had a significantly reduced warfarin dosage ($P < 0.05$). The combined contribution of these factors and clinical parameters such as advanced age, pulmonary embolism, and being a tobacco smoker interpreted about a third of the variance in warfarin dosing (see [Table 1]).[33]

CALU rs339097 variant was significantly associated with an increased dosage requirement; however, the regression analysis revealed that the effect size was not strong enough to contribute to warfarin dose prediction ($P > 0.05$).[33]

In 246 Tunisian individuals, Ajmi *et al.* (2018) revealed that the significantly increased warfarin responsiveness was indicated in the homozygous or heterozygous genotypes carrying the variant alleles of the *CYP2C9* gene (*2 or *3) or the haplotypes H1 and H7 of the *VKORC1* gene.[59] The findings indicative of the patients' "sensitive" phenotype were dramatically elevated INR measurements while on therapy and reduced dosage requirement with statistically significant difference in comparison to the reference wild-type genotype.[59]

On the other hand, a "resistant" phenotype was associated with the homozygous or heterozygous genotypes carrying the variant alleles of the SNP rs2108622 in the *CYP4F2* gene, the SNP rs1043550 in the *CALU* gene, or the haplotypes H3 and H12 of the *VKORC1* gene. The findings indicative of the patients' "resistant" phenotype were a longer duration to attain the desired range and an increased dosage requirement.[59]

Collectively, the eight genotypic factors, the four haplotypes of *VKORC1* gene (H1, H3, H7, and H12) and the two variant alleles of the *CYP2C9* gene (*2 and *3), the SNP rs2108622 in the *CYP4F2* gene, and the SNP rs1043550 in the *CALU* gene, had a combined effect that contributed to the explanation of about 50% of the dose variances.[59]

In 149 warfarin-treated Qatari patients, Bader *et al.* (2020) found that the homozygous or heterozygous genotypes for the variant alleles (*2 or *3) of the *CYP2C9* gene had a significantly reduced median of warfarin dosages ($P < 0.001$) with about 10 mg/week difference in the dosage requirement with every addition of mutated allele to the genotype.[34]

Consistently with Shahin *et al.* (2011),[33] Bader *et al.* (2020) did not find a significant effect to the SNP rs2108622 in the *CYP4F2* gene on warfarin dosing.[34]

The clinical factor such as the medical conditions (hypertension and heart failure) and being smoker as well as the genetic factors including the SNP rs9923231in the *VKORC1* gene and the variant alleles (*2 and *3) contribute to the explanation of about 40% of the variances in warfarin dosing ($P < 0.001$) in Qatari individuals.[34]

In a study on 425 Jordanian individuals, the effects of the SNPs in the *CYP4F2*, *APOE*, and *CYP2A6* genes on the warfarin dosages were investigated. The studied SNPs were rs2108622, rs7412, rs405509, and rs1801272.

The starting dose of warfarin was significantly different among the different genotypes of the SNP rs7412 in the *APOE* gene. When warfarin was initiated, the heterozygous genotype for the SNP rs1801272 in the *CYP2A6* gene had a significantly higher frequency of warfarin-sensitive individuals in comparison to the wild genotype. In the maintenance therapy duration, the heterozygous genotype for this SNP had also a significantly higher frequency of poorly responding patients and significantly different INR range in comparison to the wild genotype ($P < 0.05$).[60]

An earlier pharmacogenetic study in 2018 by Al-Eitan *et al.* highlighted a significant effect for the genetic variants in the *CYP2C9* and *VKORC1* genes on the starting dosage of warfarin. A significant difference was also noted among the different genotypes for several SNPs in the *CYP2C9* and *VKORC1* genes as well as their haplotypes in terms of category of warfarin response (whether sensitive, moderately sensitive, or resistant) ($P < 0.05$).[61]

In the Saudi Warfarin Pharmacogenetic cohort, Al Ammari *et al.* (2020) investigated 936 Saudi individuals and examined the relationship between the dosage and the duration required to attain the desired stability in the INR measurements and the participants' genotype for the SNP rs9923231 in the *VKORC1* gene.

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**Table 1: The reviewed investigations that studied the effects of pharmacogenetics on warfarin therapy in Iraq and the Middle East region**

| The studied population | Association significance of warfarin and studied genes | Contribution to explain warfarin dose variability |
|---|---|---|
| Egyptian[33] | Significant association of the "CC" genotype of *VKORC1* rs9923231 SNP with a higher dose in comparison to the other genotypes | Total (genetic and nongenetic) factors explained 31% of warfarin dose variability |
| | Significantly decreased doses of warfarin were associated with CYP2C9 SNP ($P = 0.0004$)<br>Significantly decreased doses of warfarin were associated with APOE ε2 haplotype ($P = 0.01$). Significantly decreased doses of warfarin were associated with increasing age ($P < 0.0001$) | Nongenetic factors (partial $R^2$ for age = 8.11%, for pulmonary embolism = 3%, and for smoking = 1.88%) |
| | The CALU SNP rs339097 ($P = 0.066$) and CYP4F2 SNP rs2108622 ($P = 0.314$) were not significantly predicting warfarin dosing | Genetic factors (partial $R^2$ for VKORC1 SNP genotype = 10.33%, CYP2C9*1,*2,*3,*4,*5,*8 genotype = 5.17%, and APOE genotype = 2.53%) |
| Qatari[34] | Significant association of the "AA" genotype of *VKORC1* rs9934438 SNP with a lower dose in comparison to the other genotypes ($P < 0.0001$) | Total (genetic and nongenetic) factors explained 39.2% of warfarin dose variability |
| | Significantly decreased doses of warfarin associated with an expression of one or more mutated alleles of CYP2C9*2 or *3 in comparison to nonexpressers ($P < 0.001$) | Nongenetic factors (r for hypertension = 17.8%, for heart failure = 17.6%, and for smoking =25.1%) |
| | *SNP in CYP4F2* was not significantly associated with warfarin dosing | Genetic factors (r for VKORC1 genotype = 38.2% and for CYP2C9*1,*2,*3 genotype = 33%) |
| Tunisian[59] | Significant association was found between hyperresponsiveness and acenocoumarol (warfarin-like) therapy (the requirement of decreased dosing) and allele expressers of CYP2C9*2 or *3 and of VKORC1 (H1 and H7) ($P < 0.05$) | Total (genetic and nongenetic) factors explained 48.1% of warfarin dose variability |
| | Conversely, mutant allele expressers of VKORC1 (H3 and H12), CALU SNP rs1043550, or CYP4F2 SNP rs2108622 were significantly associated with hyporesponsiveness (the requirement of increased dosing) ($P < 0.05$) | Nongenetic factors (partial R for age = −0.4 and for body mass index = 0.215)<br>Genetic factors (regression coefficients not specified) |
| Jordanian[60] | During the warfarin initiation, significantly different doses were noted among the different genotypes of the SNP rs7412 in the *APOE* gene | The study did not involve a regression analysis |
| | Additionally, the heterozygous genotype for the SNP rs1801272 in the *CYP2A6* gene had a significantly higher frequency of warfarin-sensitive individuals in comparison to the wild genotype | |
| | During the duration of warfarin maintenance therapy, the heterozygous genotype for SNP rs1801272 in the *CYP2A6* gene had also significantly different INR range in comparison to the wild genotype ($P < 0.05$) | |
| | No significant difference was found in warfarin dosing among the different genotypes of the SNP rs405509 of *APOE* or the SNP rs2108622 of *CYP4F2* ($P > 0.05$) | |
| Jordanian[61] | The warfarin dosing was significantly different among the different genotypes of the SNPs of the *CYP2C9* gene (*3 allele) and the SNPs of the *VKORC1* gene (rs10871454, rs8050894, rs9934438, and rs17708472) ($P < 0.001$). Various haplotype combinations from the aforementioned SNPs required significantly different doses. | The study did not involve a regression analysis |
| | The allelic genotypic presentation of TAT for the three studied SNPs in *CYP2C9* and CCGG for the four studied SNPs in the *VKORC1* gene required significantly different warfarin dosing in comparison to the other haplotypes. A stronger association was reported between being a mutant VKORC1 allele carrier and INR readings during the warfarin therapy initiation duration as compared to being a CYP2C9 variant allele carrier | |
| Saudi[62] | The presence of a mutant allele C for the SNP rs9923231 in the *VKORC1* gene resulted in a significantly higher warfarin dose requirement. The dose increment was even higher for the homozygous presentation as compared to the heterozygous presentation of the C allele | The total of nongenetic and genetic factors explained 31% of warfarin dose variability |
| | | The nongenetic factors explained 14%. The genetic factor being the C allele expression for the *VKORC1* SNP rs9923231 interpreted a further 17% of warfarin dose variability |

**Table 1: Continued**

| The studied population | Association significance of warfarin and studied genes | Contribution to explain warfarin dose variability |
|---|---|---|
| Iraqi[63] | In comparison to the homozygous and heterozygous genotypes for the *CYP2C9*2* and **3* alleles identified in the study, a significant increase was reported in the warfarin dosage requirement to attain the desired target range among the wild genotypes ($P < 0.05$)<br>The mutated homozygous genotypes for the SNP rs9923231 in the *VKORC1* gene were significantly associated with higher warfarin dosages as compared to the heterozygous and wild genotypes ($P < 0.05$) | The study did not involve a regression analysis |
| Iraqi[64] | The allele *3 of the *CYP2C9* gene and the genotypes for the SNP rs9923231 *VKORC1* gene were significantly affecting the dosages of warfarin. A significantly decreased dose was required in carriers of mutant alleles of the aforementioned SNPs ($P < 0.05$) | Overall, the genetic and nongenetic factors explained 54% of the variances in warfarin dosages. These factors included weight, gender, and the genotypes for the studied SNPs in the *VKORC1* and *CYP2C9* genes |

*APOE ε2* = gene encoding for apolipoprotein E epsilon 2 allele, *CYP2C9* = gene encoding cytochrome P450 family 2 subfamily C member 9 enzymes, *CYP4F2* = gene encoding cytochrome P450 family 4 subfamily F member 2 enzymes, r = regression coefficient, $R^2$ = regression coefficient squared, rs = reference SNP cluster ID

The studied genetic variant was linked to a significant increase in the warfarin dosage requirement and a significantly longer duration to attain the desired INR target. The regression analysis estimated that the single contribution of the genotypes for the SNP rs9923231 to the explanation of the warfarin dosage variability was 17%. Upon considering the genetic and nongenetic predictor factors, the combined effect interprets about a third of the warfarin dosage variability.[62]

## Iraqi Studies

In 72 patients (47 females and 25 males) with an age median of 55.3 years from Duhok-Iraq, Eissa conducted a pharmacogenetic study to investigate the impact of the SNP rs9923231 in the *VKORC1* gene and the variant alleles (*2 and *3) of the *CYP2C9* gene polymorphisms on the dosage requirements of warfarin.[63]

The frequency percentage of the SNP rs9923231 in the *VKORC1* gene was estimated to be about 35%. The frequency percentage of the variant alleles (*2) of the *CYP2C9* gene (26.4%) was higher than that of the *3 allele (10.4%) among the study participants.[63]

In comparison to the homozygous and heterozygous genotypes for the *CYP2C9*2* and **3* alleles identified in the study, a significant increase was reported in the warfarin dosage requirement to attain the desired target range among the wild genotypes ($P < 0.05$).

The mutated homozygous genotypes for the SNP rs9923231 in the *VKORC1* gene were significantly associated with higher warfarin dosages as compared to the heterozygous and wild genotypes ($P < 0.05$).[63]

Another study was carried out on patients admitted to Ibn AL-Bitar Specialized Center for cardiac surgery in Baghdad. It has been found that the frequency of the *VKORC1*-1639G allele was 58.75%, and the frequency of VKORC1-1639A allele was 41.25%. CYP2C9*3 allele was 9.4%, whereas that of CYP2C9*2 allele was 13.7%. It has been concluded that the allele *3 of the *CYP2C9* gene and the genotypes for the SNP rs9923231 *VKORC1* gene were significantly affecting the dosages of warfarin.[64]

Despite the significance of the genetic variability on warfarin dosing, the literature on the warfarin pharmacogenetics in Iraqi patients has been lacking.

The relationship between the genetic variants in the *VKORC1* and *CYP2C9* genes and warfarin maintenance dosing have been studied in two Iraqi studies (see [Table 1]).[63,64] Both studies have concluded that the genetic factors of CYP2C9*3 and VKORC1 polymorphisms were significantly associated with warfarin dosage requirements.[63,64]

However, one of these studies did not construct a dosing model.[63] The other study developed a warfarin-dosing model based on the genotypes for the *CYP2C9*3* allele and the *VKORC1* SNP rs9923231 to estimate the predicted dosage requirement of warfarin.[64] The weight, gender, and genotypes for the studied SNPs in the *VKORC1* and *CYP2C9* genes interpreted about 54% of the variances in warfarin dosages.

Nevertheless, the regression analysis was performed with a small sample size (80 patients) and did not include a separate patient group for dosing model validation. A major limitation in the study was performing the model validation with data of the same patients from which the model was developed.

Additionally, none of these studies inspected the association of other genetic polymorphisms (other than the *CYP2C9* and *VKORC1* genes) and warfarin dosage requirements. The reason may likely be attributed to the expensive cost of genetic analysis and a lack of research funding, which is a common obstacle to research efforts in Iraq.

Further studies are needed to attempt filling the gap regarding the genetic variants and the extent of their

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contribution to the warfarin dosing variability. Additional investigations are also required to examine the influence of other genetic polymorphisms linked to warfarin dosage variability. This eventually contributes to the optimization of warfarin dosing and minimization of the patient's risk for hemorrhage and thrombosis.

## Conclusion

*VKORC1* SNPs have consistently been found to be the predominant genetic factor contributing the dosing variations. The SNP rs9923231 was significantly associated with the greatest predicting capability of warfarin dosage.

However, a range of about 30%–50% of the variances in warfarin dosing was explained by the combined contribution effect of several genetic and nongenetic (clinical) factors in the regional and Iraqi studies.

Although its importance has been well documented, there is still a considerable gap in the available literature about warfarin pharmacogenetics mainly because of inconsistencies in the studies' findings. Moreover, research efforts on the pharmacogenetics of warfarin in the Iraqi population were lacking. The only studied polymorphisms were the *VKORC1* and *CYP2C9* genetic variants.

### Ethical consideration

Not applicable.

### Financial support and sponsorship

Not applicable.

### Conflicts of interest

There are no conflicts of interest.

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