
Impact of CYP2C9 and VKORC1 polymorphisms on warfarin dose and anticoagulation response in cardiac valve replacement patients in Erbil, Iraq

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ABSTRACT

Background and objective: Warfarin is the primary anticoagulant used in patients undergoing heart valve replacement surgery. Genetic variations in the CYP2C9 and VKORC1 (Vitamin K Epoxide Reductase Complex Subunit 1) genes have a significant impact on warfarin metabolism and sensitivity. However, there are limited studies on these variants in the Iraqi population. The purpose of this study was to assess the impact of the single-nucleotide polymorphisms (SNPs) VKORC1 -1639 G>A, CYP2C9*2, and CYP2C9*3 on anticoagulation response, time to reach therapeutic International Normalised Ratio (INR), and warfarin dosage requirements in patients undergoing heart valve replacement surgery.

Methods: Fifty patients (34 Kurdish, 16 Arab) participated in a prospective observational study in Erbil, Iraq, from October 2024 to March 2025. Real-time PCR was used for genotyping. INR values, warfarin dosing, and the time in days from the first day of warfarin treatment after surgery until reaching the therapeutic INR (2–3) were recorded.

Results: CYP2C9 *1/*1 was the most common genotype. VKORC1 genotype frequencies differed significantly between Kurdish and Arab patients. Warfarin maintenance dose varied significantly by CYP2C9 ($p=0.017$) and VKORC1 ($p=0.04$) genotype. Patients with CYP2C9 *2/*3 required the lowest dose (7 mg/week). CYP2C9 genotype correlated with time to therapeutic INR ($p=0.043$), while VKORC1 genotype did not.

Conclusion: The CYP2C9 and VKORC1 polymorphisms found in the studied population require lower warfarin dosages in Iraqi patients who have undergone heart valve replacement. These results demonstrate the importance of genotype-guided warfarin dosing in enhancing safety and efficacy, especially in genetically diverse populations such as Iraq.

Keywords: Warfarin, CYP2C9, VKORC1, Cardiac valve replacement

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INTRODUCTION

Thromboembolic events, such as ischaemic stroke, are potentially serious complications following valve replacement surgery. Patients who undergo heart valve replacement surgery typically require lifelong administration of warfarin as an anticoagulant (1).

Warfarin exerts its anticoagulant effect by blocking the vitamin K epoxide reductase enzyme, which is particularly challenging in the initial treatment phase because of its limited therapeutic range and considerable variability in patient response (2).

Age, use of concurrent drugs, dietary vitamin K intake, hepatic dysfunction, and heart failure can all contribute to this variability (3). Moreover, as pharmacogenetics advances and our understanding of genetic influences on individual drug responses grows, the potential for personalised medicine increases (4, 5).

Various single-nucleotide polymorphisms (SNPs) in CYP2C9 have been identified as strongly correlated with reduced enzymatic activity. CYP2C9*2 (430 C/T) and *3 (1075 A/C) are the most commonly documented variants. These SNPs result in reduced warfarin metabolism and are linked to lower CYP2C9 enzymatic activity (6). This decreased enzyme activity results in slower clearance of warfarin, leading to its accumulation in the body, which in turn causes excessive anticoagulation and an elevated risk of significant haemorrhagic consequences (7). This may lead to several phenotypes within a population, allowing individuals to be categorised as "poor metaboliser" (PM), "intermediate metaboliser" (IM), or "extensive metaboliser" (EM) (8).

Another polymorphism occurs in the VKORC1 gene, which encodes the VKOR enzyme — crucial in the coagulation cascade, enabling the conversion of

vitamin K-2,3 epoxide to physiologically active vitamin K-hydroquinone, which supports the formation of clotting factors II, VII, IX, and X. Warfarin blocks the activity of VKOR by inhibiting its function (3).

Numerous SNPs have been identified in VKORC1. Evidence indicates that the VKORC1 (rs9923231, c.-1639G/A) polymorphism is substantially associated with warfarin sensitivity and reduced dosage requirements, since it leads to reduced expression of VKOR (6, 9).

Patients possessing these polymorphisms are likely to need a reduced dose of warfarin, as they are at higher risk of bleeding as an adverse effect (10). However, limited data is available on the Iraqi population's genetics and its effect on warfarin metabolism and action.

This study aims to investigate the impact of genetic variations in CYP2C9 and VKORC1 on warfarin dosage requirements, anticoagulation response, and time to reach therapeutic INR (2–3) among patients undergoing cardiac valve replacement in Erbil city. The findings are intended to support the development of genotype-guided warfarin dosing strategies to enhance the safety and efficacy of anticoagulation therapy. The objectives of the study are to determine the prevalence of CYP2C9 and VKORC1 genotype frequencies among the study population and to examine the correlation between genetic polymorphisms and clinical measures, such as maintenance warfarin dosage and the duration required to achieve therapeutic INR levels.

METHODS

Subjects and Criteria

A prospective observational multicentre cohort study was performed between 25 October 2024 and 25 March 2025 on a total of 50 Iraqi patients of Kurdish and Arab ethnicity undergoing aortic,

mitral, and double heart valve replacement surgery in the cardiac surgery departments at the Cardiac Centre, Balsam, and Shar hospitals in Erbil, Iraq.

Inclusion criteria were patients aged over 18 with isolated mechanical valve replacement prescribed warfarin post-surgery. Exclusion criteria were malignancy, abnormal renal or liver function, hypo- or hyperthyroidism, and use of other concurrent medications that interact with warfarin.

Informed consent was obtained from patients, and a systematic interview questionnaire was used at enrolment to collect demographic data, including gender, age, ethnicity, weight, smoking history, concomitant chronic diseases, and valve type. Environmental and dietary factors affecting INR (e.g., vitamin K intake) were controlled; the warfarin drug and food interactions list was obtained from Pharmacotherapy Principles & Practice, 5th edition.

The day before surgery, a 2 ml venous blood sample was taken from each patient for genotyping, collected into an EDTA anticoagulant tube and stored at -20°C prior to DNA extraction.

The initial warfarin dose was recorded in mg/day, and the INR value was measured and recorded on the fifth day of warfarin treatment. The dose was adjusted or kept unchanged according to the cardiothoracic surgeon's decision. The maintenance dose of warfarin (mg/week) and the time (in days) needed to reach therapeutic INR were recorded. Three patients died and were lost to follow-up.

DNA Extraction and Genotyping

DNA from whole blood was extracted using the PureLink™ Genomic DNA Mini Kit (Thermo Fisher, USA), following the manufacturer's instructions. Quantification and quality assessment of total DNA concentration were performed using a TOUCH

NanoDrop, with absorbance measured at the A260/280 ratio; the acceptable range was 1.7–2.0.

The Real-Time PCR kit from SNP Biotechnology was used to analyse SNPs for the CYP2C9*2 (rs1799853) allele, the CYP2C9*3 (rs1057910) allele, and the VKORC1 -1639 G>A (rs9923231) gene. The kit provides a pre-prepared master mix specifically tailored for 5' nuclease PCR and SNP analysis. The allelic discrimination method used was TaqMan probes.

The fluorescence detection system used FAM dye for the allele/mutation, and HEX/JOE dye as an internal control to verify reaction efficiency and sample integrity. The PCR programme included initial denaturation at 95°C for 3 minutes, followed by 30 cycles of denaturation at 95°C for 15 seconds, then annealing at 60°C for 1 minute.

Statistical Analysis

All statistical analyses were performed using SPSS software version 26.0 (IBM SPSS Inc., Chicago, IL), with continuous variables presented as mean $\pm$ standard deviation (SD). Departure of allelic frequencies for the CYP2C9*2 (430C/T), *3 (1075A/C), and VKORC1 (-1639G/A) polymorphisms from Hardy-Weinberg equilibrium (HWE) was tested; a p-value > 0.05 indicated that genotype frequencies were not significantly different from HWE, confirming the population was distributed within HWE.

Variation in genotype distributions for each polymorphism, and the frequency of heterozygous, homozygous, and mutant alleles between Kurdish and Arab patients, was evaluated using chi-square tests.

According to the Shapiro-Wilk test, the distribution of initial warfarin dose, first INR, warfarin maintenance dose, and time to reach therapeutic INR deviated significantly from normality ($p=0.05$).

Non-parametric tests were therefore used. The Kruskal-Wallis test was used to assess the impact of independent variables (demographic, clinical, and genetic factors) on the required warfarin dose. Spearman's correlation was used to examine the relationship between age and weight with maintenance warfarin dose. Pairwise comparisons were used to identify significant differences in maintenance warfarin dose between each pair of genotype groups for CYP2C9 and VKORC1. Box plots were used to visually represent the dispersion of warfarin dosage among genotype groups. A p-value < 0.05 was considered statistically significant.

The present study received approval from the Research Ethics Committee of Hawler Medical University, College of Medicine (approval no. 15).

RESULTS

Demographics and Clinical Characteristics

Fifty Iraqi patients — 23 male (46%) and 27 female (54%), 34 (68%) of Kurdish ethnicity and 16 (32%) of Arab ethnicity, with a mean age of 53.06 ± 13.27 years — were placed on warfarin following heart valve replacement surgery. Twenty-two patients (44%) each had mitral and aortic valve replacement, and 6 (12%) had a double valve replacement. Mean participant weight was 75.74 ± 13.18 kg. Smoking status was: 7 (14%) smokers, 35 (70%) non-smokers, and 8 (16%) ex-smokers. Twenty-three patients (46%) had no chronic diseases, 7 (14%) had hypertension, 3 (6%) had diabetes, 5 (10%) had both hypertension and diabetes, 7 (14%) had hypertension and dyslipidaemia, and 5 (10%) had other conditions.

The mean initial warfarin dose was 4.36 ± 1.08 mg/day, ranging from 1 to 5 mg/day over the first five days; INR values measured on day 5 of treatment ranged from 0.987 to 4.14, with a mean of 1.435 ± 0.618 . A statistically significant difference

was found ($p < 0.05$) when testing the effect of the first warfarin dose on INR value among different CYP2C9 genotype groups, but not among VKORC1 genotype groups ($p > 0.05$). The duration required to reach therapeutic INR ranged from 2 to 60 days across genotype groups, with a mean of 18.72 ± 10.32 days.

The maintenance dose of warfarin needed to achieve therapeutic INR ranged from 7 to 70 mg/week (mean 25.67 ± 13.27 mg/week), and differed among CYP2C9 and VKORC1 genotypes. Mean maintenance dose was 29.24 ± 12.9 , 20.0 , 17.5 ± 8.57 , and 7.00 mg/week for $*1/*1$, $*1/*2$, $*1/*3$, and $*2/*3$, respectively, as shown in Figure 1A.

For VKORC1 genotypes, mean doses were 34.85 ± 14.47 , 24.52 ± 9.77 , and 18.46 ± 11.27 mg/week for GG, GA, and AA genotypes, respectively, as shown in Figure 1B.

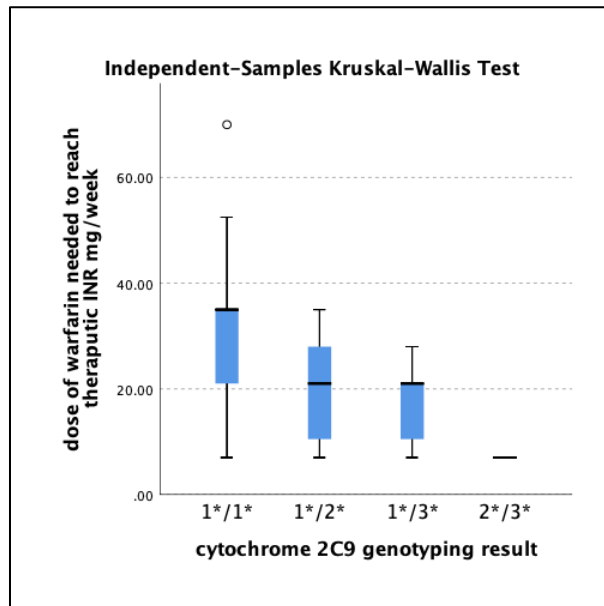


Figure 1A. Maintenance warfarin dose (mg/week) among CYP2C9 genotypes

*Homozygous *2 and *3 alleles were not detected in the tested population sample. The mean for the *1/*2 group is reported here as 20.0 mg/week; the standard deviation for this specific group could not be recovered from the source data, where it appeared triplicated/corrupted in the original text — please verify against the raw dataset before final submission.*

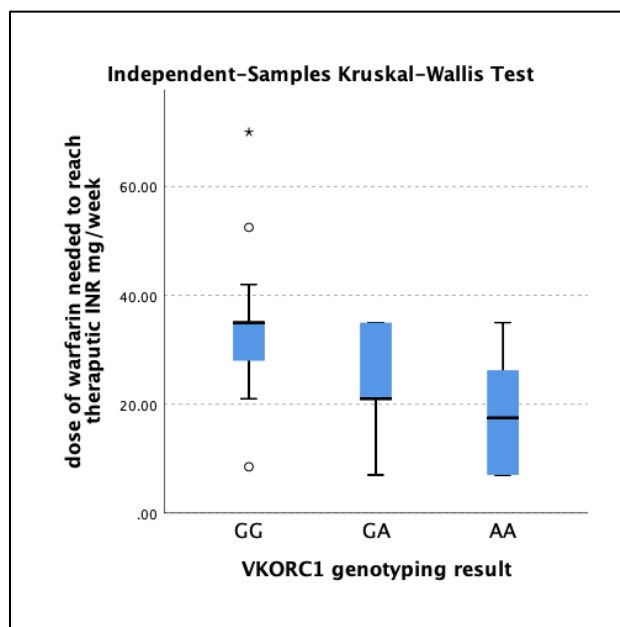


Figure 1B. Maintenance warfarin dose (mg/week) among VKORC1 genotypes

Genotype Frequencies

The prevalence of the CYP2C9*2 (rs1799853), CYP2C9*3 (rs1057910), and VKORC1 -1639 G>A

(rs9923231) alleles in Kurdish and Arab patients is summarised in Tables 1A and 1B.

Table 1A. CYP2C9 genotyping results

2C9 genotype	Kurds %	Arabs %	Total %	p*
*1/*1	70.6	68.8	70	0.481
*1/*2	11.8	25	16	
*1/*3	11.8	6.3	10	
*2/*3	5.9	0.0	4	

**p>0.05: no significant difference in CYP2C9 genotype frequencies between Kurdish and Arab patients.*

Table 1B. VKORC1 G>A genotype results

VKORC1 genotype	Kurds %	Arabs %	Total %	p*
GG	38.2	12.5	30	0.035
GA	41.2	37.5	40	
AA	20.6	50.0	30	

**p<0.05: a significant difference in VKORC1 genotype frequencies between Kurdish and Arab patients.*

Table 2 shows the association of demographic, clinical, and genetic variables with warfarin maintenance dose (n=47). Warfarin maintenance dose varied significantly by CYP2C9 genotype

(p=0.017) and VKORC1 genotype (p=0.04), but not by gender, smoking status, chronic disease, or valve type.

Table 2. Association of demographic, clinical, and genetic variables with warfarin maintenance dose (n=47)

Variable	Category	n	Mean rank	p
Gender	Male	21	26.57	0.235
	Female	26	21.92	
Smoking	Smoker	7	30.29	0.387
	Non-smoker	32	22.61	
	Ex-smoker	8	24.06	
Valve	Mitral	20	22.98	0.900
	Aortic	21	24.67	
	Double	6	25.08	
CYP2C9	*1/*1	35	27.65	0.017
	*1/*2	7	18.86	
	*1/*3	5	15.10	
	*2/*3	2	4.00	
VKORC1	GG	14	33.07	0.04
	GA	18	23.00	
	AA	15	16.73	

Pairwise comparison showed a significant difference in maintenance warfarin dose between CYP2C9 *1/*1 and both CYP2C9 *1/*3 and CYP2C9 *2/*3 ($p < 0.05$). A significant difference was also found between VKORC1 genotypes, particularly GG compared with GA and AA. Spearman's correlation showed no significant association between maintenance dose and age ($\rho = -0.040$, $p = 0.790$) or weight ($\rho = 0.018$, $p = 0.904$).

Time Needed to Reach Therapeutic INR (2–3) Within Different Genotype Groups

A statistically significant difference was found ($p < 0.05$) in the time needed to reach therapeutic INR between CYP2C9 genotype groups: wild-type allele carriers needed less time, while compound heterozygous *2/*3 carriers needed the most time among all groups. No significant difference was found ($p > 0.05$) among VKORC1 genotype groups, (Table 3).

Table 3. Association between time required to reach therapeutic INR and genotype group

Gene	Genotype	Mean rank	p
CYP2C9	*1/*1	20.59	0.043
	*1/*2	31.14	
	*1/*3	29.90	
	*2/*3	40.50	
VKORC1	GG	18.79	0.190
	GA	25.06	
	AA	27.60	

Discussion

Warfarin has a narrow therapeutic index and is nevertheless a major contributor to hospitalization from drug-related side effects. Incorrect dosing considerably raises the risk of thromboembolism, haemorrhage, hospitalizations, and mortality. The first few months of warfarin administration carry the greatest risk; a safer and more effective warfarin dosage may arise from successful attainment of therapeutic anticoagulation (11). Warfarin remains clinically significant in patient populations not appropriate for direct oral

anticoagulant (DOAC) therapy, such as those with mitral stenosis or mechanical valves, even though DOAC use has increased (5).

Polymorphisms in the CYP2C9 and VKORC1 genes have been shown to influence the pharmacodynamics and pharmacokinetics of warfarin (6).

The current study found that, for both Kurdish and Arab ethnicities combined, the frequency of the CYP2C9*1 allele was 83%, while the CYP2C9*2 and *3 variant alleles were 10% and 7%,

respectively. No significant difference was found between Kurdish and Arab ethnicity.

The frequency of the VKORC1 G allele in Kurds and Arabs was 58.8% and 31.3%, respectively, and of the A allele, 41.2% and 68.7%, respectively. A significant difference was found in VKORC1 genotyping results between the two ethnicities.

These allelic frequencies were slightly different from a study from Duhok, Iraq, by Issa A., conducted on 72 Kurdish patients (47 female, 25 male), which estimated the frequency of the VKORC1 SNP rs9923231 at roughly 35%; among participants, the CYP2C9*2 variant allele frequency was higher (26.4%) than that of the *3 allele (10.4%) (12). In another study by Ali Saleh et al. on Iraqi patients admitted to the Baghdad-based Ibn Al-Bitar Specialised Centre for Heart Surgery, which did not report patient ethnicities, results were extremely close to ours: the VKORC1 -1639G allele was present in 58.75% of cases and the -1639A allele in 41.25%, while the CYP2C9*2 allele was 13.7% and the CYP2C9*3 allele was 9.4% (13).

CYP2C9 allele frequencies in Iraq were similar to those reported in a study of an adjacent population (14), suggesting regional genetic affinities, and were also close to those reported for Egyptian and Caucasian populations in another comparative study (15).

VKORC1 allelic frequencies were similarly close to those in adjacent groups and Mediterranean basin populations, with more marked differences observed compared with South African and East Asian populations (16).

CYP2C9 is a highly polymorphic enzyme, with over 60 identified genetic variants, at least 20 of which are documented to show altered activity. The two most prevalent and well-characterised variant alleles are CYP2C9*2 and *3, both linked to

diminished enzyme activity and altered drug metabolism (17). In the present study, the effect of *3 on warfarin dose reduction was greater than that of *2, and poor metaboliser *2/*3 carriers needed a lower dose than other genotypes. The common noncoding VKORC1 variant (-1639G>A) is significantly correlated with warfarin sensitivity and reduced dosage requirements, as the -1639A polymorphism demands a lower initial warfarin dose than the -1639G polymorphism (18). The current study demonstrated that GG genotype carriers needed a higher warfarin dose to reach therapeutic INR, while AA carriers needed less. For VKORC1 genotypes, mean doses in mg/week were 34.85 ± 14.47 , 24.52 ± 9.77 , and 18.46 ± 11.27 for GG, GA, and AA, respectively. In a comparable study, the typical recommended daily warfarin dose for patients with the VKORC1 AA genotype (21.91 mg/week) was significantly lower than for those with the GG and GA genotypes (18).

The current study evaluated the time required to reach the target INR in days, a clinical endpoint commonly used since attaining a stable INR minimises subsequent changes in INR readings and considerably reduces bleeding risk (19).

A significant difference was seen in time needed between different CYP2C9 genotypes: mean time for *1/*1 was 15.9 days, versus 30 days for *2/*3 carriers. For VKORC1 genotype groups, GG carriers needed less time to reach therapeutic INR than AA carriers.

When comparing INR value on day 5 of warfarin treatment post-surgery, a significant difference was found between CYP2C9 genotype groups, but not between VKORC1 genotype groups, aligning with research indicating that VKORC1 genotype was not substantially correlated with warfarin response during the treatment's stabilisation phase (3).

The influence of CYP2C9 and VKORC1 SNPs on maintenance warfarin dose was in agreement with several studies on this subject, including those conducted in the Saudi population (7) and a West Azerbaijan, Iranian population (6).

Besides genetic variants, several factors — including patient demographics (age and weight) and clinical factors such as chronic illnesses like hypertension, heart failure, and diabetes — affect warfarin dose, and comorbidity burden more broadly has been shown to complicate medication management among elderly patients in this region (20, 21). In this study, elderly patients required a reduced warfarin dosage, possibly due to diminished liver mass and correspondingly lower hepatic VKOR levels, rendering them more warfarin-sensitive, consistent with a comparable study (6). Patients with both hypertension and diabetes required a lower warfarin dose than other patients in that same study, whereas patients with other comorbidity patterns required higher doses. No significant effects of gender, smoking, or valve type on warfarin dose were found.

There are some limitations to our study. The sample size was somewhat limited due to the specificity of the study population (isolated cardiac valve replacement patients), which may have reduced statistical power to detect small differences in warfarin dose requirements among genotype and clinical groups. Moreover, homozygous *2 and *3 alleles were not detected in this study, which prevented us from studying their effect on warfarin dose.

CONCLUSION

The current research indicates that patients possessing CYP2C9*3 and VKORC1 -1639A require a reduced warfarin dosage and are primarily classified as warfarin-sensitive, with a higher dose recorded in CYP2C9 *1/*1 carriers and a lower dose

in CYP2C9 *2/*3 carriers. There was a significant difference in the duration required to reach target INR between CYP2C9 genotypes. Moreover, the prevalence of VKORC1 genotypes differed significantly between the two ethnicities in the study population, which is essential information to evaluate prior to administering warfarin.

COMPETING INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Bezci K, Cevik M, Akdeniz CS, Canbolat IP, Yurdakul S, Sunbul M, et al. Warfarin pharmacogenetics in patients with heart valve replacement. *Gene Rep.* 2020;20(3):100769. <https://doi.org/10.1016/j.genrep.2020.100769>
2. Khaleqsefat E, Khalaj-Kondori M, JabarpourBonyadi M, Soraya H, Askari B. The contribution of VKORC1 and CYP2C9 genetic polymorphisms and patients' demographic characteristics with warfarin maintenance doses: a suggested warfarin dosing algorithm. *Iran J Pharm Res.* 2020;19(3):77-85. <https://doi.org/10.22037/ijpr.2020.1101116>
3. AL-Eitan LN, Almasri AY, Khasawneh RH. Effects of CYP2C9 and VKORC1 polymorphisms on warfarin sensitivity and responsiveness during the stabilization phase of therapy. *Saudi Pharm J.* 2019;27(4):484-90. <https://doi.org/10.1016/j.isps.2019.01.011>
4. Tidbury N, Preston J, Lip GYH. Lessons learned from the influence of CYP2C9 genotype on warfarin dosing. *Expert Opin Drug Metab Toxicol.* 2023;19(4):185-8. <https://doi.org/10.1080/17425255.2023.2220961>

5. Ali RH. Impact of genetic variations on pharmacokinetic and pharmacodynamic properties of medicines and the future of drug therapy. *Zanco J Med Sci.* 2020;24(1):65-7. <https://doi.org/10.15218/zjms.2020.009>
6. Farzamikia N, Sakhinia E, Afrasiabirad A. Pharmacogenetics-based warfarin dosing in patients with cardiac valve replacement: the effects of CYP2C9 and VKORC1 gene polymorphisms. *Lab Med.* 2018;49(1):25-34. <https://doi.org/10.1093/labmed/lmx072>
7. Al-Saikhan FI. Genetic risk assessment towards warfarin application: Saudi Arabia study with a potential to predict and prevent side effects. *Saudi J Biol Sci.* 2020;27(1):456-9. <https://doi.org/10.1016/j.sjbs.2019.11.007>
8. Waring RH. Cytochrome P450: genotype to phenotype. *Xenobiotica.* 2020;50(1):9-18. <https://doi.org/10.1080/00498254.2019.1648911>
9. Qayyum A, Najmi MH, Mansoor Q, Irfan M, Naveed AK, Hanif A, et al. Frequency of common VKORC1 polymorphisms and their impact on warfarin dose requirement in Pakistani population. *Clin Appl Thromb Hemost.* 2018;24(2):323-9. <https://doi.org/10.1177/1076029616680478>
10. Biswas M, Bendkhale SR, Deshpande SP, Thaker SJ, Kulkarni DV, Bhatia SJ, et al. Association between genetic polymorphisms of CYP2C9 and VKORC1 and safety and efficacy of warfarin: results of a 5-year audit. *Indian Heart J.* 2018;70(3):S13-9. <https://doi.org/10.1016/j.ihj.2018.02.005>
11. Kaye JB, Schultz LE, Steiner HE, Kittles RA, Cavallari LH, Karnes JH. Warfarin pharmacogenomics in diverse populations. *Pharmacotherapy.* 2017;37(9):1150-63. <https://doi.org/10.1002/phar.1982>
12. Abd Alridha AM, Al-Gburi KM, Abbood SK. Warfarin therapy and pharmacogenetics: a narrative review of regional and Iraqi studies. *Med J Babylon.* 2022;19(3):324-31. https://doi.org/10.4103/MJBL.MJBL_70_22
13. Ali Saleh M, Kadhim HM, Sahib A, Abdulamir AS, Altawil R. The effect of CYP2C9 and VKORC1 genetic polymorphism on warfarin dose requirements in a sample of Iraqi patients. *JKMU.* 2021;28(2):139-49. <https://doi.org/10.22062/jkmu.2021.91609>
14. Ijam AH, Mshimesh BAR, Abdulamir AS, Alsaad SF. Analysis of cytochrome P450 2C9 gene polymorphism in a sample of Iraqi hypertensive patients. *Med J Babylon.* 2024;21(3):653-8. https://doi.org/10.4103/MJBL.MJBL_1650_23
15. Qayyum A, Najmi MH, Mansoor Q, Farooqi Z ur R, Naveed AK, Hanif A, et al. Frequency of common CYP2C9 polymorphisms and their impact on warfarin dose requirement in Pakistani population. *Clin Appl Thromb Hemost.* 2017;23(7):800-6. <https://doi.org/10.1177/1076029616654264>
16. Altawil Y, Youssef LA. Frequencies of VKORC1 -1639G>A and rs397509427 in patients on warfarin and healthy Syrian subjects. *Cardiovasc Ther.* 2023;8898922. <https://doi.org/10.1155/2023/8898922>
17. Parikh SJ, Kamat S, Phillips M, Boyson SP, Yarbrough T, Davie D, et al. Insights into the genetic variations of human cytochrome P450 2C9: structural analysis, characterization and comparison. *Int J Mol Sci.* 2021;22(19):10206. <https://doi.org/10.3390/ijms221910206>
18. Soltani Banavandi MJ, Satarzadeh N. Association between VKORC1 gene polymorphism and

warfarin dose requirement and frequency of VKORC1 gene polymorphism in patients from Kerman province. *Pharmacogenomics J.* 2020;20(4):574-8.

<https://doi.org/10.1038/s41397-019-0146-5>

19. Shaw K, Amstutz U, Kim RB, Lesko LJ, Turgeon J, Michaud V, et al. Clinical practice recommendations on genetic testing of CYP2C9 and VKORC1 variants in warfarin therapy. *Ther Drug Monit.* 2015;37(4):428-36.
<https://doi.org/10.1097/ftd.0000000000000192>
20. Olie RH, Winckers K, Rocca B, Ten Cate H. Oral anticoagulants beyond warfarin. *Annu Rev Pharmacol Toxicol.* 2024;64(1):551-75.
<https://doi.org/10.1146/annurev-pharmtox-032823-122811>
21. Muhamed DJ, Dauod AS, Dunham RE. Multimorbidity, polypharmacy and cognitive assessment among a sample of elderly people in Erbil. *Adv Med J.* 2026;11(1):148-54.
<https://doi.org/10.56056/amj.2026.439>