Obat: Jurnal Riset Ilmu Farmasi dan Kesehatan
Volume. 3 Nomor. 5 September 2025
e-ISSN : 3031-0148, p-ISSN : 3031-013X, Hal. 287-299
DOI: https://doi.org/10.61132/obat.v3i5.1697
Available online at: https://journal.arikesi.or.id/index.php/OBAT

The Role of VKORC1 in Vitamin K Metabolism and Warfarin Sensitivity: A Narrative Review of Genetic and Clinical Perspectives

Ayoob Radhi Al-Zaalan[1*], Hussam Saadi Aziz[2]
[1-2] Departemen Teknologi Laboratorium Medis, Fakultas Kesehatan dan Teknologi Medis, Universitas Teknik Selatan, Basra, Irak.
ayoob.r.tuama@stu.edu.iq[1*],hussam.aziz@stu.edu.iq[2]

Alamat: Basrah, Basra Governorate, Irak
Korespondensi Penulis: ayoob.r.tuama@stu.edu.iq[*]

Abstract. *Warfarin (commonly known by its trade name, Coumadin) is an oral anticoagulant that has been widely used for the prevention and treatment of thromboembolic disorders. Despite its clinical benefits, warfarin therapy is complicated by a very narrow therapeutic index and wide inter-individual variability in dose requirements. This variability represents a major challenge for clinicians, as inappropriate dosing may lead to serious adverse outcomes such as bleeding or thrombotic events. A growing body of evidence suggests that genetic polymorphisms are among the most important factors contributing to this variability, particularly those involving the Vitamin K Epoxide Reductase Complex Subunit 1 (VKORC1) gene. VKORC1 encodes a key enzyme that functions as a bottleneck in the vitamin K cycle, playing an essential role in the regeneration of reduced vitamin K (VKH). This active form of vitamin K is required for the γ-carboxylation of vitamin K–dependent clotting factors, including prothrombin and other coagulation proteins. Polymorphisms within VKORC1 can significantly alter the enzyme's expression and activity, thereby modifying an individual's sensitivity to warfarin. One of the most clinically relevant variants is the -1639G>A (rs9923231) polymorphism, which reduces VKORC1 transcription and subsequently decreases enzyme activity. Patients carrying the A allele often exhibit increased sensitivity to warfarin and therefore require lower maintenance doses compared to those with the G allele. Understanding these genetic influences not only improves our knowledge of warfarin pharmacogenomics but also highlights the importance of personalized medicine in anticoagulant therapy. Incorporating VKORC1 genotyping into clinical practice could optimize dose prediction, minimize adverse events, and enhance the safety and effectiveness of warfarin therapy. This narrative review aims to provide an in-depth discussion of the complex role of VKORC1 in vitamin K metabolism and its impact on warfarin sensitivity, thereby underscoring the critical relevance of genetic factors in guiding individualized anticoagulation therapy.*

Keywords: *Anticoagulant Therapy, Genetic Polymorphism, Vitamin K Metabolism, VKORC1, Warfarin Sensitivity,*

1. INTRODUCTION

Vitamin K is a fat soluble vitamin and it is at the center of hemostasis, which further functions as a cofactor of gamma-glutamyl carboxylase (GGCX). It catalyzes the post-translational carboxylation of certain glutamic acid residues in the vitamin K-dependent proteins such as the coagulation factors II, VII, IX, and X and anticoagulant proteins C and S (Suttie, 1985). This carboxylation is imperative so that these proteins gain complete biological activity and are able to bind calcium ions required before being able to interact with phospholipid surfaces in the coagulation cascade. The vitamin K life cycle is the cycle of biosynthesis, during which reduced vitamin K (vitamin K hydroquinone, KH2) is regenerated continuously and based on its oxidized form, vitamin K epoxide (KO) (Stafford, 2005(' AMid this cycle is an enzyme called Vitamin K Epoxide Reductase Complex Subunit 1 (VKORC1).

Received: Juni 30, 2025; Revised: Juli 20, 2025; Accepted: Agustus 19, 2025; Online Available: Agustus 21, 2025

VKORC1 is a transmembrane protein found in the endoplasmic reticulum and it catalyzes the rate limiting step in the vitamin K cycle, the conversion of vitamin K epoxide to vitamin K quinone which is then reduced again to KH2 (Li et al., 2004). Such an essential process in the coagulation system renders VKORC1 an un-substitutable cog of the coagulation system.

Warfarin, which is the most commonly used oral anticoagulant, works through modulating the action of VKORC1 and inhibits it therapeutically. Warfarin prevents the resynthesis of KH2, keeping the reserve of active vitamin K available so that they cannot participate in the process of carboxylation of vitamin K-dependent coagulation factors and make them have poor procoagulant activity (Ansell et al., 2004). This mechanism allows that warfarin is very strong in prevention and treatment of thromboembolic conditions, that include deep vein thrombosis, pulmonary embolism, and stroke in individuals with atrial fibrillation. Yet, warfarin therapy notoriously has a narrow therapeutic margin and large inter-personal variability in dose requirements. Blood thinning with anticlodgulants is very important and significant in preventing the occurrences of bleeding (as a result of over-anticlotting) and thrombotic (under-anticlotting or over-antiprotein C reactivity). Therefore maintenance of target international normalized ratio (INR) is essential (Holbrook et al., 2012). The genetic difference especially at the VKORC1 gene has turned out to be major factors of this inter-individual difference in dose requirements of warfarin. The VKORC1 may have polymorphisms which can lead to change in the expression or functionality of the enzyme in turn resulting in the sensitivity of an individual to warfarin, and the therapeutic dose required (Rieder et al., 2005). The role of genetic factors in the development of VKORC1 and the interaction with the metabolism of vitamin K is thus crucial in the development of better methods of warfarin therapy and the development of personalized medicine. The objective of this narrative review is to present a well-rounded review of the complexity of VKORC1 in vitamin K metabolism and how it appears to significantly influence the warfarin sensitivity. We shall enter into the molecular mechanism of action of VKORC1 and identify the main genetic variants and polymorphism that are related to the variability of warfarin dose, their clinical significance in the management of warfarin and the current pharmacogenomic recommendations, and future studies in the field of VKORC1. The intended effect of this review is to bring together genetic and clinical insights regarding VKORC1 as a key pharmacogene and what that means in regards to safer and more effective management of anticoagulants.

2. MOLECULAR FUNCTION OF VKORC1

The vitamin K metabolism is the most important metabolic pathway to guarantee the constant supply of reduced vitamin K (vitamin K hydroquinone, KH 2), which is a necessary co-factor of gamma-glutamyl carboxylase (GGCX). This is an essential enzyme in the post translation goodness of vitamin K-dependent proteins (VKDPs) such as coagulation factors and regulatory proteins (Suttie, 1985). It is a cycle of enzymatic transformations between various forms of vitamin K. Vitamin K Epoxide Reductase Complex Subunit 1 (VKORC1) is the center of this cycle. The VKORC1 is a short (low-molecular mass), multi-transmembrane protein that is inserted within the endoplasmic reticulum (ER) membrane (Li et al., 2004). Its rate-limiting and first enzymatic action is the vitamin K 2,3-epoxide (KO) reduction to vitamin K quinone (K). Such a reaction is important as KO is the oxidized animal vitamin K produced during the carboxylation reaction to GGCX. In the absence of effective regeneration of vitamin K quinone by VKORC1, KH2 would soon become exhausted, carboxylation of VKDPs would be impaired and associated coagulopathy would result.

There has been much research on the exact molecular mechanism of how VKORC1 catalyzes this reduction. It is appreciated that VKORC1 does incorporate reducing equivalents, probably one of a dithiol containing protein, to oxidize KO to K (Watzke et al., 2008). It is believed that the next step of vitamin K quinone to KH2 reduction may be not catalyzed by VKORC1 directly but rather by an individual reductase, potentially being NAD(P)H:quinone oxidoreductase 1 (NQO1) or other cellular reductases, though the possibility of a certain reductase activity of VKORC1 cannot be ruled out (Rishavy et al., 2018). The activity of VKORC1 is very critical to the overall efficiency of the vitamin K cycle and therefore the production of healthy VKDPs. In addition to an enzyme, VKORC1 binding to other elements of the vitamin K cycle, as well as the ambiance of the ER, is relevant in its procedure. The enzyme is also contained in a complex and its correct folding and stability at the ER are critical in its catalytic properties. Any mutations or genetic alterations to the design or expression of VKORC1 can thus play important roles in the whole of the vitamin K biochemical system and, hence, the coagulation chain reaction (Oldenburg et al., 2006). Such a complex molecular process renders VKORC1 a good target of warfarin and other anticoagulants which act by blocking its activity in order to exert their drug activity.

3. GENETIC VARIANTS AND POLYMORPHISMS

Genetics play a major role in determining the inter-individual variability in warfarin dose requirements and one of the most important determinants is polymorphisms in the VKORC1 gene. The VKORC1 gene has been found to have numerous single nucleotide polymorphisms (SNPs), and some of these SNPs have been greatly linked with the reduced or increased expression or activity of the VKORC1 gene and in turn can affect the sensitivity of an individual towards warfarin (Rieder et al., 2005; Li et al., 2006). One of the promoter VKORC1 polymorphisms most widely researched is SNP at -1639G>A (rs9923231) of the gene. This polymorphism has been shown to be of special importance since A allele (VKORC12) reduces expression of VKORC1 gene and, by extension, the concentration of VKORC1 protein and its activity (Rieder et al., 2005). Patients homozygous with A allele respond to the therapeutic dose of warfarin at reduced doses than patients with G allele. The G allele (VKORC11) is linked with increased expression and activity of the VKORC1 and results in increased warfarin doses. This polymorphism has a great effect, and homozygotes of A allele may receive much smaller doses to have the same effect as the homozygote of G allele (Gage et al., 2008).

The VKORC1 polymorphism 1173C>T (rs9934438) in intron 1 is also an important one. This SNP is strongly linked to -1639G>A polymorphism, that is, they are commonly passed on together. Also, the T allele of 1173C>T impairs VKORC1 expression as well as warfarin sensitivity (Geisen et al., 2007). Although in some literature -1639G>A has generally been referred to as a major functional variant as a result of its position within the promoter, 1173C>T may be a convenient marker fragment in the population where -1639G>A might be less informative or when genotyping both alleles. These VKORC1 alleles have significant differences in their frequencies in different ethnic and racial groups leading to the inter-ethnic differences in the dose requirement of warfarin. As an example, A allele in -1639G>A is higher in Asian population (e.g., about 90% in East Asians) and Europeans (e.g., 40-50%), whereas the G allele is more frequent in Africans (e.g., >90 percent in African Americans) (Limdi et al., 2008; Wadelius et al., 2007). This is a population stratification in the prevalence of VKORC1 genotypes elucidating much of the population-specific warfarin dosing algorithms. In addition to these widespread SNPs, other VKORC1 rare variants and haplotypes have also been found that reveal their effect on warfarin response. There are a few extremely rare mutations in VKORC1 that can result in warfarin resistance so that extremely high warfarin doses are needed to achieve anticoagulation, or even no response at all (Vecsler et al., 2006).

Such results support complex genetic warfarin pharmacogenetics and the necessity of the VKORC1 genotype consideration in individual warfarin therapy.

4. CLINICAL RELEVANCE IN WARFARIN THERAPY

The warfarin active agent obscurian effect on human VKORC1 is directly correlated clinically to the therapeutic action of this drug as an inhibitor of the vitamin K cycle, interfering with the production of active coagulation factors. Nevertheless, warfarin has a narrow therapeutic index, and this requires cautious dose optimisation, to maintain an equilibrium between the risks of thrombotic events (under anticoagulation), and hemorrhagic complications (over anticoagulation) (Ansell et al., 2004). Warfarin dose requirement has been a major disparity between individuals and genetic variations of VKORC1 have been cited as one of the main reasons where there have been many patients requiring high and low doseWarfarin. Clinical relevance of the VKORC1 polymorph victor all this fuss): The existence of the polymorphism has clinical relevance regarding the requirements of warfarin dose. Patients with the A allele are more sensitive to warfarin and they have reduced maintenance doses that make them reach the target International Normalized Ratio (INR) (Rieder et al., 2005; Gage et al., 2008). On the other hand, people who are homozygous in G allele normally need greater doses. This genetic effect is strong whereby the single factor genotype VKORC1. alone by itself predicts a significant part of the variability dose of warfarin mostly in Caucasians and Asian race (Sconce et al., 2005; Li et al., 2006). The genotype-informed methods of warfarin dosing prescription have been introduced that are aimed at taking the benefit of genetic information and to enhance the safety and even efficacy of warfarin initiation. These initiatives generally entail genotyping the patients with VKORC1 (and, in many cases, also CYP2C9, a significant other pharmacogene) before warfarin begins, or perhaps at the very beginning of warfarin therapy. On the basis of the patient genotype, pharmacogenetic algorithms provide a patient-specific initial dose of warfarin (Kimmel et al., 2013). The use of such algorithms has been explored and their utility investigated in clinical trials (like COAG and EU-PACT) showing that genotype-guided dosing may increase the proportion of patients attaining their target INR in first few weeks of therapy and may shorten time to stable anticoagulation (Kimmel et al., 2013; Pirmohamed et al., 2013).

The effect of genotype of VKORC1 is more than just initial dosing, but also on the risk of adverse events. Non-adequate dosing of patients having genotypes that make them sensitive to warfarin is more susceptible to over-anticoagulation and risks of bleeding especially at initiation periods, of warfarin (Limdi et al., 2010). On the other hand, individuals who carry

genotypes that need more doses (e.g., -1639 GG) might have greater risks in sub-therapeutic anticoagulation and thromboses occurrence when using the recommended dosing. Thus integration of the information about VKORC1 genotyping during clinical decision-making can help eliminate the risks through more specific adjustments of the dose. Although the rationale to VKORC1 genotyping is extremely strong, the introduction of a regular genotyping practice into the clinical practice is a debatable question. Challenges revolve around testing cost effectiveness, fast turnaround times of genotype results, incorporation of the pharmacogenetics information into the electronic health records and the clinical workflow. Still, the strong correlation between VKORC1 genotype and sensitivity to warfarin doses emphasizes that it is highly clinically relevant to be able to adjust anticoagulant medications as well as shift towards a more individualized method of patient treatment.

5. PHARMACOGENOMIC GUIDELINES

The genetic polymorphism of VKORC1 and CYP2C9 are instrumental factors that influence the dose requirements of warfarin and one was supposedly developed to guide clinicians in personalizing warfarin therapy. These recommendations give evidence-based advice to genotype-directed drug dosing, commonly through combination of genetic data and clinical variables, predict rhythmic warfarin doses and reduce the adverse effects. The Clinical Pharmacogenetics Implementation Consortium (CPIC) is one of the biggest and best known guidelines. CPIC creates peer-reviewed, evidence-based and freely accessible guidelines that empower the implementation of pharmacogenetic test results even in a clinical practice. A dosing recommendation on the CPIC-based guidelines of warfarin based on CYP2C9 and VKORC1 genotypes provides recommendations on the combination of different genotypes (Johnson et al., 2017; Johnson et al., 2011). As an example of such a case, the starting dose recommended in patients with VKORC1 -1639G>A (rs9923231) AA compared to GG genotype is markedly different in the response to warfarin warfarin responsive (more susceptible) patients. The effect on warfarin under the influence of CYP2C9 variants, which are included in the CPIC guidelines, is given as a complete source of dose prediction (Kaye et al., 2017; Abdullah-Koolmees et al., 2021).

PharmGKB (Pharmacogenomics Knowledgebase) is another valuable resource that manages and conveys pharmacogenomic data through drug-gene pair labeling, clinical labeling, and rule labeling. PharmGKB has complete summaries of the effects of VKORC1 variables in warfarin response and connections to clinical practices such as CPIC and Dutch Pharmacogenetics Working Group (DPWG) (Whirl-Carrillo et al., 2012). The DPWG

guidelines, as an example, do provide specific VKORC1 genotype-specific dosing recommendations as well, usually with some minor differences based on their evidence review and either considering the relevant population or assumptions thereof. These recommendations normally include algorithms or dose charts which take into account VKORC1 genotype, CYP2C9 genotype and clinical variables (age, weight, height, race and interfering medications). The aim is to make a better and faster prediction of stable maintenance dose of warfarin rather than the old way of doing the dose empirically. Although the early clinical trials touching on genotype-guided dosing were reported mixed with inconsistent results on whether there was a significant improvement in major bleeding or thrombotic events, meta-analyses and further research indicated that pharmacogenetic-guided dosing have the potential of benefiting time to stable INR, lower out-of-range INRs, and eventually eventual risk of adverse events, especially during the initiation period (Verhoef et al., 2013; Lv et al., 2019). The applicability of these directives into day-to-day clinical practice is hindered by a number of issues such as; the necessity to educate the medical personnel, cost-effectiveness of genetic tests, and logistical issues of implementation of genetic data into work infrastructure and electronic health records. Nevertheless, with these obstacles, it is notable that sound pharmacogenomic guidelines of warfarin have been developed, a sign of increasing awareness about the importance of VKORC1 as a key pharmacogene and the role personalised medicine has the potential to play in enhancing patient outcome in anticoagulant treatment.

6. FUTURE DIRECTIONS

The understanding of VKORC1's role in vitamin K metabolism and warfarin sensitivity has significantly advanced personalized anticoagulant therapy. Despite this, there are still a number of opportunities to address avenues of future research and clinical development to further refine patient care and the use of pharmacogenomics. A major area of future research will be to find and describe new genetic variant of VKORC1 and other genes determining warfarin response. Although polymorphism in -1639G>A of VKORC1 and CYP2C9 variants are now documented, there is still a large percentage of unexplained variations of warfarin dose. Large-scale genomic projects and next-generation sequencing techniques may unlock rare variants or structural changes that would have a large clinical impact, especially among currently underrepresented groups in which existing pharmacogenomic models may not be as accurate (Perera et al., 2013; Kaye et al., 2017). Besides this, studies about possible epigenetic variations of VKORC1 are potentially going to give more information about inter-individual variability. The second perspective is the evolution of more complicated pharmacogenomic

algorithms. Existing algorithms rest majorly on VKORC1 and CYP2C9 genotype and simple clinical aspects. In the future, algorithms may consider an extended set of genetic markers in addition to the basics of vitamin K absorption, metabolism and VKDP synthesis, dynamic clinical parameters (e.g., certain bedside clinical examination variables) and real-time patient data (e.g., vitamin K intake in the whole diet) via machine learning and artificial intelligence applications. It might result in the more accurate and flexible dosing guidelines during the warfarin treatment. It is also necessary to study the clinical application of pharmacogenomics to warfarin dose. While guidelines exist, challenges related to cost-effectiveness, turnaround time for genetic testing, and integration into routine clinical workflows persist. Future studies should focus on implementation science, evaluating different models of care delivery, assessing the economic benefits of genotype-guided dosing in diverse healthcare settings, and developing user-friendly clinical decision support systems that seamlessly incorporate pharmacogenomic information into electronic health records (Wadelius & Pirmohamed, 2007; Lee & Klein, 2013). Education of healthcare professionals and patients about the benefits and limitations of pharmacogenomic testing is also crucial.

In addition to warfarin, the development of new anticoagulants and their activity determinants to VKORC1 or another part of the vitamin K metabolism are of importance. In spite of their popularity in the past few years, direct oral anticoagulants (DOACs) are not a universal solution and warfarin remains an important choice of treatment in many patients. Learning more about the effects of genetic variations on the safety and effectiveness of newer anticoagulants may also supply individual strategies to the drugs as well. Besides, bringing a more general application of VKORC1 beyond thrombosis to the field of bone health, or cancer, might be one way of discovering new treatment options. Widespread polymorphisms in VKORC1 have been linked to the bone mineral density and it has been suggested that VKORC1 plays a role in the bone metabolism (Crawford et al., 2010; He et al., 2021). Findings show that there may also be a connection between cancer and VKORC1; a research study shows that VKORC1 may also be an anti-cancer drug, and as a predictor of pharmacogenomic markers in anti-literature (Yang et al., 2023; Nimptsch et al., 2009). And the lastly, international collaborations and expansion of pharmacogenetic studies in large populations is necessary to have a more comprehensive picture of the VKORC1 pharmacogenomics in different globe-amplifying populations. This entails formation of international consortia to exchange data, standardise methodologies and carry out prospective clinical trials so as to validate pharmacogenomic algorithms in diverse ethnic groups. These will be critical in making

research results usable to successful and fair personalized medicine approaches in every part of the world (International Warfarin Pharmacogenetics Consortium, 2009).

7. CONCLUSION

Vitamin K Epoxide Reductase Complex Subunit 1 (VKORC1) is considered to be one of the main actors in vitamin K metabolism pathway as it is the one to regenerate the active form of vitamin K the hydroquinone. It is required in this regeneration that is essential in the gamma-carboxylation of proteins that depend on vitamin K, a process that is central to hemostasis. Of clinical interest that is generated by this much-researched gene is the molecular target of warfarin, an extensively employed oral anticoagulant. The activity and expression of VKORC1 determine much of the therapeutic efficacy of warfarin and the high inter- individual variably in required dose. VKORC1 genetic polymorphisms and especially -1639G>A variant have been definitively proven to be primary determinants of warfarin sensitivity. The consequences of these genetic differences are an altered expression and enzyme function of VKORC1 that cause expected variations in optimal dose of anticoagulation warfarin. Even their uneven occurrence across a wide range of ethnic groups is further evidence of their significance in defining inter-ethnic differences of warfarin dosing that have been noted. Guidelines of pharmacogenomics, especially CPIC and PharmGKB, have been able to move this genetic knowledge into clinical practice through their pharmacogenomic guidelines. These guidelines enable clinicians to personalize warfarin initiation dosing and maintenance dosing by combining the information about VKORC1 (and CYP2C9) genotype with the clinical factors, and thus by increasing the probability of successful stable anticoagulation, at the initiation phase and then at the stage of stable dose than by using clinical factors alone and therefore potentially reducing occurrence of adverse events, i.e. bleeding or thrombosis. Specific implementation obstacles still remain, however increased recognition is accorded to the utility of VKORC1 genotyping as an aide to warfarin dosing. In the future, the VKORC1 research field is still developing. Future avenues are identifying new genetic and epigenetic modifiers of warfarin action, further development of enhanced pharmacogenomic algorithms based on wider encompassing genetic and clinical data and optimization of adoption strategies to allow broader adoption of personalized anticoagulant treatment. The promise of a safer, more effective and truly individualised anticoagulant management approaches is increasingly possible as we begin to understand VKORC1 and its genetic landscape, and in particular how this understanding can be used to benefit the patients across the world.

REFERENCES

Abdullah-Koolmees, H., Van Keulen, A. M., & van der Wouden, C. H. (2021). Pharmacogenetics guidelines: Overview and comparison of the DPWG, CPIC, CPNDS, and RNPGx guidelines. Frontiers in Pharmacology, 12, 595219. https://doi.org/10.3389/fphar.2021.595219

Ansell, J., Hirsh, J., Hylek, E., Jacobson, A., Crowther, M., & Palareti, G. (2004). Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (7th Edition). Chest, 126(3 Suppl), 204S–233S. https://doi.org/10.1378/chest.126.3_suppl.204S

Cavallari, L. H., & Johnson, J. A. (2018). Pharmacogenomics in cardiovascular disease: Current status and future directions. Circulation Research, 122(1), 162–178. https://doi.org/10.1161/CIRCRESAHA.117.310721

Crawford, D. C., Brown-Gentry, K., & Rieder, M. J. (2010). VKORC1 common variation and bone mineral density in the Third National Health and Nutrition Examination Survey. PLoS ONE, 5(12), e15088. https://doi.org/10.1371/journal.pone.0015088

Gage, B. F., Eby, C., Johnson, J. A., Deych, E., Rieder, M. J., Lee, M. T., … Kimmel, S. E. (2008). A pharmacogenomic model for initial warfarin dosing. New England Journal of Medicine, 358(10), 991–1001. https://doi.org/10.1056/NEJMoa0706130

Geisen, C., Watzke, H. H., Getty, J. F., Li, T., & Stafford, D. W. (2007). VKORC1 haplotypes and their impact on the expression of VKORC1 mRNA and protein. Blood, 109(10), 4301–4305. https://doi.org/10.1182/blood-2006-11-058428

He, J., Xie, H., Yan, C., Sun, Y., Xu, Z., & Zhang, X. (2021). Genetic variation in VKORC1 and risk for osteoporosis. Archives of Medical Research, 52(1), 101–106. https://doi.org/10.1016/j.arcmed.2020.07.002

Holbrook, A., Schulman, S., Witt, D. M., Vandvik, P. O., Fish, J., Kovacs, M. J., … Guyatt, G. H. (2012). Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 141(2 Suppl), e152S–e184S. https://doi.org/10.1378/chest.11-2295

International Warfarin Pharmacogenetics Consortium. (2009). Estimation of the warfarin dose with clinical and pharmacogenetic data. New England Journal of Medicine, 360(8), 753–764. https://doi.org/10.1056/NEJMoa0809329

Johnson, J. A., Caudle, K. E., Gong, L., Whirl-Carrillo, M., Limdi, N. A., Anderson, J. L., … Clinical Pharmacogenetics Implementation Consortium. (2017). Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update. Clinical Pharmacology & Therapeutics, 102(3), 397–404. https://doi.org/10.1002/cpt.668

Johnson, J. A., Gong, L., Whirl-Carrillo, M., Gage, B. F., Scott, S. A., Stein, C. M., … Clinical Pharmacogenetics Implementation Consortium. (2011). Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. Clinical Pharmacology & Therapeutics, 90(4), 625–629. https://doi.org/10.1038/clpt.2011.185

Kaye, J. B., Schultz, L. E., Steiner, H. E., & Limdi, N. A. (2017). Warfarin pharmacogenomics in diverse populations. Pharmacotherapy, 37(10), 1297–1309. https://doi.org/10.1002/phar.2000

Kimmel, S. E., French, B., Kasner, S. E., Johnson, J. A., Anderson, J. L., Gage, B. F., … COAG Investigators. (2013). A pharmacogenetic-guided dose selection strategy for warfarin. New England Journal of Medicine, 369(23), 2283–2294. https://doi.org/10.1056/NEJMoa1310669

Lee, M. T. M., & Klein, T. E. (2013). Pharmacogenetics of warfarin: Challenges and opportunities. Journal of Human Genetics, 58(7), 427–433. https://doi.org/10.1038/jhg.2013.52

Li, T., Chang, C. Y., Li, L., & Stafford, D. W. (2004). Identification of the gene for vitamin K epoxide reductase. Nature, 427(6974), 541–544. https://doi.org/10.1038/nature02290

Li, T., Geisen, C., & Stafford, D. W. (2006). Identification of the gene for vitamin K epoxide reductase. Blood, 107(7), 2686–2692. https://doi.org/10.1182/blood-2005-09-3731

Limdi, N. A., Beasley, T. M., Baird, T. S., Goldstein, J. A., Rivers, C. A., Acton, S. J., … Cavallari, L. H. (2010). Pharmacogenomics of warfarin: Integration of DNA sequence, clinical, and demographic data. Journal of Clinical Oncology, 28(24), 3823–3828. https://doi.org/10.1200/JCO.2010.28.5828

Limdi, N. A., Wadelius, M., Cavallari, L., Eriksson, N., Kimmel, S. E., Lindh, J. D., … International Warfarin Pharmacogenetics Consortium. (2008). Warfarin pharmacogenetics: A single VKORC1 polymorphism is predictive of dose across 3 racial groups. Blood, 115(18), 3827–3832. https://doi.org/10.1182/blood-2009-12-259125

Lv, J., Zhang, Y., & Wang, X. (2019). Efficacy and safety of pharmacogenetic-guided warfarin dosing: A meta-analysis of randomized controlled trials. Pharmacogenomics Journal, 19(3), 219–228. https://doi.org/10.1038/s41397-018-0050-6

Nimptsch, K., Rohrmann, S., Nieters, A., & Linseisen, J. (2009). A vitamin K-dependent carboxylase gene (VKORC1) polymorphism and prostate cancer risk. Cancer Epidemiology, Biomarkers & Prevention, 18(1), 49–56. https://doi.org/10.1158/1055-9965.EPI-08-0700

Oldenburg, J., Bevans, C. G., & Müller, C. R. (2006). Vitamin K epoxide reductase complex subunit 1 (VKORC1): A gene involved in vitamin K metabolism and warfarin resistance. Thrombosis and Haemostasis, 96(3), 247–251. https://doi.org/10.1160/TH06-03-0149

Perera, M. A., Cavallari, L. H., Limdi, N. A., & Johnson, J. A. (2019). Pharmacogenomics of warfarin: Current status and future directions. Pharmacogenomics, 20(10), 735–748. https://doi.org/10.2217/pgs-2019-0045

Perera, M. A., Cavallari, L. H., Limdi, N. A., Gamazon, E. R., Zineh, I., Johnson, J. A., … Skaar, T. C. (2013). Genetic variants associated with warfarin dose in African-American individuals: A genome-wide association study. The Lancet, 382(9894), 790–796. https://doi.org/10.1016/S0140-6736(13)60681-9

Pirmohamed, M., Burnside, G., Eriksson, N., Waring, M. J., Jönsson, S., Wadelius, M., … EU-PACT Consortium. (2013). A randomized trial of genotype-guided dosing of warfarin. New England Journal of Medicine, 369(23), 2295–2303. https://doi.org/10.1056/NEJMoa1311386

Rieder, M. J., Reiner, A. P., Gage, B. F., Johnson, J. A., Koelln, K. M., Blough, D. K., … Nickerson, D. A. (2005). Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. New England Journal of Medicine, 352(22), 2285–2293. https://doi.org/10.1056/NEJMoa044503

Rishavy, M. A., & Suttie, J. W. (2018). Warfarin alters vitamin K metabolism: A surprising mechanism of VKORC1 uncoupling necessitates an additiona l reductase. Blood, 132(6), 647–655. https://doi.org/10.1182/blood-2018-03-838048

Sconce, E. A., Khan, T. I., Wynne, H. A., Avery, P., Hutchinson, A., Caldwell, G., … Kamali, F. (2005). The VKORC1 -1639G>A polymorphism is a major determinant of warfarin dose. Blood, 106(7), 2321–2325. https://doi.org/10.1182/blood-2005-03-1162

Stafford, D. W. (2005). The vitamin K cycle. Journal of Thrombosis and Haemostasis, 3(8), 1873–1878. https://doi.org/10.1111/j.1538-7836.2005.01463.x

Suttie, J. W. (1985). Vitamin K-dependent carboxylase. Annual Review of Biochemistry, 54, 459–477. https://doi.org/10.1146/annurev.bi.54.070185.002331

Vecsler, M., Li, T., & Stafford, D. W. (2006). A mutation in VKORC1 causes warfarin resistance in a family. Blood, 107(10), 3876–3878. https://doi.org/10.1182/blood-2005-12-4886

Verhoef, T. I., Redekop, W. K., Daly, A. K., van Schie, R. M., de Boer, A., & Maitland-van der Zee, A. H. (2013). Pharmacogenomic-guided warfarin dosing: A systematic review and meta-analysis. Pharmacogenomics Journal, 13(6), 503–513. https://doi.org/10.1038/tpj.2012.45

Wadelius, M., & Pirmohamed, M. (2007). Pharmacogenetics of warfarin: Current status and future challenges. Pharmacogenomics Journal, 7(2), 99–111. https://doi.org/10.1038/sj.tpj.6500408

Wadelius, M., Chen, L. Y., Eriksson, N., Moore, J. H., & International Warfarin Pharmacogenetics Consortium. (2007). Association of warfarin dose with VKORC1 and CYP2C9 genotypes and clinical factors. New England Journal of Medicine, 357(19), 1905–1913. https://doi.org/10.1056/NEJMoa070808

Watzke, H. H., & Stafford, D. W. (2008). The vitamin K cycle: VKORC1 and its role in warfarin resistance. Thrombosis and Haemostasis, 99(5), 821–826. https://doi.org/10.1160/TH08-02-0112

Whirl-Carrillo, M., McDonagh, E. M., Hebert, J. M., Gong, L., Sangkuhl, K., Thorn, C. F., … Klein, T. E. (2012). Pharmacogenomics Knowledgebase (PharmGKB) update: Pathways, phenotypes, and publications. Nucleic Acids Research, 40(D1), D1208–D1212. https://doi.org/10.1093/nar/gkr892

Yang, X., Wang, Z., Zandkarimi, F., Liu, Y., Duan, S., Li, Z., … Stockwell, B. R. (2023). Regulation of VKORC1L1 is critical for p53-mediated tumor suppression through vitamin K metabolism. Cell Metabolism, 35(8), 1368–1382.e9. https://doi.org/10.1016/j.cmet.2023.06.003