Warfarin Therapy and the Genotypes *CYP2C9* and *VKORC1*

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Introduction

Warfarin is an anticoagulant that acts by reducing the activity of vitamin K-dependent clotting factors. It is used in the prevention and treatment of thrombotic disorders. The dose of warfarin must be tailored for each patient according to the patient's INR response and the condition being treated.

A patient's *CYP2C9* and *VKORC1* genotype can be used to help determine the optimal starting dose of warfarin. The *CYP2C9* gene encodes one of the main enzymes involved in the metabolism of warfarin. Several variant *CYP2C9* alleles are associated with reduced enzyme activity and lower clearance rates of warfarin. Patients who carry at least one copy of such a variant allele (such as *CYP2C9*2* and *CYP2C9*3*) have reduced metabolism leading to higher warfarin concentrations. On average, they require a lower daily warfarin dose than patients who are homozygous for the wild-type *CYP2C9*1* allele.

The *VKORC1* gene encodes the vitamin K epoxide reductase enzyme, the target of warfarin. Patients who carry the -1639G>A polymorphism in the promoter region of the *VKORC1* gene are more sensitive to warfarin and require lower doses.

The FDA-approved warfarin drug label provides a dosing table based on *CYP2C9* and *VKORC1* genotypes (Table 1). The label states if the patient's *CYP2C9* and/or *VKORC1* genotype are known, to consider these ranges in choosing the initial doses, but whether this strategy reduces warfarin-related adverse events is controversial. The label also states that patients with *CYP2C9 *1/*3, *2/*2, *2/*3*, and **3/*3* may require more time (longer than 2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen than patients without these CYP variants (1).

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However, the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that this dosing table should only be used when electronic access is not possible. Instead, CPIC recommends that whenever possible, the pharmacogenetic algorithms available on http://www.warfarindosing.org should be used to predict the optimal warfarin dose (2). Although one randomized trial found that genotype-guided dosing might improve INR control after warfarin initiation (3), the largest completed trial found no benefit. (4). The largest trial of pharmacogenetic dosing of warfarin (ClinicalTrials.gov Identifier: NCT01006733) is expected to have results in December 2016.

Table 1. Three Ranges of Expected Maintenance Warfarin Doses based on *CYP2C9* and *VKORC1* Genotypes, adapted from the FDA drug label.

VKORC1	*CYP2C9*					
	**1/*1*	**1/*2*	**1/*3*	**2/*2*	**2/*3*	**3/*3*
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

Ranges are derived from multiple published clinical studies. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited *VKORC1* variants may also be important determinants of warfarin dose. This table is adapted from the FDA-approved drug label for Coumadin (warfarin) (1).

Drug: Warfarin

Warfarin is an anticoagulant used in the prevention and treatment of venous thrombosis, pulmonary embolism, and the complications associated with atrial fibrillation and/or cardiac valve replacement. Warfarin is sometimes prescribed to reduce the risk of stroke after a myocardial infarction (MI).

Warfarin has no direct effect on an established thrombus. However, once a thrombus has occurred (e.g., deep venous thrombosis), the goal of warfarin therapy is to prevent further extension of the formed clot and to prevent secondary thromboembolic complications that may be fatal (e.g., pulmonary embolism).

Warfarin exerts its anticoagulant effect by inhibiting the enzyme encoded by *VKORC1*, which catalyzes the conversion of vitamin K epoxide to the active reduced form of vitamin K, vitamin K hydroquinone. Vitamin K hydroquinone is an essential cofactor in the synthesis of several clotting factors—it promotes the synthesis of γ-carboxyglutamic acid residues in the proteins essential for biological activity. The decreased availability of vitamin K hydroquinone leads to decreased activity of the clotting factors II, VII, IX, and X, and the anticoagulant proteins C and S (5).

Warfarin is administered as a racemic mixture of the *R* and *S* stereoisomers. (*S*)-warfarin is two to five times more potent than (*R*)-warfarin, and is mainly metabolized by CYP2C9. (*R*)-warfarin is mainly metabolized via CYP3A4, with involvement of several other cytochrome P450 enzymes (6).

The initial and maintenance dosing of warfarin must be individualized for each patient. The goal of warfarin therapy is to achieve an international normalized ratio (INR) in a target range for the condition being treated (most commonly 2-3). This involves selecting an initial starting dose, followed by regular testing of the INR so that the dose of warfarin can be adjusted until the appropriate daily maintenance dose is determined. In general, the duration of anticoagulant therapy varies by clinical indication and should be continued until the danger of thrombosis and embolism has passed.

Selecting the initial dose of warfarin should be based on the expected maintenance dose, having taken into account the factors known to influence warfarin dose. Using an optimal starting dose for an individual may reduce the time taken to reach a stable INR, and reduce the risk of having either a high INR (with a risk of bleeding) or a low INR (with a risk of thrombosis) (2). Appropriate dosing of warfarin varies widely between individuals, and not all factors responsible for the variability in warfarin dose are known or easily quantified.

Known factors that influence an individual's response to the first dose of warfarin include clinical factors (e.g., age, race, body weight, sex, concomitant medications—including those that compete for binding to albumin, comorbidities, diet, nutritional status) and genetic factors (e.g., *CYP2C9* and *VKORC1* genotypes). Therefore, the initial dose should be modified to take into account these and any additional patient-specific factors that may influence warfarin response.

The FDA-approved drug label for warfarin suggests considering a lower initial and maintenance dose of warfarin for elderly and/or debilitated patients, and in Asian patients. The drug label recommends against the routine use of loading doses because this practice may increase hemorrhagic and other complications and does not offer more rapid protection against clot formation.

Warfarin can cause major or fatal bleeding. Bleeding is more likely to occur within the first month, and the risk factors include a high intensity of anticoagulation (INR greater than 4), age greater than or equal to 65, and a history of highly variable INRs. Other serious adverse events associated with warfarin therapy include necrosis of the skin and other tissues, particularly when used prematurely to manage thrombosis associated with heparin-induced thrombocytopenia (HIT).

Gene: *CYP2C9*

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs in the liver. The *CYP450* genes are very polymorphic and can result in reduced, absent, or increased enzyme activity.

CYP450 isozymes involved in the metabolism of warfarin include CYP2C9 and CYP3A4. The more potent warfarin *S*-enantiomer is metabolized by CYP2C9 while the *R*-enantiomer is metabolized by CYP1A2 and CYP3A4. The FDA-drug label for warfarin

states that drugs that inhibit or induce CYP2C9, CYP1A2, and/or CYP3A4 have the potential to alter the effect (INR) of warfarin by altering the exposure of warfarin.

*CYP2C9*1* is the wild-type allele and is associated with normal enzyme activity and the normal metabolizer phenotype.

Two common allelic variants associated with reduced enzyme activity are *CYP2C9*2* (Arg144Cys) and *CYP2C9**3 (Ile359Leu). Compared to normal metabolizers, patients who inherit one or two copies of **2* or **3* are more sensitive to warfarin—they require lower doses and are at a greater risk of bleeding during warfarin initiation (7-10).

The frequencies of the *CYP2C9* alleles vary between different ethnic groups (11-13). The **2* allele is more common in Caucasian (10-20%) than Asian (1-3%) or African (0-6%) populations (14). The **3* allele is less common (<10% in most populations) and extremely rare in African populations (15). In African Americans, it is likely that other *CYP2C9* variants such as *CYP2C9*5*, **6*, **8*, and **11* contribute to the variability in patient response to warfarin (2).

Gene: *VKORC1*

The *VKORC1* gene encodes the vitamin K epoxide reductase enzyme. It catalyzes the rate-limiting step in vitamin K recycling, and it is the target of the drug warfarin.

A common non-coding variant, -1639G>A, is associated with an increased sensitivity to warfarin (16). The polymorphism occurs in the promoter region of *VKORC1* and is thought to alter a transcription factor binding site, leading to lower protein expression. As a result, patients starting warfarin therapy who are –1639A carriers require lower initial and maintenance doses of the drug than –1639G carriers.

The –1639G>A allele frequency varies among different ethnic groups. It is the major allele (around 90%) in Asian populations, and may be a contributing factor for lower warfarin dosing requirements often observed in patients of Asian descent. It is also common in Caucasians (around 40%) and African Americans (around 14%) (17-19).

Less commonly, missense mutations in *VKORC1* can lead to warfarin resistance (20, 21).

Genetic Testing

VKORC1 and *CYP2C9* genotypes are the most important genetic determinants of warfarin dosing. The contribution of *VKORC1* to the variation in dose requirement is larger (approximately 30%) than the contribution of *CYP2C9* (usually less than 10%) (22).

Individuals who are most likely to benefit from genetic testing are those who have yet to start warfarin therapy. However, genotype-guided warfarin dosing is not the standard of care in most healthcare systems, and most (but not all) recent studies have reported that, in general, the use of genotype-guided dosing algorithms did not improve anticoagulation control in the first few weeks of warfarin therapy (4, 23-27).

Genetic testing is available for *CYP2C9* and *VKORC1*. The variants that are routinely tested for are *CYP2C9*2*, *CYP2C9*3*, and −1639G>A. These variants are used in the FDA table to guide therapy, and also in the International Warfarin Pharmacogenomics Consortium (IWPC) algorithm.

Other variants that are not routinely tested for include the *CYP2C9*6* and **8*, alleles, the genes *CYP4F2*, *EPHX1*, and *GGX* (which all have a role in the vitamin-K cycle), and the gene *CALU* (a cofactor in the VKOR complex) (2, 28). Including these additional genotypes in an expanded dosing algorithm improves warfarin dose prediction in African-Americans, while maintaining high performance in European-Americans (29).

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2015 Statement from the US Food and Drug Administration (FDA):

Dosing Recommendations without Consideration of Genotype

If the patient's *CYP2C9* and *VKORC1* genotypes are not known, the initial dose of warfarin is usually 2 to 5 mg once daily. Determine each patient's dosing needs by close monitoring of the INR response and consideration of the indication being treated. Typical maintenance doses are 2 to 10 mg once daily.

Dosing Recommendations with Consideration of Genotype

Table 1 displays three ranges of expected maintenance COUMADIN doses observed in subgroups of patients having different combinations of *CYP2C9* and *VKORC1* gene variants […]. If the patient's *CYP2C9* and/or *VKORC1* genotype are known, consider these ranges in choosing the initial dose. Patients with *CYP2C9 *1/*3*, **2/*2*, **2/*3*, and **3/*3* may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen than patients without these CYP variants.

Please review the complete therapeutic recommendations that are located here: (1)

2014 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC): The pharmacogenetic algorithms available on http://www.warfarindosing.org should be used whenever possible to determine the dose of warfarin required. Such algorithms have been derived from large studies across different ethnic populations, and they take into account both the genetic and non-genetic factors that influence the variability in warfarin response. The existence of rare genetic variants may be responsible

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labelled all formulations containing the generic drug.

for individuals whose warfarin dosing is not well predicted. However, overall the dosing equations are well validated and fairly precise. Only if electronic access to a pharmacogenetic algorithm is not possible should the table-based dosing approach be used, which is preferable to a fixed-dose approach.

Please review the complete therapeutic recommendations that are located here: (2, 30).

Table 2. Recommended daily warfarin doses (mg/day) to achieve a therapeutic INR based on *CYP2C9* and *VKORC1* genotype using the warfarin product insert approved by the US Food and Drug Administration

VKORC1: –1639G>A	*CYP2C9**1/*1	*CYP2C9**1/*2	*CYP2C9**1/*3	*CYP2C9**2/*2	*CYP2C9**2/*3	*CYP2C9**3/*3
GG	5-7	5-7	3-4	3-4	3-4	0.5-2
GA	5-7	3-4	3-4	3-4	0.5-2	0.5-2
AA	3-4	3-4	0.5-2	0.5-2	0.5-2	0.5-2

Table is adapted from Johnson JA, Gong L, Whirl-Carrillo M, Gage BF, Scott SA, Stein CM, Anderson JL, Kimmel SE, Lee MT, Pirmohamed M, Wadelius M, Klein TE, Altman RB; Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. Clinical pharmacology and therapeutics. 2011;90(4):625–9 (2).

Nomenclature

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2C9*2*	430C>T Arg144Cys	NM_000771.3:c.430C>T	NP_000762.2:p.Arg144Cys	rs1799853
*CYP2C9*3*	1075A>C Ile359Leu	NM_000771.3:c.1075A>C	NP_000762.2:p.Ile359Leu	rs1057910
VKORC1: -1639G>A	-1639G>A	NM_024006.4:c.-1639G>A	Not applicable - variant occurs in a non-coding region	rs9923231

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

Nomenclature for Cytochrome P450 enzymes is available from the Human Cytochrome P450 (CYP) Allele Nomenclature Database: http://www.cypalleles.ki.se/

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First edition:

The Pharmacogenomics Knowledgebase: http://www.pharmgkb.org

The Clinical Pharmacogenetics Implementation Consortium: http://www.pharmgkb.org/page/cpic

References

1. COUMADIN- warfarin sodium tablet) [package insert]. Princeton, NJ: Bristol-Myers Squibb Pharma Company; 2015. Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d91934a0-902e-c26c-23ca-d5accc4151b6
2. Johnson J.A., Gong L., Whirl-Carrillo M., Gage B.F., et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. Clinical pharmacology and therapeutics. 2011;90(4):625–9. PubMed PMID: 21900891.
3. Pirmohamed M., Burnside G., Eriksson N., Jorgensen A.L., et al. A randomized trial of genotype-guided dosing of warfarin. N Engl J Med. 2013;369(24):2294–303. PubMed PMID: 24251363.
4. Furie B. Do pharmacogenetics have a role in the dosing of vitamin K antagonists? N Engl J Med. 2013;369(24):2345–6. PubMed PMID: 24251364.
5. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Warfarin Pathway Pharmacodynamics: Simplified diagram of the target of warfarin action and downstream genes and effects [Cited 2012 Feb 24]. Available from: http://www.pharmgkb.org/pathway/PA145011114
6. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Warfarin Pathway Pharmacokinetics: Representation of the candidate genes involved in transport, metabolism and clearance of warfarin [Cited 2012 Feb 24]. Available from: http://www.pharmgkb.org/pathway/PA145011113
7. Higashi M.K., Veenstra D.L., Kondo L.M., Wittkowsky A.K., et al. Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. JAMA. 2002;287(13):1690–8. PubMed PMID: 11926893.
8. Aithal G.P., Day C.P., Kesteven P.J., Daly A.K. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. Lancet. 1999;353(9154):717–9. PubMed PMID: 10073515.
9. Limdi N.A., McGwin G., Goldstein J.A., Beasley T.M., et al. Influence of CYP2C9 and VKORC1 1173C/T genotype on the risk of hemorrhagic complications in African-American and European-American patients on warfarin. Clinical pharmacology and therapeutics. 2008;83(2):312–21. PubMed PMID: 17653141.
10. Lindh J.D., Holm L., Andersson M.L., Rane A. Influence of CYP2C9 genotype on warfarin dose requirements--a systematic review and meta-analysis. European journal of clinical pharmacology. 2009;65(4):365–75. PubMed PMID: 19031075.
11. Sistonen J., Fuselli S., Palo J.U., Chauhan N., et al. Pharmacogenetic variation at CYP2C9, CYP2C19, and CYP2D6 at global and microgeographic scales. Pharmacogenetics and genomics. 2009;19(2):170–9. PubMed PMID: 19151603.

12. Solus J.F., Arietta B.J., Harris J.R., Sexton D.P., et al. Genetic variation in eleven phase I drug metabolism genes in an ethnically diverse population. Pharmacogenomics. 2004;5(7):895–931. PubMed PMID: 15469410.
13. Lee C.R., Goldstein J.A., Pieper J.A. Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. Pharmacogenetics. 2002;12(3):251–63. PubMed PMID: 11927841.
14. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Haplotype CYP2C9*2 [Cited 2012 Feb 22]. Available from: http://www.pharmgkb.org/haplotype/PA165816543
15. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Haplotype CYP2C9*3 [Cited 2012 Feb 22]. Available from: http://www.pharmgkb.org/haplotype/PA165816544
16. PharmGKB [Internet]. Palo Alto (CA): Stanford University. VIP Variant in VKORC1 [Cited 2012 Feb 24]. Available from: http://www.pharmgkb.org/rsid/rs9923231 - tabview=tab2
17. Geisen C., Watzka M., Sittinger K., Steffens M., et al. VKORC1 haplotypes and their impact on the inter-individual and inter-ethnical variability of oral anticoagulation. Thrombosis and haemostasis. 2005;94(4):773–9. PubMed PMID: 16270629.
18. Obayashi K., Nakamura K., Kawana J., Ogata H., et al. VKORC1 gene variations are the major contributors of variation in warfarin dose in Japanese patients. Clinical pharmacology and therapeutics. 2006;80(2):169–78. PubMed PMID: 16890578.
19. Ross K.A., Bigham A.W., Edwards M., Gozdzik A., et al. Worldwide allele frequency distribution of four polymorphisms associated with warfarin dose requirements. Journal of human genetics. 2010;55(9):582–9. PubMed PMID: 20555338.
20. Loebstein R., Dvoskin I., Halkin H., Vecsler M., et al. A coding VKORC1 Asp36Tyr polymorphism predisposes to warfarin resistance. Blood. 2007;109(6):2477–80. PubMed PMID: 17110455.
21. Rost S., Fregin A., Ivaskevicius V., Conzelmann E., et al. Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. Nature. 2004;427(6974):537–41. PubMed PMID: 14765194.
22. Verhoef T.I., Redekop W.K., Daly A.K., van Schie R.M., et al. Pharmacogenetic-guided dosing of coumarin anticoagulants: algorithms for warfarin, acenocoumarol and phenprocoumon. Br J Clin Pharmacol. 2014;77(4):626–41. PubMed PMID: 23919835.
23. Verhoef T.I., Ragia G., de Boer A., Barallon R., et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. N Engl J Med. 2013;369(24): 2304–12. PubMed PMID: 24251360.
24. Stergiopoulos K., Brown D.L. Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. JAMA Intern Med. 2014;174(8):1330–8. PubMed PMID: 24935087.
25. Kimmel S.E., French B., Kasner S.E., Johnson J.A., et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. N Engl J Med. 2013;369(24):2283–93. PubMed PMID: 24251361.

26. Finkelman B.S., French B., Bershaw L., Kimmel S.E. Factors affecting time to maintenance dose in patients initiating warfarin. Pharmacoepidemiol Drug Saf. 2015;24(3):228–36. PubMed PMID: 25504915.
27. Belley-Cote E.P., Hanif H., D'Aragon F., Eikelboom J.W., et al. Genotype-guided versus standard vitamin K antagonist dosing algorithms in patients initiating anticoagulation. A systematic review and meta-analysis. Thromb Haemost. 2015;114(4):768–77. PubMed PMID: 26158747.
28. Nagai R., Ohara M., Cavallari L.H., Drozda K., et al. Factors influencing pharmacokinetics of warfarin in African-Americans: implications for pharmacogenetic dosing algorithms. Pharmacogenomics. 2015;16(3):217–25. PubMed PMID: 25712185.
29. Ramirez A.H., Shi Y., Schildcrout J.S., Delaney J.T., et al. Predicting warfarin dosage in European-Americans and African-Americans using DNA samples linked to an electronic health record. Pharmacogenomics. 2012;13(4):407–18. PubMed PMID: 22329724.
30. *Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline information for warfarin and CYP2C9, VKORC1*. 2014 06/19/2014 23 May 2016]; Available from: https://www.pharmgkb.org/guideline/PA166104949

Related Summaries by Gene

Celecoxib Therapy and *CYP2C9* Genotype

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Warfarin response

Tests in GTR by Gene

CYP2C9 gene

VKORC1 gene