Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C9* and *VKORC1* Genotypes and Warfarin Dosing

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Warfarin is a widely used anticoagulant with a narrow therapeutic index and large interpatient variability in the dose required to achieve target anticoagulation. Common genetic variants in the cytochrome P450-2C9 (CYP2C9) and vitamin K–epoxide reductase complex (VKORC1) enzymes, in addition to known nongenetic factors, account for ~50% of warfarin dose variability. The purpose of this article is to assist in the interpretation and use of *CYP2C9* and *VKORC1* genotype data for estimating therapeutic warfarin dose to achieve an INR of 2–3, should genotype results be available to the clinician. The Clinical Pharmacogenetics Implementation Consortium (CPIC) of the National Institutes of Health Pharmacogenomics Research Network develops peer-reviewed gene–drug guidelines that are published and updated periodically on http://www.pharmgkb.org based on new developments in the field.[1]

FOCUSED LITERATURE REVIEW

The **Supplementary Notes** online include a systematic literature review of *CYP2C9* and *VKORC1* genotype and warfarin dosing, which forms the basis for this guideline.

DRUG: WARFARIN

Warfarin (Coumadin and others) is the most commonly used oral anticoagulant worldwide, with annual prescriptions typically equaling 0.5–1.5% of the population. It is prescribed for treatment and prevention of thrombotic disorders.[2] Although highly efficacious, warfarin's narrow therapeutic index and wide interindividual variability make its dosing notoriously challenging.[3–5] Complications from inappropriate warfarin dosing are among the adverse events most frequently reported to the US Food and Drug Administration (FDA) and one of the most common reasons for emergency room visits.[6]

Warfarin is often dosed empirically: an initial dose is prescribed, typically followed by at least weekly measurement of the INR and subsequent dose adjustment. The initial dose is often based on population averages (e.g., 3–5 mg/day), but stable doses to achieve an INR of 2–3 can range from 1–20 mg/day. The iterative process to define the appropriate dose can take weeks to months, and during this period patients are at increased risk of over- or under-anticoagulation and thus at risk of thromboembolism or bleeding.

Warfarin pharmacology and pharmacokinetics

Figure 1 highlights key elements of warfarin pharmacology and pharmacokinetics. Warfarin inhibits vitamin K–epoxide reductase complex[7] and is administered as a racemic mixture, with S-warfarin being more potent than R-warfarin.[2]

GENES: *CYP2C9* AND WARFARIN

CYP2C9 is a hepatic drug-metabolizing enzyme in the CYP450 superfamily[8] and is the primary metabolizing enzyme of S-warfarin (**Figure 1**). The *CYP2C9* gene has more than 30 known variant alleles (http://www.cypalleles.ki.se/cyp2c9.htm; **Supplementary Tables S1** and **S2** online). Individuals homozygous for the reference *CYP2C9* allele (*CYP2C9*1*) have the "normal metabolizer" phenotype. Each named *CYP2C9* star (*) allele is defined by a genotype at one or more specific single-nucleotide polymorphisms (SNPs) and is associated with enzyme activity (**Supplementary Table S1**). The two most

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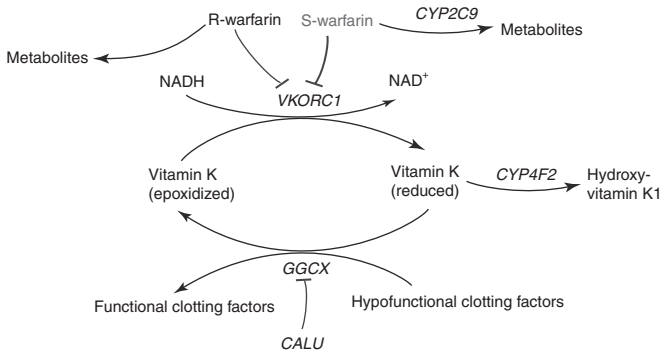

Figure 1 Schematic representation of warfarin metabolism and its mechanism of action. Warfarin is administered via a racemic mixture of the *R*- and *S*- stereoisomers. S-warfarin is three to five times more potent than R-warfarin and is metabolized predominantly to 7- and 6-hydroxyl metabolites via CYP2C9. Warfarin exerts its anticoagulant effect through inhibition of its molecular target, VKORC1, which in turn limits availability of reduced vitamin K, leading to decreased formation of functionally active clotting factors. These clotting factors are glycoproteins that are postranslationally carboxylated by γ-glutamyl carboxylase (GGCX) to Gla-containing proteins. The endoplasmic reticulum chaperone protein calumenin (CALU) can bind to and inhibit GGCX activity. The metabolism of reduced vitamin K to hydroxyvitamin K1 is catalyzed by CYP4F2, which removes vitamin K from the vitamin K cycle. Adapted from the warfarin pharmacokinetics (PK) and pharmacodynamics (PD) pathways provided at PharmGKB, <http://www.pharmgkb.org/do/serve?objId=PA451906&objCls=Drug#tabview=tab4>.

common variants with reduced enzyme activity among individuals of European ancestry are *CYP2C9*2* (rs1799853) and *CYP2C9*3* (rs1057910).[8] The frequencies of the *CYP2C9* variant alleles differ between racial/ethnic groups.[8,9]

In vitro and *ex vivo* studies suggest that *CYP2C9*2* and **3* impair metabolism of S-warfarin by ~30–40% and ~80–90%, respectively.[8] As compared with patients who are homozygous for *CYP2C9*1*, individuals who inherit one or two copies of *CYP2C9*2* or **3* are at greater risk of bleeding during warfarin therapy,[5,10,11] require lower doses to achieve similar levels of anticoagulation, and require more time to achieve a stable INR.[10,12] Additional *CYP2C9* variant alleles with reduced activity (*CYP2C9*5, *6, *8,* and **11*) contribute to dose variability among African Americans (**Supplementary Table S3**). Including these additional *CYP2C9* variants in dosing algorithms for warfarin may improve predictability for African Americans.

VKORC1 AND WARFARIN

VKORC1 encodes the vitamin K–epoxide reductase protein, the target enzyme of warfarin.[7,13] VKORC1 catalyzes the conversion of vitamin K–epoxide to vitamin K, which is the rate-limiting step in vitamin K recycling.[14]

A common noncoding variant (−1639G>A, rs9923231) is significantly associated with warfarin sensitivity and reduced dose requirements, as −1639A carriers require lower initial warfarin doses than −1639G carriers.[4,9,15–18] The −1639G>A polymorphism alters a *VKORC1* transcription factor binding site, leading to lower protein expression.[4,16]

Including other common *VKORC1* SNPs or haplotypes in dosing algorithms does not further improve warfarin dose prediction.[9,17]

The −1639G>A allele frequency varies among different ethnic groups (**Supplementary Table S2** online) and largely explains the differences in average dose requirements among whites, blacks, and Asians.[18] Several rare nonsynonymous *VKORC1* variants confer warfarin resistance (high-dose requirements); these are detailed in **Supplementary Table S3**.[19]

LINKING GENETIC VARIABILITY TO VARIABILITY IN DRUG-RELATED PHENOTYPES

CYP2C9 and *VKORC1* polymorphisms account for up to 18 and 30%, respectively, of the variance in stable warfarin dose among patients of European ancestry,[9,17,18,20] but these variants explain less of the dose variability in patients of Asian or African ancestry. Other genes of potential importance are discussed in **Supplementary Note S1** online.

In 2007, the FDA modified the warfarin label, stating that *CYP2C9* and *VKORC1* genotypes may be useful in determining the optimal initial dose of warfarin.[21] The label was further updated in 2010 to include a table (**Table 1**) describing recommendations for initial dosing ranges for patients with different combinations of *CYP2C9* and *VKORC1* genotypes.

Genetic test interpretation

Most clinical laboratories report *CYP2C9* genotype using the star (*) allele nomenclature and may provide interpretation of the patient's predicted metabolizer phenotype. Alleles other than **2* and **3* might not be tested, influencing the accuracy of the genotype-based dose prediction, which is particularly relevant in those of African ancestry who more commonly carry other *CYP2C9* variant alleles. *VKORC1* is typically reported by −1639G>A (or the linked 1173C>T) genotype, with accompanying interpretation of warfarin sensitivity. Of note, most commercial genotyping platforms do not detect rare *CYP2C9* and *VKORC1* variants that may influence warfarin dosing (**Supplementary Note S2** and **Supplementary Table S3**).

Genetic test options

Commercially available genetic testing options change frequently, but several platforms are available for *CYP2C9*/*VKORC1* genotyping, some of which have been approved by the FDA (**Supplementary Note S2**).

Incidental findings

No diseases have been linked to *CYP2C9* variants independent of drug metabolism and response. Similarly, no diseases have been consistently linked to common *VKORC1* variants routinely interrogated in warfarin pharmacogenetics tests.

RECOMMENDATIONS FOR WARFARIN MAINTENANCE (CHRONIC) DOSAGE BASED ON GENETIC INFORMATION

We use the three-tiered rating system described previously (and in **Supplementary Note S3** online)[1] in which ratings of A, strong; B, moderate; and C, optional are applied based on the evidence reviewed. The recommendations for dosing based on genotype contained herein are rated as level A, or strong,

Table 1 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

Reproduced from updated warfarin (Coumadin) product label.

and are derived from numerous observational studies and some prospective studies that suggest the ability to more accurately identify stable therapeutic warfarin dose requirements through use of both genetic and clinical information. However, there are limited prospective data from randomized trials on the use of genetic information to guide warfarin dosing (summarized in **Supplementary Note S4**), and the impact on clinical outcomes is unknown, although several such studies are currently ongoing, the largest of which are described in **Supplementary Note S5**.

Numerous studies have derived warfarin-dosing algorithms that use both genetic and nongenetic factors to predict warfarin dose.[17,18,20] Two algorithms perform well in estimating stable warfarin dose across different ethnic populations;[17,18] these were created using more than 5,000 subjects. Dosing algorithms using genetics outperform nongenetic clinical algorithms and fixed-dose approaches in dose prediction.[17,18] The greatest benefit of genetics in warfarin dosing is likely to be in patients requiring less than 21 mg/week or more than 49 mg/week (constituting >40% of all patients). Genetics-based algorithms also better predict warfarin dose than the FDA-approved warfarin label table.[22] Therefore, the use of pharmacogenetic algorithm-based dosing is recommended when possible, although if electronic means for such dosing are not available, the table-based dosing approaches (**Table 1**) are suggested. The range of doses by *VKORC1* genotype and the range of dose recommendations/predictions by the FDA table and algorithm are shown in **Figure 2**.

Pharmacogenetic algorithm-based warfarin dosing

The best way to estimate the expected stable dose of warfarin is to use the algorithms available on http://www.warfarindosing.org (offering both high-performing algorithms[17,18]). The dosing algorithm published by the International Warfarin Pharmacogenetics Consortium is also online, at <http://www.pharmgkb.org/do/serve?objId=PA162372936&objCls=Dataset#tabview=tab2>. The two algorithms provide very similar dose recommendations. The clinical and genetic information used in one or both algorithms is shown in Box 1. These algorithms compute the anticipated stable daily warfarin dose to one decimal, and the clinician must then prescribe a regimen (e.g., an estimate of 4.3 mg/day might be given as 4 mg daily except 5 mg two days per week).

Approach to pharmacogenetics-based warfarin dosing without access to dosing algorithms

Table 1 summarizes the average dose ranges based on *CYP2C9*2* and **3* and *VKORC1* genotypes, as recommended

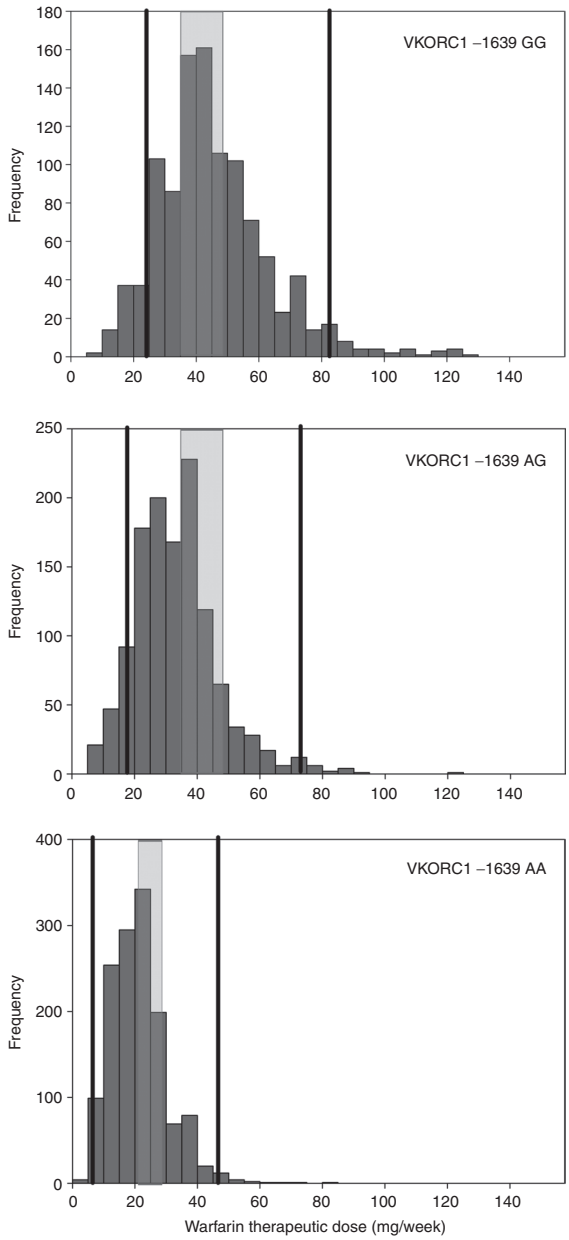

Figure 2 Frequency histograms of stable therapeutic warfarin doses in mg/week, stratified by *VKORC1* –1639G>A genotype in 3,616 patients recruited by the International Warfarin Pharmacogenetics Consortium (IWPC) who did not carry the *CYP2C9*2* or **3* allele (i.e., coded as **1*1* for US Food and Drug Administration (FDA) table and algorithm dosing). The range of doses within each genotype group recommended on the FDA table is shown via the shaded rectangle. The range of doses predicted using the IWPC dosing algorithm in these 3,616 patients is shown by the solid lines.

in the FDA-approved warfarin (Coumadin) product label. The specific dose selected within that range should take into account other important variables, such as patient age, body size, and interacting drugs. The published evidence strongly supports our level A (strong) recommendation that, if genetic information is available, warfarin dosing should be estimated using a pharmacogenetic dosing algorithm, but in the absence of access to such an algorithm, a genotype dosing table is superior to other approaches that ignore genetic information in predicting stable warfarin dose.[22]

Other considerations

Supplementary Note S6 summarizes other considerations in the dosing of warfarin, including clinical factors and interacting drugs, some of which are included in the pharmacogenetic dosing algorithms (see **Box 1**). Other genes of potential importance are detailed in **Supplementary Note S1** and **Tables S3** and **S4**, including a nonsynonymous SNP in *CYP4F2*. Most clinical genotyping platforms do not yet include this SNP, and neither do the dosing tables or algorithms. **Supplementary Note S6** also discusses incorporation of genetic information into the initial dose, as well as alternatives to warfarin.

Potential benefits and risks for the patient

Several ongoing, randomized controlled clinical trials are evaluating the risks and benefits of using genetics to dose warfarin (**Supplementary Note S5**). Incorporation of genetic information has the potential to shorten the time to attain stable INR, increase the time within the therapeutic INR range, and reduce underdosing or overdosing during the initial treatment period.[23] If these benefits are realized, they may combine to reduce the risk of bleeding and thromboembolic events.[24] There are also potential risks. For example, the use of genetic information to guide dosing may lead to false security and inadequate INR monitoring. Genetics-guided dosing may increase the risk for overdosing or underdosing, although current evidence suggests that this is not likely.[18] Genetic information may affect patient decisions about warfarin—those requiring lower than average warfarin doses may believe they can take warfarin less frequently. The cost–benefit of genetics-guided therapy depends on the cost of genotyping and the reduction in adverse events,[25] and most insurance plans currently do not pay for warfarin pharmacogenetic testing. Although there is substantial evidence associating *CYP2C9* and *VKORC1* variants with warfarin dosing, there is sparse randomized clinical trial evidence showing better outcomes. Although *CYP2C9/VKORC1* genotyping is reliable when performed in qualified laboratories, an additional risk to the patient is an error in genotyping or reporting of genotype. Genotypes are lifelong test results, so such an error could have adverse health implications for the life of the patient.

Caveats: appropriate use and/or potential misuse of genetic tests

Many pharmacogenetic dosing algorithms are focused on a target INR of 2–3,[18] so their utility outside this range is limited; however, some algorithms accommodate the target INR explicitly.[17] Pharmacogenetics-guided warfarin dosing should not alter the requirements for regular INR monitoring. There are very few data on warfarin pharmacogenetics and the performance of dosing algorithms in children,[26] so no recommendations are made in this regard. There are patients for whom genetic testing is likely to be of little or no benefit, including those who have already had long-term treatment with stable warfarin doses and those who are unable to achieve stable dosing owing to variable adherence or dietary vitamin K intake. The greatest potential benefit is early in the course of therapy (before therapy initiation or in the first few days);[27] however, there may also be benefit several weeks into therapy.[28] It is likely that patients on therapy for many weeks to months, with careful INR monitoring, will derive little benefit from subsequent warfarin pharmacogenetics testing.[29]

Box 1 Patient characteristics utilized in the Gage algorithm,[17] the International Warfarin Pharmacogenetics Consortium[18] algorithm, or both

- Age
- Sex
- Race
- Weight
- Height
- Smoking status
- Warfarin indication
- Target international normalized ratio
- Interacting drugs
  - Inhibitors: amiodarone, statins, sulfamethoxazole, azole antifungals
  - Inducers: rifampin, phenytoin, carbamazepine
- Genetic variables
  - *CYP2C9* genotype
  - *VKORC1* genotype
  - The Gage algorithm can also incorporate *CYP4F2* and *GGCX* genotypes

Disclaimer

CPIC guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making and to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. The guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. They do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health-care provider to determine the best course of treatment for a patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made solely by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to persons or property arising out of or related to any use of CPIC's guidelines, or for any errors or omissions.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

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CONFLICT OF INTEREST

All authors are members of the International Warfarin Pharmacogenetics Consortium. S.E.K. is the principal investigator for the US-based COAG trial; J.L.A., B.F.G., and J.A.J. are members of the COAG executive committee; and S.A.S. and C.M.S. are investigators in COAG. B.F.G. is principal investigator of the GIFT trial, and J.L.A. is an investigator. M.P. is the UK chief investigator for the EU-PACT trial, and M.W. is the principal investigator in Sweden; the views presented here are their own and are not presented on behalf of the EU-PACT investigators collectively. The EU-PACT trial is funded by the EU-FP7 framework. M.T.M.L. is the principal investigator for the Taiwan-based pharmacogenetic dosing of warfarin randomized trial. S.E.K. receives additional funding from the National Institutes of Health for research on warfarin pharmacogenetics, has received funding from the Aetna Foundation for warfarin-related research, has received an honorarium for a talk on warfarin from Ortho McNeill, and has received grants from and served as a consultant to several pharmaceutical companies, all unrelated to warfarin. J.A.J. is on an advisory committee for Medco. R.B.A. is a consultant to 23andme.com.

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