

**Supplement to:  
Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for  
Pharmacogenetics-guided Warfarin Dosing: 2016 Update**

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## GUIDELINE UPDATES

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for warfarin dosing is published in full on <http://www.pharmgkb.org> and <https://cpicpgx.org/guidelines/>. Relevant information will be reviewed periodically and updated guidelines published online.

## LITERATURE REVIEW

We searched the PubMed® database (1966 to August 2016) for the following keywords: ((cytochrome P450 2C9 or CYP2C9) OR (VKORC1) OR (cytochrome P450 4F2 or CYP4F2) AND (warfarin) AND English [Language]). Using these search terms, 1221 publications were identified. In addition, studies annotated in PharmGKB (<http://www.pharmgkb.org>) were identified. Study inclusion criteria included publications that included analyses for the association between *CYP2C9/VKORC1/CYP4F2* genotypes and metabolism of warfarin or warfarin-related adverse drug events or clinical outcomes. Non-English manuscripts were excluded. Following application of these inclusion criteria, 151 publications were reviewed and included in the evidence tables (**Supplemental Tables S1- S7**).

The *CYP2C9/VKORC1/CYP4F2* frequency tables (<https://www.pharmgkb.org/page/cyp2c9RefMaterials>; <https://www.pharmgkb.org/page/vkorc1RefMaterials>; <https://www.pharmgkb.org/page/cyp4f2RefMaterials>) were made by searching the PubMed® database (1995 to 2016). The following criteria were used for *CYP2C9*: (CYP2C9 or 2C9 or cytochrome P4502C9) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity OR population) with filter limits set to retrieve “full-text” and “English” literature. In addition, reports were also identified from citations by others or review articles. Studies were considered for inclusion in the *CYP2C9* frequency table if: (1) the ethnicity of the population was clearly indicated, (2) either allele frequencies or genotype frequencies were reported, (3) the method by which the genes were genotyped was indicated, (4) the sample population consisted of at least 50 individuals with a few exceptions (e.g., smaller cohorts that were part of larger studies) and (5) the study represented an original publication (no reviews or meta-analyses). Similar search strategies were used for *VKORC1* and *CYP4F2* genes. Allele frequencies reported in phase 3 1000 Genomes were also included (<http://browser.1000genomes.org/index.html>) (1).

## **DRUG: WARFARIN**

### **Background**

Warfarin is administered as a racemic mixture of *R*- and *S*- stereoisomers. *S*-warfarin is 3-5 times more potent as a vitamin K antagonist than *R*-warfarin (2). The stereoisomers are extensively metabolized by different hepatic microsomal enzymes. *S*-warfarin is metabolized predominantly to 7- and 6- hydroxyl metabolites via CYP2C9 (**Figure 1, main manuscript**), whereas *R*-warfarin is mainly metabolized via CYP3A4 with involvement of CYP1A1, CYP1A2, CYP2C8, CYP2C9, CYP2C18 and CYP2C19 (3-6).

Warfarin exerts its anticoagulant effect through inhibition of its molecular target Vitamin K epoxide reductase complex (VKORC1) (7). VKORC1 catalyzes the conversion of oxidized Vitamin K to reduced Vitamin K with the help of microsomal epoxide hydrolase (EPHX1). Warfarin blocks this reaction, which leads to decreased availability of the reduced Vitamin K that serves as a cofactor for gamma-glutamyl carboxylase (GGCX), and blocks the formation of functionally active clotting factors, leading to reduced coagulation (8-11).

## Dosing algorithms

### IWPC warfarin pharmacogenetic dosing algorithm (12)

5.6044

- 0.2614 x Age in decades
  - + 0.0087 x Height in cm
  - + 0.0128 x Weight in kg
  - 0.8677 x *VKORC1* A/G
  - 1.6974 x *VKORC1* A/A
  - 0.4854 x *VKORC1* genotype unknown
  - 0.5211 x *CYP2C9*\*1/\*2
  - 0.9357 x *CYP2C9*\*1/\*3
  - 1.0616 x *CYP2C9*\*2/\*2
  - 1.9206 x *CYP2C9*\*2/\*3
  - 2.3312 x *CYP2C9*\*3/\*3
  - 0.2188 x *CYP2C9* genotype unknown
  - 0.1092 x Asian race
  - 0.2760 x Black or African American
  - 0.1032 x Missing or Mixed race
  - + 1.1816 x Enzyme inducer status
  - 0.5503 x Amiodarone status
- = Square root of weekly warfarin dose\*\*

\*\*The output of this algorithm must be squared to compute weekly dose in mg and divided by 7 to get the daily dose.

### Gage, et al. (13)

Estimated daily warfarin dose (mg/day) =  $\text{Exp} (0.9751 - 0.3238 \times \text{VKOR}_{1639} + 0.4317 \times \text{BSA} - 0.4008 \times \text{CYP2C9}^*3 - 0.00745 \times \text{Age} - 0.2066 \times \text{CYP2C9}^*2 + 0.2029 \times \text{Target INR} - 0.2538 \times \text{Amiodarone} + 0.0922 \times \text{Smokes} - 0.0901 \times \text{AA}_{\text{Race}} + 0.0664 \times \text{Prior}_{\text{DVT\_PE}})$

where exp is the exponential function, BSA is in m<sup>2</sup>, the SNPs are coded 0 if absent, 1 if heterozygous, and 2 if homozygous, and race is coded as 1 if African American and 0 otherwise.

### EU-PACT Loading Dose algorithm (14)

Loading dose (LD) over three days is calculated from the predicted maintenance dose (MD) as follows:

$$\text{LD}_3 = \text{MD} / (1 - \exp(-\kappa t))(1 + \exp(-\kappa t) + \exp(-2\kappa t))$$

MD is the IWPC predicted weekly maintenance dose in mg divided by 7 days.

$\kappa$  is the elimination rate constant for the *CYP2C9* genotypes:

$$*1/*1 = 0.0189\text{h}^{-1}$$

$$*1/*2 = 0.0158\text{h}^{-1}$$

$$*1/*3 = 0.0132\text{h}^{-1}$$

$$*2/*2 = 0.0130\text{h}^{-1}$$

$$*2/*3 = 0.009h^{-1}$$

$$*3/*3 = 0.0075h^{-1}$$

$\tau$  is the warfarin dosing interval, use 24 (24h) for once daily dosing

The loading dose regimen is gradually reduced, i.e. Day 1 dose > Day 2 dose > Day 3 dose:

Loading on Day 1: (LD3-MD) x 1.5 + MD

Loading on Day 2: ((LD3-MD) x 1 + MD

Loading on Day 3: (LD3-MD) x 0.5 + MD

### **Lenzini, et al. (15)**

Pharmacogenetic refinement algorithm: maintenance dose (mg/week) =

$EXP(3.10894 - 0.00767 \times \text{age} - 0.51611 \times \ln(\text{INR}) - 0.23032 \times VKORC1-1639 G>A - 0.14745 \times CYP2C9*2 - 0.3077 \times CYP2C9*3 + 0.24597 \times \text{BSA} + 0.26729 \times \text{Target INR} - 0.09644 \times \text{African origin} - 0.2059 \times \text{stroke} - 0.11216 \times \text{diabetes} - 0.1035 \times \text{amiodarone use} - 0.19275 \times \text{fluvastatin use} + 0.0169 \times \text{dose}_2 + 0.02018 \times \text{dose}_3 + 0.01065 \times \text{dose}_4)$   
where VKORC1 -1639 G>A is entered as 0 for G/G, 1 for A/G and 2 for A/A, CYP2C9 SNPs are coded 0 if absent, 1 if heterozygous, and 2 if homozygous, and race is coded as 1 if African origin and 0 otherwise.

### **Other considerations**

**Clinical factors.** As highlighted in the dosing algorithms, clinical/demographic factors also significantly influence warfarin dose variability, the most significant of these being body size and age. An additional factor that is known to affect INR stability is patient non-adherence (16, 17). As with any drug, the patient should be counseled to ensure that there is an understanding of the importance of adherence to the prescribed warfarin regimen. In addition, genotype does not alter the importance of patient adherence.

**Drug interactions.** Drug interactions are common with warfarin, and significant interactions include both enzyme induction and enzyme inhibition. Smoking also causes enzyme induction. The dosing algorithms take into account some, but not all of the clinically important drug interactions with warfarin. Therefore, it is important to interpret the results of genetic testing in the context of other co-administered drugs.

**Other genes.** Variants in *CALU* and *GGCX* have been shown to affect warfarin dose and contribute to warfarin dose variations in some but not all populations. The effects of these variants are weaker than those of *CYP2C9* and/or *VKORC1*. Evidence linking these genes and other genes/variants to warfarin phenotype are presented in **Supplemental Table S6**.

Calumenin, encoded by gene *CALU*, is a Ca<sup>2+</sup>-binding protein retained in the endoplasmic reticulum. It binds to gamma—glutamyl carboxylase (GGCX) as an inhibitory chaperone to inhibit the vitamin K cycle and also affects the activity and warfarin sensitivity of VKORC1 (18). Genetic variations in *CALU* have been studied for their effect on warfarin dosing. One patient homozygous for the *CALU* rs2290228 variant allele was found with exceptionally high warfarin requirement (20mg/d) (19). However, this SNP and other *CALU* SNPs (rs11653, rs2307040, rs339054 and rs1006023) have not been shown to be significantly associated with warfarin dose in other studies (20). A new variant, rs339097 in *CALU*, has been identified that predicts higher warfarin dose in African Americans populations, with the G allele of rs339097 associated with a 14.5% higher therapeutic warfarin dose (21). Since variations in *VKORC1*, *CYP2C9* and *CYP4F2* genes only account for ~10% of the warfarin dose variations in African Americans, in contrast to ~35% in whites, identifying this additional SNP in *CALU* may help with prediction of warfarin dose, especially in the African American population. This variant is also more common in African Americans with minor allele frequencies of 11–14%, but only 0.2% in Caucasians. The correlation between rs339097 and higher warfarin dose requirement was confirmed in a study of 207 Egyptian patients (22).

Gamma-glutamyl carboxylase (GGCX) is a critical component of the vitamin K cycle (**Figure 1, main manuscript**) and catalyzes the post-translational carboxylation of vitamin K-dependent proteins (23). Many of these vitamin K-dependent proteins (clotting factors F2, F7, F9, F10 and protein C, S, Z) are involved in coagulation cascades. GGCX mediates the conversion of glutamate (Glu) residues to gamma carboxyl glutamate (Gla) on these proteins to make them functionally active with the reduced vitamin K serving as an essential cofactor. Rare non-synonymous mutations in *GGCX* have been linked with clotting disorders such as vitamin K-dependent clotting factor deficiency (VKCFD1, (24)) and Pseudoxanthoma Elasticum (PXE)-like disorder with multiple coagulation factor deficiency (25). Due to its pivotal role in the blood coagulations, genetic variations in the *GGCX* gene have been investigated for their impact on warfarin maintenance dose. One variant, rs11676382, was found to be associated with warfarin dose and explained 2% of total variance (26). This finding was confirmed in a large cohort (985 patients, mostly whites) where rs11676382 was shown to be a significant (p=0.03) predictor of residual dosing error and was associated with a 6.1% reduction in warfarin dose (95% CI: 0.6%-

11.4%) per G allele (11). Another variant in *GGCX*, rs12714145, was shown to be associated with warfarin dose in a Swedish cohort (201 patients, (27)), but failed to be replicated in subsequent studies (11, 20, 28, 29).

Genetic variation in folate homeostasis has also been shown to impact warfarin response. An association between lower warfarin dose requirements and the folate homeostasis gene, folypolyglutamate synthase gene (*FPGS*; rs7856096), has been reported in African Americans (30). However, this genetic variation does not appear to influence warfarin dose requirements in European-Americans and Egyptians (31).

***Alternative therapies to warfarin.*** For over five decades coumarin anticoagulants, the most popular of which is warfarin, have been the only oral anticoagulants available world-wide. The approval of non-vitamin K anticoagulants, also known as novel oral anticoagulants (NOACs: dabigatran, rivaroxaban, apixaban and edoxaban) provides an alternative to warfarin therapy in those with atrial fibrillation (32-36). While DOACs are not known to be influenced by genetic variability in *CYP2C9* and *VKORC1*, their pharmacokinetics or efficacy may be influenced by other genes (37). Advantages for NOACs include their rapid onset of anticoagulation, dosing simplicity for the clinician, and lack of need for monitoring. There are also disadvantages, which include twice daily dosing (dabigatran and apixaban), varying bioavailability (6 to over 80%), varying dependence on renal function for elimination (25 to 80%), the inability to monitor therapeutic effect, costs, limited clinical trial data for indications other than atrial fibrillation, contraindications for mechanic heart valves, and a 30-day shelf life once opened (dabigatran), among others (38, 39). As new oral anticoagulants gain market share, reliance on warfarin will decline. However, warfarin will continue to be widely utilized world-wide.

## **LEVELS OF EVIDENCE LINKING GENOTYPE TO PHENOTYPE**

The evidence summarized in **Supplemental Tables S1-S7** is graded (40) on a scale of high, moderate, and weak, based upon the level of evidence:

**High:** Evidence includes consistent results from well-designed, well-conducted studies.



**Moderate:** Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence.

**Weak:** Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Every effort was made to present evidence from high-quality studies, which provided the framework for the strength of therapeutic recommendations (**Main manuscript Table 2**).

## **STRENGTH OF RECOMMENDATIONS**

CPIC's therapeutic recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: in vivo pharmacokinetic and pharmacodynamic data, in vitro enzyme activity of tissues expressing wild-type or variant-containing gene, in vitro enzyme activity from tissues isolated from individuals of known genotypes, and in vivo pre-clinical and clinical pharmacokinetic and pharmacodynamic studies. The gene-based dosing recommendations in this guideline take into consideration the effects that *CYP2C9/VKORC1/CYP4F2* genetic variants may have on both clinical outcomes and warfarin pharmacokinetics.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of antiretroviral agents (41):

**Strong** recommendation for the statement: "The evidence is high quality and the desirable effects clearly outweigh the undesirable effects."

**Moderate** recommendation for the statement: "There is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

**Optional** recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.

**SUPPLEMENTAL TABLE S1. EVIDENCE LINKING *CYP2C9* TO WARFARIN PHENOTYPE**

<b>Type of experimental model</b>	<b>Major findings</b>	<b>References</b>	<b>Level of evidence*</b>
<b>In vitro</b>	CYP2C9 is the primary enzyme catalyzing the metabolism and inactivation of S-warfarin.	Rettie, <i>et al.</i> (1992) (3) Rettie, <i>et al.</i> (1994) (42) Yamazaki, <i>et al.</i> (1998) (43)	High
<b>In vitro</b>	<i>CYP2C9*2</i> is associated with reduced catalytic activity. Substrate affinity is not affected substantially by the *2 haplotype, but the maximum rate of metabolism (Vmax) is reduced to approximately 50% of that for <i>CYP2C9*1</i> (wild-type).	Rettie, <i>et al.</i> (1994) (42) Yamazaki, <i>et al.</i> (1998) (43) Tang, <i>et al.</i> (2001) (44) Lee, <i>et al.</i> (2002) (45) Ho, <i>et al.</i> (2003) (46) Kirchheiner, <i>et al.</i> (2005) (47)	High
<b>In vitro</b>	<i>CYP2C9*3</i> is associated with significantly reduced (nearly abolished for homozygotes) function of CYP2C9.	Lee, <i>et al.</i> (2002) (45) Ho, <i>et al.</i> (2003) (46) Kirchheiner, <i>et al.</i> (2005) (47)	High
<b>Clinical</b>	Individuals with <i>CYP2C9*2</i> and <i>CYP2C9*3</i> exhibit impaired metabolism of S-warfarin, leading to longer half-life of the drug.	Rettie, <i>et al.</i> (1994) (42) Aithal, <i>et al.</i> (1999) (48) Kirchheiner, <i>et al.</i> (2005) (47) Daly, <i>et al.</i> (2006) (49) Lindh, <i>et al.</i> (2009) (50)	High

<b>Clinical</b>	Individuals with <i>CYP2C9</i> *2 and <i>CYP2C9</i> *3 have reduced warfarin maintenance dose.	Margaglione, <i>et al.</i> (2000) (51) Taube, <i>et al.</i> (2000) (52) Wadelius, <i>et al.</i> (2005) (27) Samardzija, <i>et al.</i> (2008) (53) Takeuchi, <i>et al.</i> (2009) (54) Klein, <i>et al.</i> (2009) (12) Pautas, <i>et al.</i> (2010) (28) Cavallari, <i>et al.</i> (2011) (55) Valentin, <i>et al.</i> (2012) (56) Liang, <i>et al.</i> (2012) (57) El Din, <i>et al.</i> (2012) (58) Lee, <i>et al.</i> (2012) (59) Pathare, <i>et al.</i> (2012) (60) Liang, <i>et al.</i> (2013) (61) Santos, <i>et al.</i> (2013) (62) Ozer, <i>et al.</i> (2013) (63) Limdi, <i>et al.</i> (2015) (64)	High
<b>Clinical</b>	<i>CYP2C9</i> variants with reduced activity ( <i>CYP2C9</i> *5, *6, *8, and *11 alleles) have reduced warfarin maintenance dose. These variants most commonly occur in individuals of African ancestry.	Redman, <i>et al.</i> (2004) (65) Tai, <i>et al.</i> (2005) (66) Limdi, <i>et al.</i> (2007) (67) Scott, <i>et al.</i> (2009) (68) Cavallari, <i>et al.</i> (2010) (69) Shahin, <i>et al.</i> (2011) (22) Liu, <i>et al.</i> (2012) (70) Cavallari, <i>et al.</i> (2013) (71) Limdi, <i>et al.</i> (2015) (64)	High
<b>Clinical</b>	<i>CYP2C</i> rs12777823 variant is associated with reduced warfarin dose in African Americans, independent of <i>CYP2C9</i> *2 and <i>CYP2C9</i> *3.	Perera, <i>et al.</i> (2013) (72) Drozda, <i>et al.</i> (2015) (73) Limdi, <i>et al.</i> (2015)(64)	High
<b>Clinical</b>	With empiric warfarin dosing, individuals with <i>CYP2C9</i> *2 and <i>CYP2C9</i> *3 have shorter time to therapeutic INR.	<b>Supports statement:</b> Ruud, <i>et al.</i> (2008) (74) Jorgensen, <i>et al.</i> (2009) (75) Limdi, <i>et al.</i> (2009) (76)	Weak

		<p>Pautas, <i>et al.</i> (2010) (28)          McMillin, <i>et al.</i> (2010) (77)          Ozer, <i>et al.</i> (2010) (78)          Zhong, <i>et al.</i> (2011) (79)</p> <p><b>Does not support statement:</b>          Higashi, <i>et al.</i> (2002) (80)          Limdi, <i>et al.</i> (2008) (81)          Schwarz, <i>et al.</i> (2008) (82)          Li, <i>et al.</i> (2009) (83)          Wadelius, <i>et al.</i> (2009) (84)          Lund, <i>et al.</i> (2012) (85)          Biss, <i>et al.</i> (2012) (86)</p>	
<b>Clinical</b>	With empiric warfarin dosing, individuals with <i>CYP2C9*2</i> and <i>CYP2C9*3</i> require more time to achieve stable dose.	<p><b>Supports statement:</b>          Higashi, <i>et al.</i> (2002) (80)          Meckley, <i>et al.</i> (2008) (87)          Limdi, <i>et al.</i> (2008) (81)          Schwarz, <i>et al.</i> (2008) (82)          Caraco, <i>et al.</i> (2008) (88)          Kim, <i>et al.</i> (2009) (89)          Jorgensen, <i>et al.</i> (2009) (75)          Lund, <i>et al.</i> (2012) (85)</p> <p><b>Does not support statement:</b>          Lima, <i>et al.</i> (2008) (90)          Biss, <i>et al.</i> (2012) (86)          Finkelman, <i>et al.</i> (2015) (91)</p>	High
<b>Clinical</b>	With empiric warfarin dosing, individuals with <i>CYP2C9*2</i> and <i>CYP2C9*3</i> have less time in INR therapeutic range (TTR) early in the course of therapy.	<p><b>Supports statement:</b>          Meckley, <i>et al.</i> (2008) (87)          Lima, <i>et al.</i> (2008) (90)          Limdi, <i>et al.</i> (2009) (76)          Wadelius, <i>et al.</i> (2009) (84)          Skov, <i>et al.</i> (2013) (92)</p>	Moderate

		<b>Does not support statement:</b> Taube, <i>et al.</i> (2000) (52) Moreau, <i>et al.</i> (2012) (93)	
<b>Clinical</b>	With empiric warfarin dosing, individuals with <i>CYP2C9*2</i> and <i>CYP2C9*3</i> are at increased risk of over-anticoagulation (INR>4).	<b>Supports statement:</b> Higashi, <i>et al.</i> (2002) (80) Peyvandi, <i>et al.</i> (2004) (94) Voora, <i>et al.</i> (2005) (95) Kealey, <i>et al.</i> (2007) (96) Anderson, <i>et al.</i> (2007) (97) Meckley, <i>et al.</i> (2008) (87) Schwarz, <i>et al.</i> (2008) (82) Lima, <i>et al.</i> (2008) (90) Ruud, <i>et al.</i> (2008) (74) Jorgensen, <i>et al.</i> (2009) (75) Kim, <i>et al.</i> (2009) (89) Limdi, <i>et al.</i> (2009) (76) Wadelius, <i>et al.</i> (2009) (84) Molden, <i>et al.</i> (2010) (98) Pautas, <i>et al.</i> (2010) (28) Moon, <i>et al.</i> (2011) (99) Biss, <i>et al.</i> (2012) (86) Ma, <i>et al.</i> (2012) (100) Yang, <i>et al.</i> (2013) (101) Gaikwad, <i>et al.</i> (2013) (102) Kawai, <i>et al.</i> (2014) (103) Mega, <i>et al.</i> (2015) (104)	High
		<b>Does not support statement:</b> Taube, <i>et al.</i> (2000) (52) Limdi, <i>et al.</i> (2008) (81) Li, <i>et al.</i> (2009) (83) Lund, <i>et al.</i> (2012) (85) Santos, <i>et al.</i> (2013) (62)	

		Valentin, <i>et al.</i> (2014) (105)	
<b>Clinical</b>	With empiric warfarin dosing, individuals with <i>CYP2C9</i> *2 and <i>CYP2C9</i> *3 are at increased risk of bleeding.	<p><b>Supports statement:</b></p> <p>Ogg, <i>et al.</i> (1999) (106)  Margaglione, <i>et al.</i> (2000) (51)  Higashi, <i>et al.</i> (2002) (80)  Sanderson, <i>et al.</i> (2005) (107)  Samardzija, <i>et al.</i> (2008) (53)  Meckley, <i>et al.</i> (2008) (87)  Caraco, <i>et al.</i> (2008) (88)  Lima, <i>et al.</i> (2008) (90)  Ngow, <i>et al.</i> (2008) (108)  Limdi, <i>et al.</i> (2008) (109)  Wadelius, <i>et al.</i> (2009) (84)  Ma, <i>et al.</i> (2012) (100)  Yang, <i>et al.</i> (2013) (101)  Gaikwad, <i>et al.</i> (2013) (102)  Tomek, <i>et al.</i> (2013) (110)  Ucar, <i>et al.</i> (2013) (111)  Kawai, <i>et al.</i> (2014)(103)  Valentin, <i>et al.</i> (2014) (105)  Mega, <i>et al.</i> (2015) (104)</p> <p><b>Does not support statement:</b></p> <p>Wadelius, <i>et al.</i> (2004) (112)  Limdi, <i>et al.</i> (2009) (76)  Esmerian, <i>et al.</i> (2011) (113)  Lund, <i>et al.</i> (2012) (85)  An, <i>et al.</i> (2014) (114)  Roth, <i>et al.</i> (2014) (115)</p>	High
<b>Clinical</b>	<i>CYP2C9</i> *1/*14 and *1/*13 are associated with decreased warfarin dose in Korean patients	<p>Kim, <i>et al.</i> (2009) (89)  Lee, <i>et al.</i> (2014) (116)</p>	Moderate

<b>Clinical</b>	<i>CYP2C9</i> rs7089580 variant is associated with higher warfarin dose in African Americans. It is also associated with higher S-warfarin clearance and <i>CYP2C9</i> expression.	Perera, <i>et al.</i> (2011) (117) Hernandez, <i>et al.</i> (2015) (118)	High
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\*Rating scheme described in the Supplemental Material



**SUPPLEMENTAL TABLE S2. EVIDENCE LINKING *VKORC1* TO WARFARIN PHENOTYPE**

Type of experimental model	Major findings	References	Level of evidence*
<b>In vitro</b>	<i>VKORC1-1639G&gt;A</i> variant is associated with <i>VKORC1</i> expression.	Rieder, <i>et al.</i> (2005) (119) Yuan, <i>et al.</i> (2005) (120)	High
<b>Clinical</b>	VKORC1 is the protein target for warfarin.	Li, <i>et al.</i> (2004) (121) Rost, <i>et al.</i> (2004) (7)	High
<b>Clinical</b>	<i>VKORC1-1639G&gt;A</i> variant (and SNPs in high linkage disequilibrium with it) is associated with reduced warfarin maintenance dose.	Wadelius, <i>et al.</i> (2005) (27) Rieder, <i>et al.</i> (2005) (119) Yuan, <i>et al.</i> (2005) (120) Schelleman, <i>et al.</i> (2007) (122) Cooper, <i>et al.</i> (2008) (123) Takeuchi, <i>et al.</i> (2009) (54) Klein, <i>et al.</i> (2009) (12) Limdi, <i>et al.</i> (2010) (124) Pautas, <i>et al.</i> (2010) (28) Suriapranata, <i>et al.</i> (2011) (125) Liang, <i>et al.</i> (2012) (57) El Din, <i>et al.</i> (2012) (58) Lee, <i>et al.</i> (2012) (59) Valentin, <i>et al.</i> (2012) (56) Pathare, <i>et al.</i> (2012) (60) Santos, <i>et al.</i> (2013) (62) Ozer, <i>et al.</i> (2013) (63) Limdi, <i>et al.</i> (2015) (64)	High
<b>Clinical</b>	With empiric warfarin dosing, individuals with <i>VKORC1-1639G&gt;A</i> are likely to require shorter time to	Schelleman, <i>et al.</i> (2007) (122) Meckley, <i>et al.</i> (2008) (87)	High

	achieve first INR in therapeutic range, but have no difference in time to stable dose.	<p>Limdi, <i>et al.</i> (2008) (81)  Schwarz, <i>et al.</i> (2008) (82)  Jorgensen, <i>et al.</i> (2009) (75)  Kim, <i>et al.</i> (2009) (89)  Limdi, <i>et al.</i> (2009) (76)  Li, <i>et al.</i> (2009) (83)  Wadelius, <i>et al.</i> (2009) (84)  Ozer, <i>et al.</i> (2010) (78)  McMillin, <i>et al.</i> (2010) (77)  Pautas, <i>et al.</i> (2010) (28)  Cavallari, <i>et al.</i> (2011) (55)  Zhong, <i>et al.</i> (2011) (79)  Lund, <i>et al.</i> (2012) (85)  Biss, <i>et al.</i> (2012) (86)  Finkelman, <i>et al.</i> (2015) (91)</p>	
<b>Clinical</b>	With empiric warfarin dosing, individuals with <i>VKORC1-1639G&gt;A</i> have less time in INR therapeutic range (TTR) early in the course of therapy.	<p><b>Supports statement:</b>  Wadelius, <i>et al.</i> (2009) (84)  Giansante, <i>et al.</i> (2012) (126)  Skov, <i>et al.</i> (2013) (92)</p> <p><b>Does not support statement:</b>  Meckley, <i>et al.</i> (2008) (87)  Moreau, <i>et al.</i> (2012) (93)</p>	Moderate
<b>Clinical</b>	With empiric warfarin dosing, <i>VKORC1-1639G&gt;A</i> is associated with increased risk of over-anticoagulation (INR>4) in Caucasians and Asians but not in African Americans.	<p><b>Supports statement:</b>  Anderson, <i>et al.</i> (2007) (97)  Schelleman, <i>et al.</i> (2007) (122)  Meckley, <i>et al.</i> (2008) (87)  Limdi, <i>et al.</i> (2008) (81)  Schwarz, <i>et al.</i> (2008) (82)  Kim, <i>et al.</i> (2009) (89)  Limdi, <i>et al.</i> (2009) (76)  Wadelius, <i>et al.</i> (2009) (84)  Molden, <i>et al.</i> (2010) (98)</p>	High

		<p>Pautas, <i>et al.</i> (2010) (28)  Moon, <i>et al.</i> (2011) (99)  Lund, <i>et al.</i> (2012) (85)  Biss, <i>et al.</i> (2012) (86)  Yang, <i>et al.</i> (2013) (101)  Gaikwad, <i>et al.</i> (2013) (102)</p>	
		<p><b>Does not support statement:</b>  Ma, <i>et al.</i> (2012) (100)</p>	
<b>Clinical</b>	With empiric warfarin dosing and INR monitoring, individuals with <i>VKORC1-1639G&gt;A</i> are NOT at increased risk for major or minor bleeding event.	<p><b>Supports statement:</b>  Meckley, <i>et al.</i> (2008) (87)  Limdi, <i>et al.</i> (2008) (109)  Limdi, <i>et al.</i> (2009) (76)  Wadelius, <i>et al.</i> (2009) (84)  Esmerian, <i>et al.</i> (2011) (113)  Giansante, <i>et al.</i> (2012) (126)  Ma, <i>et al.</i> (2012) (100)  Yang, <i>et al.</i> (2013) (101)  Kawai, <i>et al.</i> (2014) (103)  An, <i>et al.</i> (2014) (114)  Roth, <i>et al.</i> (2014) (115)</p>	Moderate
		<p><b>Does not support statement:</b>  Lund, <i>et al.</i> (2012) (85)  Gaikwad, <i>et al.</i> (2013) (102)  Tomek, <i>et al.</i> (2013) (110)  Valentin, <i>et al.</i> (2014) (105)</p>	
<b>Clinical</b>	Multiple rare nonsynonymous SNPs in <i>VKORC1</i> (V29L (rs104894539), D36Y (rs61742245), V45A (rs104894540), R58G (rs104894541), V66M (rs72547529), R98W (rs72547528), L128R (rs104894542)) confer warfarin resistance.	<p>Rost, <i>et al.</i> (2004) (7)  Harrington, <i>et al.</i> (2005) (127)  Bodin, <i>et al.</i> (2005) (128)  Harrington, <i>et al.</i> (2008) (129)  Scott, <i>et al.</i> (2008) (130)  Shahin, <i>et al.</i> (2011) (22)</p>	High

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Kurnik, *et al.* (2012) (131)

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\*Rating scheme described in the Supplemental Material

**SUPPLEMENTAL TABLE S3. EVIDENCE LINKING CYP4F2 TO WARFARIN PHENOTYPE**

<b>Type of experimental model</b>	<b>Major findings</b>	<b>References</b>	<b>Level of evidence</b>
<b>Clinical</b>	<i>CYP4F2</i> (rs2108622, V433M) variant allele is associated with a modest effect leading to higher warfarin dose in Europeans and Asians.	Stec, <i>et al.</i> (2007) (132) Caldwell, <i>et al.</i> (2008) (133) McDonald, <i>et al.</i> (2009) (134) Takeuchi, <i>et al.</i> (2009) (54) Singh, <i>et al.</i> (2010) (135) Cen, <i>et al.</i> (2010) (136) Sagreiya, <i>et al.</i> (2010) (137) Wells, <i>et al.</i> (2010) (138) Perini, <i>et al.</i> (2010) (139) Lubitz, <i>et al.</i> (2010) (140) Cavallari, <i>et al.</i> (2010) (69) Pautas, <i>et al.</i> (2010) (28) Shahin, <i>et al.</i> (2011) (22) Kringen, <i>et al.</i> (2011) (141) Liang, <i>et al.</i> (2012) (57) Lee, <i>et al.</i> (2012) (59) Pathare, <i>et al.</i> (2012) (60) Bress, <i>et al.</i> (2012) (142) Nakamura, <i>et al.</i> (2012) (143) Liang, <i>et al.</i> (2012) (144) Rusdiana, <i>et al.</i> (2013) (145) Roth, <i>et al.</i> (2014) (115) Wypasek, <i>et al.</i> (2014) (146) Shendre, <i>et al.</i> (2016) (147)	Moderate

**SUPPLEMENTAL TABLE S4. EVIDENCE COMPARING PHARMACOGENETICS WARFARIN DOSING ALGORITHMS TO STANDARD OF CARE DOSING<sup>a</sup> OR CLINICAL ALGORITHMS**

Type of experimental model	Major findings	Reference	Level of evidence <sup>b</sup>
<b>Pharmacogenetics dosing algorithm vs standard of care dosing<sup>a</sup></b>			
<b>Clinical</b>	More accurate prediction of dose	Anderson, <i>et al.</i> (2007) (148) IWPC, <i>et al.</i> (2009) (149)	High
<b>Clinical</b>	Shorter time to stable dose with pharmacogenetics algorithm	Huang, <i>et al.</i> (2009) (150) Borgman, <i>et al.</i> (2012) (151) Wang, <i>et al.</i> (2012) (152) Pirmohamed, <i>et al.</i> (2013) (14)	High
<b>Clinical</b>	Improved percent of time in therapeutic range (TTR) with pharmacogenetics algorithm	Huang <i>et al.</i> (2009) (150) Borgman, <i>et al.</i> (2012) (151) Anderson, <i>et al.</i> (2012) (153) Pirmohamed, <i>et al.</i> (2013) (14)	High
<b>Clinical</b>	Reduced number of times with INR >4 with pharmacogenetics algorithm	Anderson, <i>et al.</i> (2007) (148) Anderson, <i>et al.</i> (2012) (153) Pirmohamed, <i>et al.</i> (2013) (14)	High
		<b>Does not support statement:</b> Anderson, <i>et al.</i> (2007) (148) McMillin, <i>et al.</i> (2010) (77) Borgman, <i>et al.</i> (2012) (151)	
<b>Clinical</b>	Reduced number of times with INR <1.5 with pharmacogenetics algorithm	Anderson, <i>et al.</i> (2012) (153)	Moderate

<b>Clinical</b>	Dosing with a pharmacogenetics algorithm does not reduce bleeding risk	McMillin, <i>et al.</i> (2010) (77) Pirmohamed, <i>et al.</i> (2013) (14)	Weak
		<b>Does not support statement:</b> Anderson, <i>et al.</i> (2012) (153)	
<b>Pharmacogenetics dosing algorithm including <i>CYP2C9</i>*2, *3 and <i>VKORC1</i> vs clinical algorithm</b>			
<b>Clinical</b>	More accurate dose prediction in non-blacks	Lenzini, <i>et al.</i> (2008) (154) IWPC, <i>et al.</i> (2009) (149) Burmester, <i>et al.</i> (2011) (155) Kimmel, <i>et al.</i> (2013) (156)	High
<b>Clinical</b>	Does not more accurately predict dose in blacks	Kimmel, <i>et al.</i> (2013) (156)	High
<b>Clinical</b>	Does not improve time to stable dose	Burmester, <i>et al.</i> (2011) (155) Kimmel, <i>et al.</i> (2013) (156) Jonas, <i>et al.</i> (2013) (157)	High
<b>Clinical</b>	Does not improve percent of time in therapeutic range (TTR)	Burmester, <i>et al.</i> (2011) (155) Jonas, <i>et al.</i> (2013) (157) Kimmel, <i>et al.</i> (2013) (156)	High
		<b>Does not support statement:</b> Lenzini, <i>et al.</i> (2008) (154)	
<b>Clinical</b>	Does not reduce number of times with INR >4	Burmester, <i>et al.</i> (2011) (155) Kimmel, <i>et al.</i> (2013) (156) Jonas, <i>et al.</i> (2013) (157)	High
<b>Clinical</b>	Does not reduce percentage of time below therapeutic range (INR<2)	Kimmel, <i>et al.</i> (2013) (156)	High
<b>Clinical</b>	Does not decrease bleeding risk	Lenzini, <i>et al.</i> (2008) (154) Kimmel, <i>et al.</i> (2013) (156) Jonas, <i>et al.</i> (2013) (157)	Weak

<sup>a</sup>**Standard of care:** Standard of care for warfarin dosing is not same in all studies but is the standard of care relative to protocols incorporating genetic factors and/or clinical factors into the dosing consideration. It is usually a fixed initial dose (with or without a loading regimen), followed by dose modification according to results of the International Normalized Ratio (INR) or prothrombin time (PT) until a stable warfarin maintenance dose is achieved.

<sup>b</sup>Rating scheme described in the Supplemental Material

Note: Clinical utility studies not including *VKORC1* variant information are excluded from the analysis (Hillman 2005, Caraco 2008).



**SUPPLEMENTAL TABLE S5. PRIMARY PHARMACOGENETICS WARFARIN DOSING ALGORITHMS USED IN PROSPECTIVE CLINICAL TRIALS**

<b>Algorithm (ref)</b>	<b>Prospective clinical trial utilizing algorithm (ref)</b>	<b>Notes</b>
IWPC (12)	COUMAGEN-II (153)	Modified version to accommodate different INR targets and smoking status
	EU-PACT (14)	Modified version used to calculate maintenance dose
Gage, <i>et al.</i> (13)	COAG (156)	Used for first 3 days of warfarin therapy
	GIFT	Not yet reported
Avery, <i>et al.</i> (158)	EU-PACT (14)	Modified version to account for <i>CYP2C9</i> allelic variants on the pharmacokinetics of warfarin was used to calculate loading dose for days of 1-3 therapy
Lenzini, <i>et al.</i> (15)	COAG (156)	Used to determine dose revision on day 4, 5, or both of therapy
	EU-PACT (14)	Modified version (by removing diabetes, African origin, stroke, and fluvastatin use) used to determine dose revision on days of 4-5 therapy based on the INR value on day 4.

**SUPPLEMENTAL TABLE S6. ADDITIONAL FINDINGS WITH WEAK/MODERATE EVIDENCE LINKING OTHER GENES/VARIANTS TO WARFARIN PHENOTYPE (NOT PART OF RECOMMENDATION)**

<b>Type of experimental model</b>	<b>Major findings</b>	<b>References</b>
<b>In vitro</b>	<i>CYP2C9</i> *12 allele is associated decreased enzyme activity.	O'Brien, <i>et al.</i> (2013) (159)
<b>Clinical</b>	<i>CYP2C9</i> *1/*57 is associated with hyper sensitivity to coumarin anticoagulants with multiple bleeding episodes and supra-elevated INRs.	Nahar, <i>et al.</i> (2013) (160)
<b>Clinical</b>	<i>CYP2C9</i> rs17847036 GG genotype is associated with low dosage requirements in Indonesians	Suriapranata, <i>et al.</i> (2011) (125)
<b>Clinical</b>	<i>VKORC1-8191</i> (rs61162043) variant is associated with higher warfarin dose in African Americans.	Perera, <i>et al.</i> (2011) (117)
<b>Clinical</b>	The <i>VKORC1</i> rs17886199 A-allele is associated with lower warfarin dose in African Americans, independent of the <i>VKORC1 1173C&gt;T</i> and <i>CYP2C9</i> *2 and *3 variants.	Schelleman, <i>et al.</i> (2010) (161)
<b>Clinical</b>	<i>CYP4F2</i> rs2189784 (but not rs2108622) is associated with time-to-therapeutic INR.	Zhang, <i>et al.</i> (2009) (162)
<b>Clinical</b>	Variant rs339097 in <i>CALU</i> predicts higher warfarin dose in African Americans populations.	Voora, <i>et al.</i> (2010) (21) Shahin, <i>et al.</i> (2011) (22)

<b>Clinical</b>	Variant rs1043550 in <i>CALU</i> does not predict higher warfarin dose in Caucasians.	Glurich, <i>et al.</i> (2013) (163)
<b>Clinical</b>	rs11676382 in <i>GGCX</i> was shown to be a significant with a reduction in warfarin dose.	Rieder, <i>et al.</i> (2007) (26) King, <i>et al.</i> (2010) (11) Wypasek, <i>et al.</i> (2014) (146) Sun, <i>et al.</i> (2015) (164)
<b>Clinical</b>	rs12714145/rs7568458 in <i>GGCX</i> are not associated with warfarin dose.	<b>Supports statement:</b> Cha, <i>et al.</i> (2007) (29) Wadelius, <i>et al.</i> (2007) (20) Wadelius, <i>et al.</i> (2009) (84) Pautas, <i>et al.</i> (2010) (28) King, <i>et al.</i> (2010) (11)  <b>Does not support statement:</b> Huang, <i>et al.</i> (2011) (165)
<b>Clinical</b>	Chinese patients carrying the <i>CYP2C19</i> rs3814637CC or <i>GGCX</i> rs699664AA genotype need higher warfarin doses.	Liang, <i>et al.</i> (2013) (61)
<b>Clinical</b>	Apolipoprotein E genotype is associated with duration of time to reach a stable warfarin dose in African-American patients.	Shahin, <i>et al.</i> (2011) (22) Cavallari, <i>et al.</i> (2011) (166)
<b>Clinical</b>	<i>NQO1</i> *2 (rs1800566) and <i>CYP4F2</i> V433M alleles are associated with higher therapeutic warfarin dose requirements in Hispanic-Americans, but not African-Americans.	Bress, <i>et al.</i> (2012) (142)
<b>Clinical</b>	<i>GATA4</i> regulates <i>CYP2C9</i> expression. <i>GATA4</i> SNPs (rs2645400 and rs4841588) are predictive of stable warfarin dose.	Jeong, <i>et al.</i> (2015) (167)

**SUPPLEMENTAL TABLE S7. EVIDENCE LINKING *CYP2C9*, *VKORC1*, AND *CYP4F2* TO WARFARIN PHENOTYPE IN PEDIATRIC PATIENTS**

Type of experimental model	Major findings	References	Level of evidence*
Clinical	Children with <i>CYP2C9</i> *2 and <i>CYP2C9</i> *3 have reduced warfarin maintenance dose.	<p><b>Supports statement:</b>  Nowak-Gottl, <i>et al.</i> (2010) (168)  Biss, <i>et al.</i> (2012) (86)  Moreau, <i>et al.</i> (2012) (93)  Shaw, <i>et al.</i> (2014) (169)  Hamberg, <i>et al.</i> (2014) (170)  Hawcutt, <i>et al.</i> (2014) (171)  Dilge Taskin, <i>et al.</i> (2016) (172)</p> <p><b>Does not support statement:</b>  Nguyen, <i>et al.</i> (2013) (173)  Kamal El-Din, <i>et al.</i> (2014) (174)</p>	High
Clinical	With empiric warfarin dosing, children with <i>CYP2C9</i> *2 and <i>CYP2C9</i> *3 are at increased risk of over-anticoagulation.	Biss, <i>et al.</i> (2013) (175) Shaw, <i>et al.</i> (2014) (169) Hawcutt, <i>et al.</i> (2014) (171)	Moderate
Clinical	With empiric warfarin dosing, children with <i>CYP2C9</i> *3 are at increased risk of bleeding.	Shaw, <i>et al.</i> (2014) (169)	Moderate
Clinical	<i>VKORC1</i> -1639G>A variant (and SNPs in high linkage disequilibrium with it) is associated with reduced warfarin maintenance dose in children.	<p><b>Supports statement:</b>  Nowak-Gottl, <i>et al.</i> (2010) (168)  Kato, <i>et al.</i> (2011) (176)  Biss, <i>et al.</i> (2012) (86)  Moreau, <i>et al.</i> (2012) (93)  Nguyen, <i>et al.</i> (2013) (173)  Hawcutt, <i>et al.</i> (2014) (171)  Shaw, <i>et al.</i> (2014) (169)</p>	High

		Hamberg, <i>et al.</i> (2014) (170) Wakamiya, <i>et al.</i> (2016) (177) Dilge Taskin, <i>et al.</i> (2016) (172)	
		<b>Does not support statement:</b> Hirai, <i>et al.</i> (2013) (178) Kamal El-Din, <i>et al.</i> (2014) (174) Shaw, <i>et al.</i> (2014) (169)	
Clinical	With empiric warfarin dosing, children with <i>VKORC1-1639G&gt;A</i> are likely to require shorter time to achieve first INR in therapeutic range.		Moderate
Clinical	With empiric warfarin dosing, children with <i>VKORC1-1639G&gt;A</i> have more time in INR therapeutic range (TTR).	Hawcutt, <i>et al.</i> (2014) (171)	Weak
Clinical	With empiric warfarin dosing, <i>VKORC1-1639G&gt;A</i> is associated with increased risk of over-anticoagulation (INR > 4 or INR exceeding target range) in children.	Biss, <i>et al.</i> (2013) (175) Shaw, <i>et al.</i> (2014) (169) Hawcutt, <i>et al.</i> (2014) (171) (p=0.02, but not statistically significant after FDR adjustment)	High
Clinical	<i>CYP4F2</i> (rs2108622, V433M) variant allele is associated with a modest effect leading to higher warfarin dose in children.	<b>Supports statement:</b> Hirai, <i>et al.</i> (2013) (178)  <b>Does not support statement:</b> Biss, <i>et al.</i> (2012) (86) Hamberg, <i>et al.</i> (2014) (170) Wakamiya, <i>et al.</i> (2016) (177)	Weak

\*Rating scheme described in the Supplemental Material

## REFERENCES

- (1) Genomes Project, C. *et al.* A global reference for human genetic variation. *Nature* **526**, 68-74 (2015).
- (2) Choonara, I.A., Haynes, B.P., Cholerton, S., Breckenridge, A.M. & Park, B.K. Enantiomers of warfarin and vitamin K1 metabolism. *British journal of clinical pharmacology* **22**, 729-32 (1986).
- (3) Rettie, A.E. *et al.* Hydroxylation of warfarin by human cDNA-expressed cytochrome P-450: a role for P-4502C9 in the etiology of (S)-warfarin-drug interactions. *Chem Res Toxicol* **5**, 54-9 (1992).
- (4) Zhang, Z., Fasco, M.J., Huang, Z., Guengerich, F.P. & Kaminsky, L.S. Human cytochromes P4501A1 and P4501A2: R-warfarin metabolism as a probe. *Drug Metab Dispos* **23**, 1339-46 (1995).
- (5) Wienkers, L.C., Wurden, C.J., Storch, E., Kunze, K.L., Rettie, A.E. & Trager, W.F. Formation of (R)-8-hydroxywarfarin in human liver microsomes. A new metabolic marker for the (S)-mephenytoin hydroxylase, P4502C19. *Drug Metab Dispos* **24**, 610-4 (1996).
- (6) Ngui, J.S. *et al.* In vitro stimulation of warfarin metabolism by quinidine: increases in the formation of 4'- and 10-hydroxywarfarin. *Drug Metab Dispos* **29**, 877-86 (2001).
- (7) Rost, S. *et al.* Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. *Nature* **427**, 537-41 (2004).
- (8) Wadelius, M. & Pirmohamed, M. Pharmacogenetics of warfarin: current status and future challenges. *The pharmacogenomics journal* **7**, 99-111 (2007).
- (9) Stehle, S., Kirchheiner, J., Lazar, A. & Fuhr, U. Pharmacogenetics of oral anticoagulants: a basis for dose individualization. *Clinical pharmacokinetics* **47**, 565-94 (2008).
- (10) Limdi, N.A. & Veenstra, D.L. Warfarin pharmacogenetics. *Pharmacotherapy* **28**, 1084-97 (2008).
- (11) King, C.R. *et al.* Gamma-glutamyl carboxylase and its influence on warfarin dose. *Thrombosis and haemostasis* **104**, 750-4 (2010).
- (12) Klein, T.E. *et al.* Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* **360**, 753-64 (2009).
- (13) Gage, B.F. *et al.* Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. *Clin Pharmacol Ther* **84**, 326-31 (2008).
- (14) Pirmohamed, M. *et al.* A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med* **369**, 2294-303 (2013).
- (15) Lenzini, P. *et al.* Integration of genetic, clinical, and INR data to refine warfarin dosing. *Clin Pharmacol Ther* **87**, 572-8 (2010).
- (16) Waterman, A.D., Milligan, P.E., Bayer, L., Banet, G.A., Gatchel, S.K. & Gage, B.F. Effect of warfarin nonadherence on control of the International Normalized Ratio. *Am J Health Syst Pharm* **61**, 1258-64 (2004).
- (17) Platt, A.B. *et al.* Can we predict daily adherence to warfarin?: Results from the International Normalized Ratio Adherence and Genetics (IN-RANGE) Study. *Chest* **137**, 883-9 (2010).
- (18) Wajih, N., Sane, D.C., Hutson, S.M. & Wallin, R. The inhibitory effect of calumenin on the vitamin K-dependent gamma-carboxylation system. Characterization of the system in normal and warfarin-resistant rats. *The Journal of biological chemistry* **279**, 25276-83 (2004).

- (19) Vecsler, M. *et al.* Combined genetic profiles of components and regulators of the vitamin K-dependent gamma-carboxylation system affect individual sensitivity to warfarin. *Thrombosis and haemostasis* **95**, 205-11 (2006).
- (20) Wadelius, M. *et al.* Association of warfarin dose with genes involved in its action and metabolism. *Human genetics* **121**, 23-34 (2007).
- (21) Voora, D. *et al.* A polymorphism in the VKORC1 regulator calumenin predicts higher warfarin dose requirements in African Americans. *Clin Pharmacol Ther* **87**, 445-51 (2010).
- (22) Shahin, M.H. *et al.* Genetic and nongenetic factors associated with warfarin dose requirements in Egyptian patients. *Pharmacogenet Genomics* **21**, 130-5 (2011).
- (23) Stafford, D.W. The vitamin K cycle. *J Thromb Haemost* **3**, 1873-8 (2005).
- (24) Weston, B.W. & Monahan, P.E. Familial deficiency of vitamin K-dependent clotting factors. *Haemophilia* **14**, 1209-13 (2008).
- (25) Vanakker, O.M. *et al.* Pseudoxanthoma elasticum-like phenotype with cutis laxa and multiple coagulation factor deficiency represents a separate genetic entity. *J Invest Dermatol* **127**, 581-7 (2007).
- (26) Rieder, M.J., Reiner, A.P. & Rettie, A.E. Gamma-glutamyl carboxylase (GGCX) tagSNPs have limited utility for predicting warfarin maintenance dose. *J Thromb Haemost* **5**, 2227-34 (2007).
- (27) Wadelius, M. *et al.* Common VKORC1 and GGCX polymorphisms associated with warfarin dose. *Pharmacogenomics J* **5**, 262-70 (2005).
- (28) Pautas, E. *et al.* Genetic factors (VKORC1, CYP2C9, EPHX1, and CYP4F2) are predictor variables for warfarin response in very elderly, frail inpatients. *Clin Pharmacol Ther* **87**, 57-64 (2010).
- (29) Cha, P.C. *et al.* High-resolution SNP and haplotype maps of the human gamma-glutamyl carboxylase gene (GGCX) and association study between polymorphisms in GGCX and the warfarin maintenance dose requirement of the Japanese population. *J Hum Genet* **52**, 856-64 (2007).
- (30) Daneshjou, R. *et al.* Genetic variant in folate homeostasis is associated with lower warfarin dose in African Americans. *Blood* **124**, 2298-305 (2014).
- (31) Hamadeh, I.S. *et al.* Impact of GGCX, STX1B and FPGS Polymorphisms on Warfarin Dose Requirements in European-Americans and Egyptians. *Clin Transl Sci* **9**, 36-42 (2016).
- (32) Connolly, S.J. *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *The New England journal of medicine* **361**, 1139-51 (2009).
- (33) Granger, C.B. *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* **365**, 981-92 (2011).
- (34) Connolly, S.J. *et al.* Apixaban in patients with atrial fibrillation. *N Engl J Med* **364**, 806-17 (2011).
- (35) Giugliano, R.P. *et al.* Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* **369**, 2093-104 (2013).
- (36) Patel, M.R. *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* **365**, 883-91 (2011).
- (37) Pare, G. *et al.* Genetic determinants of dabigatran plasma levels and their relation to bleeding. *Circulation* **127**, 1404-12 (2013).



- (38) Authors/Task Force, M. *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC Endorsed by the European Stroke Organisation (ESO). *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*, (2016).
- (39) Di Biase, L. Use of Direct Oral Anticoagulants in Patients With Atrial Fibrillation and Valvular Heart Lesions. *J Am Heart Assoc* **5**, (2016).
- (40) Valdes, R., Payne, D.A. & Linder, M.W. Laboratory analysis and application of pharmacogenetics to clinical practice. In: *The National Academy of Clinical Biochemistry (NACB) - Laboratory Medicine Practice Guidelines* (Washington, DC, 2010).
- (41) Adolescents, P.o.A.G.f.A.a. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 1-166 (2011).
- (42) Rettie, A.E., Wienkers, L.C., Gonzalez, F.J., Trager, W.F. & Korzekwa, K.R. Impaired (S)-warfarin metabolism catalysed by the R144C allelic variant of CYP2C9. *Pharmacogenetics* **4**, 39-42 (1994).
- (43) Yamazaki, H., Inoue, K. & Shimada, T. Roles of two allelic variants (Arg144Cys and Ile359Leu) of cytochrome P4502C9 in the oxidation of tolbutamide and warfarin by human liver microsomes. *Xenobiotica* **28**, 103-15 (1998).
- (44) Tang, C. *et al.* In-vitro metabolism of celecoxib, a cyclooxygenase-2 inhibitor, by allelic variant forms of human liver microsomal cytochrome P450 2C9: correlation with CYP2C9 genotype and in-vivo pharmacokinetics. *Pharmacogenetics* **11**, 223-35 (2001).
- (45) Lee, C.R., Goldstein, J.A. & Pieper, J.A. Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. *Pharmacogenetics* **12**, 251-63 (2002).
- (46) Ho, P.C., Abbott, F.S., Zanger, U.M. & Chang, T.K. Influence of CYP2C9 genotypes on the formation of a hepatotoxic metabolite of valproic acid in human liver microsomes. *Pharmacogenomics J* **3**, 335-42 (2003).
- (47) Kirchheiner, J. & Brockmoller, J. Clinical consequences of cytochrome P450 2C9 polymorphisms. *Clin Pharmacol Ther* **77**, 1-16 (2005).
- (48) 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* **353**, 717-9 (1999).
- (49) Daly, A.K. & King, B.P. Contribution of CYP2C9 to variability in vitamin K antagonist metabolism. *Expert Opin Drug Metab Toxicol* **2**, 3-15 (2006).
- (50) Lindh, J.D., Holm, L., Andersson, M.L. & Rane, A. Influence of CYP2C9 genotype on warfarin dose requirements--a systematic review and meta-analysis. *Eur J Clin Pharmacol* **65**, 365-75 (2009).
- (51) Margaglione, M. *et al.* Genetic modulation of oral anticoagulation with warfarin. *Thrombosis and haemostasis* **84**, 775-8 (2000).
- (52) Taube, J., Halsall, D. & Baglin, T. Influence of cytochrome P-450 CYP2C9 polymorphisms on warfarin sensitivity and risk of over-anticoagulation in patients on long-term treatment. *Blood* **96**, 1816-9 (2000).



- (53) Samardzija, M. *et al.* Association of CYP2C9 gene polymorphism with bleeding as a complication of warfarin therapy. *Collegium antropologicum* **32**, 557-64 (2008).
- (54) Takeuchi, F. *et al.* A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose. *PLoS Genet* **5**, e1000433 (2009).
- (55) Cavallari, L.H., Momary, K.M., Patel, S.R., Shapiro, N.L., Nutescu, E. & Viana, M.A. Pharmacogenomics of warfarin dose requirements in Hispanics. *Blood cells, molecules & diseases* **46**, 147-50 (2011).
- (56) Valentin, II *et al.* Prediction of warfarin dose reductions in Puerto Rican patients, based on combinatorial CYP2C9 and VKORC1 genotypes. *The Annals of pharmacotherapy* **46**, 208-18 (2012).
- (57) Liang, R. *et al.* Impact of CYP2C9\*3, VKORC1-1639, CYP4F2rs2108622 genetic polymorphism and clinical factors on warfarin maintenance dose in Han-Chinese patients. *Journal of thrombosis and thrombolysis* **34**, 120-5 (2012).
- (58) El Din, M.S., Amin, D.G., Ragab, S.B., Ashour, E.E., Mohamed, M.H. & Mohamed, A.M. Frequency of VKORC1 (C1173T) and CYP2C9 genetic polymorphisms in Egyptians and their influence on warfarin maintenance dose: proposal for a new dosing regimen. *International journal of laboratory hematology* **34**, 517-24 (2012).
- (59) Lee, K.E. *et al.* Effects of CYP4F2 gene polymorphisms on warfarin clearance and sensitivity in Korean patients with mechanical cardiac valves. *Therapeutic drug monitoring* **34**, 275-82 (2012).
- (60) Pathare, A. *et al.* Warfarin pharmacogenetics: development of a dosing algorithm for Omani patients. *J Hum Genet* **57**, 665-9 (2012).
- (61) Liang, Y. *et al.* Association of genetic polymorphisms with warfarin dose requirements in Chinese patients. *Genetic testing and molecular biomarkers* **17**, 932-6 (2013).
- (62) Santos, P.C. *et al.* CYP2C9 and VKORC1 polymorphisms influence warfarin dose variability in patients on long-term anticoagulation. *Eur J Clin Pharmacol* **69**, 789-97 (2013).
- (63) Ozer, M. *et al.* Impact of genetic factors (CYP2C9, VKORC1 and CYP4F2) on warfarin dose requirement in the Turkish population. *Basic & clinical pharmacology & toxicology* **112**, 209-14 (2013).
- (64) Limdi, N.A. *et al.* Race influences warfarin dose changes associated with genetic factors. *Blood* **126**, 539-45 (2015).
- (65) Redman, A.R., Dickmann, L.J., Kidd, R.S., Goldstein, J.A., Ritchie, D.M. & Hon, Y.Y. CYP2C9 genetic polymorphisms and warfarin. *Clin Appl Thromb Hemost* **10**, 149-54 (2004).
- (66) Tai, G. *et al.* In-vitro and in-vivo effects of the CYP2C9\*11 polymorphism on warfarin metabolism and dose. *Pharmacogenet Genomics* **15**, 475-81 (2005).
- (67) Limdi, N., Goldstein, J., Blaisdell, J., Beasley, T., Rivers, C. & Acton, R. Influence of CYP2C9 Genotype on warfarin dose among African American and European Americans. *Per Med* **4**, 157-69 (2007).
- (68) Scott, S.A., Jaremko, M., Lubitz, S.A., Kornreich, R., Halperin, J.L. & Desnick, R.J. CYP2C9\*8 is prevalent among African-Americans: implications for pharmacogenetic dosing. *Pharmacogenomics* **10**, 1243-55 (2009).
- (69) Cavallari, L.H. *et al.* Genetic and clinical predictors of warfarin dose requirements in African Americans. *Clin Pharmacol Ther* **87**, 459-64 (2010).

- (70) Liu, Y. *et al.* Decreased warfarin clearance associated with the CYP2C9 R150H (\*8) polymorphism. *Clin Pharmacol Ther* **91**, 660-5 (2012).
- (71) Cavallari, L.H. *et al.* CYP2C9 promoter region single-nucleotide polymorphisms linked to the R150H polymorphism are functional suggesting their role in CYP2C9\*8-mediated effects. *Pharmacogenet Genomics* **23**, 228-31 (2013).
- (72) Perera, M.A. *et al.* Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study. *Lancet* **382**, 790-6 (2013).
- (73) Drozda, K. *et al.* Poor warfarin dose prediction with pharmacogenetic algorithms that exclude genotypes important for African Americans. *Pharmacogenet Genomics* **25**, 73-81 (2015).
- (74) Ruud, E., Holmstrom, H., Bergan, S. & Wesenberg, F. Oral anticoagulation with warfarin is significantly influenced by steroids and CYP2C9 polymorphisms in children with cancer. *Pediatric blood & cancer* **50**, 710-3 (2008).
- (75) Jorgensen, A.L. *et al.* Genetic and environmental factors determining clinical outcomes and cost of warfarin therapy: a prospective study. *Pharmacogenet Genomics* **19**, 800-12 (2009).
- (76) Limdi, N.A., Wiener, H., Goldstein, J.A., Acton, R.T. & Beasley, T.M. Influence of CYP2C9 and VKORC1 on warfarin response during initiation of therapy. *Blood cells, molecules & diseases* **43**, 119-28 (2009).
- (77) McMillin, G.A. *et al.* Gene-based warfarin dosing compared with standard of care practices in an orthopedic surgery population: a prospective, parallel cohort study. *Therapeutic drug monitoring* **32**, 338-45 (2010).
- (78) Ozer, N. *et al.* The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements in an adult Turkish population. *Heart and vessels* **25**, 155-62 (2010).
- (79) Zhong, S.L. *et al.* The influence of genetic polymorphisms and interacting drugs on initial response to warfarin in Chinese patients with heart valve replacement. *Eur J Clin Pharmacol* **67**, 581-90 (2011).
- (80) Higashi, M.K. *et al.* Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. *Jama* **287**, 1690-8 (2002).
- (81) Limdi, N.A. *et al.* Influence of CYP2C9 and VKORC1 on warfarin dose, anticoagulation attainment and maintenance among European-Americans and African-Americans. *Pharmacogenomics* **9**, 511-26 (2008).
- (82) Schwarz, U.I. *et al.* Genetic determinants of response to warfarin during initial anticoagulation. *N Engl J Med* **358**, 999-1008 (2008).
- (83) Li, C., Schwarz, U.I., Ritchie, M.D., Roden, D.M., Stein, C.M. & Kurnik, D. Relative contribution of CYP2C9 and VKORC1 genotypes and early INR response to the prediction of warfarin sensitivity during initiation of therapy. *Blood* **113**, 3925-30 (2009).
- (84) Wadelius, M. *et al.* The largest prospective warfarin-treated cohort supports genetic forecasting. *Blood* **113**, 784-92 (2009).
- (85) Lund, K., Gaffney, D., Spooner, R., Etherington, A.M., Tansey, P. & Tait, R.C. Polymorphisms in VKORC1 have more impact than CYP2C9 polymorphisms on early warfarin International Normalized Ratio control and bleeding rates. *British journal of haematology* **158**, 256-61 (2012).

- (86) Biss, T.T. *et al.* VKORC1 and CYP2C9 genotype and patient characteristics explain a large proportion of the variability in warfarin dose requirement among children. *Blood* **119**, 868-73 (2012).
- (87) Meckley, L.M., Wittkowsky, A.K., Rieder, M.J., Rettie, A.E. & Veenstra, D.L. An analysis of the relative effects of VKORC1 and CYP2C9 variants on anticoagulation related outcomes in warfarin-treated patients. *Thrombosis and haemostasis* **100**, 229-39 (2008).
- (88) Caraco, Y., Blotnick, S. & Muszkat, M. CYP2C9 genotype-guided warfarin prescribing enhances the efficacy and safety of anticoagulation: a prospective randomized controlled study. *Clin Pharmacol Ther* **83**, 460-70 (2008).
- (89) Kim, H.S. *et al.* Effect of CYP2C9 and VKORC1 genotypes on early-phase and steady-state warfarin dosing in Korean patients with mechanical heart valve replacement. *Pharmacogenet Genomics* **19**, 103-12 (2009).
- (90) Lima, M.V., Ribeiro, G.S., Mesquita, E.T., Victor, P.R. & Vianna-Jorge, R. CYP2C9 genotypes and the quality of anticoagulation control with warfarin therapy among Brazilian patients. *Eur J Clin Pharmacol* **64**, 9-15 (2008).
- (91) Finkelman, B.S., French, B., Bershaw, L. & Kimmel, S.E. Factors affecting time to maintenance dose in patients initiating warfarin. *Pharmacoepidemiology and drug safety* **24**, 228-36 (2015).
- (92) Skov, J., Bladbjerg, E.M., Leppin, A. & Jespersen, J. The influence of VKORC1 and CYP2C9 gene sequence variants on the stability of maintenance phase warfarin treatment. *Thromb Res* **131**, 125-9 (2013).
- (93) Moreau, C. *et al.* Vitamin K antagonists in children with heart disease: height and VKORC1 genotype are the main determinants of the warfarin dose requirement. *Blood* **119**, 861-7 (2012).
- (94) Peyvandi, F., Spreafico, M., Siboni, S.M., Moia, M. & Mannucci, P.M. CYP2C9 genotypes and dose requirements during the induction phase of oral anticoagulant therapy. *Clin Pharmacol Ther* **75**, 198-203 (2004).
- (95) Voora, D. *et al.* Prospective dosing of warfarin based on cytochrome P-450 2C9 genotype. *Thrombosis and haemostasis* **93**, 700-5 (2005).
- (96) Kealey, C. *et al.* Warfarin and cytochrome P450 2C9 genotype: possible ethnic variation in warfarin sensitivity. *Pharmacogenomics* **8**, 217-25 (2007).
- (97) Anderson, J.L. *et al.* Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. *Circulation* **116**, 2563-70 (2007).
- (98) Molden, E., Okkenhaug, C. & Ekker Solberg, E. Increased frequency of CYP2C9 variant alleles and homozygous VKORC1\*2B carriers in warfarin-treated patients with excessive INR response. *Eur J Clin Pharmacol* **66**, 525-30 (2010).
- (99) Moon, H.W. *et al.* The effect of CYP2C9, VKORC1 genotypes and old age on warfarin pharmacologic sensitivity in Korean patients with thromboembolic disease. *Annals of clinical and laboratory science* **41**, 229-35 (2011).
- (100) Ma, C. *et al.* Influence of warfarin dose-associated genotypes on the risk of hemorrhagic complications in Chinese patients on warfarin. *International journal of hematology* **96**, 719-28 (2012).
- (101) Yang, J. *et al.* Influence of CYP2C9 and VKORC1 genotypes on the risk of hemorrhagic complications in warfarin-treated patients: a systematic review and meta-analysis. *International journal of cardiology* **168**, 4234-43 (2013).

- (102) Gaikwad, T., Ghosh, K., Kulkarni, B., Kulkarni, V., Ross, C. & Shetty, S. Influence of CYP2C9 and VKORC1 gene polymorphisms on warfarin dosage, over anticoagulation and other adverse outcomes in Indian population. *European journal of pharmacology* **710**, 80-4 (2013).
- (103) Kawai, V.K. *et al.* Genotype and risk of major bleeding during warfarin treatment. *Pharmacogenomics* **15**, 1973-83 (2014).
- (104) Mega, J.L. *et al.* Genetics and the clinical response to warfarin and edoxaban: findings from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet* **385**, 2280-7 (2015).
- (105) Valentin, II *et al.* Pharmacogenetic association study of warfarin safety endpoints in Puerto Ricans. *Puerto Rico health sciences journal* **33**, 97-104 (2014).
- (106) Ogg, M.S., Brennan, P., Meade, T. & Humphries, S.E. CYP2C9\*3 allelic variant and bleeding complications. *Lancet* **354**, 1124 (1999).
- (107) Sanderson, S., Emery, J. & Higgins, J. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGENet systematic review and meta-analysis. *Genetics in medicine : official journal of the American College of Medical Genetics* **7**, 97-104 (2005).
- (108) Ngow, H. *et al.* Role of pharmacodiagnostic of CYP2C9 variants in the optimization of warfarin therapy in Malaysia: a 6-month follow-up study. *Xenobiotica* **38**, 641-51 (2008).
- (109) Limdi, N.A. *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. *Clin Pharmacol Ther* **83**, 312-21 (2008).
- (110) Tomek, A. *et al.* The bleeding risk during warfarin therapy is associated with the number of variant alleles of CYP2C9 and VKORC1 genes. *Cardiology* **125**, 182-91 (2013).
- (111) Ucar, M., Alagozlu, H., Sahin, S. & Ozdemir, O. The relationship between CYP2C9 gene polymorphisms and upper gastrointestinal bleeding in patients who used warfarin. *Medicinski glasnik : official publication of the Medical Association of Zenica-Doboj Canton, Bosnia and Herzegovina* **10**, 50-4 (2013).
- (112) Wadelius, M. *et al.* Warfarin sensitivity related to CYP2C9, CYP3A5, ABCB1 (MDR1) and other factors. *Pharmacogenomics J* **4**, 40-8 (2004).
- (113) Esmerian, M.O. *et al.* Influence of CYP2C9 and VKORC1 polymorphisms on warfarin and acenocoumarol in a sample of Lebanese people. *Journal of clinical pharmacology* **51**, 1418-28 (2011).
- (114) An, S.H., Lee, K.E., Chang, B.C. & Gwak, H.S. Association of gene polymorphisms with the risk of warfarin bleeding complications at therapeutic INR in patients with mechanical cardiac valves. *Journal of clinical pharmacy and therapeutics* **39**, 314-8 (2014).
- (115) Roth, J.A. *et al.* Genetic risk factors for major bleeding in patients treated with warfarin in a community setting. *Clin Pharmacol Ther* **95**, 636-43 (2014).
- (116) Lee, Y.M., Eggen, J., Soni, V., Drozda, K., Nutescu, E.A. & Cavallari, L.H. Warfarin dose requirements in a patient with the CYP2C9\*14 allele. *Pharmacogenomics* **15**, 909-14 (2014).
- (117) Perera, M.A. *et al.* The missing association: sequencing-based discovery of novel SNPs in VKORC1 and CYP2C9 that affect warfarin dose in African Americans. *Clin Pharmacol Ther* **89**, 408-15 (2011).



- (118) Hernandez, W. *et al.* Novel single nucleotide polymorphism in CYP2C9 is associated with changes in warfarin clearance and CYP2C9 expression levels in African Americans. *Translational research : the journal of laboratory and clinical medicine* **165**, 651-7 (2015).
- (119) Rieder, M.J. *et al.* Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *N Engl J Med* **352**, 2285-93 (2005).
- (120) Yuan, H.Y. *et al.* A novel functional VKORC1 promoter polymorphism is associated with inter-individual and inter-ethnic differences in warfarin sensitivity. *Human molecular genetics* **14**, 1745-51 (2005).
- (121) Li, T., Chang, C.Y., Jin, D.Y., Lin, P.J., Khvorova, A. & Stafford, D.W. Identification of the gene for vitamin K epoxide reductase. *Nature* **427**, 541-4 (2004).
- (122) Schelleman, H. *et al.* Warfarin response and vitamin K epoxide reductase complex 1 in African Americans and Caucasians. *Clin Pharmacol Ther* **81**, 742-7 (2007).
- (123) Cooper, G.M. *et al.* A genome-wide scan for common genetic variants with a large influence on warfarin maintenance dose. *Blood* **112**, 1022-7 (2008).
- (124) Limdi, N.A. *et al.* Warfarin pharmacogenetics: a single VKORC1 polymorphism is predictive of dose across 3 racial groups. *Blood* **115**, 3827-34 (2010).
- (125) Suriapranata, I.M. *et al.* Genetic factors associated with patient-specific warfarin dose in ethnic Indonesians. *BMC medical genetics* **12**, 80 (2011).
- (126) Giansante, C. *et al.* Oral anticoagulation and VKORC1 polymorphism in patients with a mechanical heart prosthesis: a 6-year follow-up. *Journal of thrombosis and thrombolysis* **34**, 506-12 (2012).
- (127) Harrington, D.J., Underwood, S., Morse, C., Shearer, M.J., Tuddenham, E.G. & Mumford, A.D. Pharmacodynamic resistance to warfarin associated with a Val66Met substitution in vitamin K epoxide reductase complex subunit 1. *Thrombosis and haemostasis* **93**, 23-6 (2005).
- (128) Bodin, L., Horellou, M.H., Flaujac, C., Lorient, M.A. & Samama, M.M. A vitamin K epoxide reductase complex subunit-1 (VKORC1) mutation in a patient with vitamin K antagonist resistance. *J Thromb Haemost* **3**, 1533-5 (2005).
- (129) Harrington, D.J. *et al.* Pharmacodynamic resistance to warfarin is associated with nucleotide substitutions in VKORC1. *J Thromb Haemost* **6**, 1663-70 (2008).
- (130) Scott, S.A., Edelmann, L., Kornreich, R. & Desnick, R.J. Warfarin pharmacogenetics: CYP2C9 and VKORC1 genotypes predict different sensitivity and resistance frequencies in the Ashkenazi and Sephardi Jewish populations. *American journal of human genetics* **82**, 495-500 (2008).
- (131) Kurnik, D. *et al.* Effect of the VKORC1 D36Y variant on warfarin dose requirement and pharmacogenetic dose prediction. *Thrombosis and haemostasis* **108**, 781-8 (2012).
- (132) Stec, D.E., Roman, R.J., Flasch, A. & Rieder, M.J. Functional polymorphism in human CYP4F2 decreases 20-HETE production. *Physiol Genomics* **30**, 74-81 (2007).
- (133) Caldwell, M.D. *et al.* CYP4F2 genetic variant alters required warfarin dose. *Blood* **111**, 4106-12 (2008).
- (134) McDonald, M.G., Rieder, M.J., Nakano, M., Hsia, C.K. & Rettie, A.E. CYP4F2 is a vitamin K1 oxidase: An explanation for altered warfarin dose in carriers of the V433M variant. *Molecular pharmacology* **75**, 1337-46 (2009).

- (135) Singh, O., Sandanaraj, E., Subramanian, K., Lee, L.H. & Chowbay, B. The influence of CYP4F2 rs2108622 (V433M) on warfarin dose requirement in Asian patients. *Drug Metab Pharmacokinet*, (2010).
- (136) Cen, H.J. *et al.* CYP4F2 rs2108622: a minor significant genetic factor of warfarin dose in Han Chinese patients with mechanical heart valve replacement. *Br J Clin Pharmacol* **70**, 234-40 (2010).
- (137) Sagreiya, H. *et al.* Extending and evaluating a warfarin dosing algorithm that includes CYP4F2 and pooled rare variants of CYP2C9. *Pharmacogenet Genomics* **20**, 407-13 (2010).
- (138) Wells, P.S. *et al.* A regression model to predict warfarin dose from clinical variables and polymorphisms in CYP2C9, CYP4F2, and VKORC1: Derivation in a sample with predominantly a history of venous thromboembolism. *Thromb Res* **125**, e259-64 (2010).
- (139) Perini, J.A., Struchiner, C.J., Silva-Assuncao, E. & Suarez-Kurtz, G. Impact of CYP4F2 rs2108622 on the stable warfarin dose in an admixed patient cohort. *Clin Pharmacol Ther* **87**, 417-20 (2010).
- (140) Lubitz, S.A. *et al.* Comparative performance of gene-based warfarin dosing algorithms in a multiethnic population. *J Thromb Haemost* **8**, 1018-26 (2010).
- (141) Kringen, M.K. *et al.* Genetic variation of VKORC1 and CYP4F2 genes related to warfarin maintenance dose in patients with myocardial infarction. *J Biomed Biotechnol* **2011**, 739751 (2011).
- (142) Bress, A., Patel, S.R., Perera, M.A., Campbell, R.T., Kittles, R.A. & Cavallari, L.H. Effect of NQO1 and CYP4F2 genotypes on warfarin dose requirements in Hispanic-Americans and African-Americans. *Pharmacogenomics* **13**, 1925-35 (2012).
- (143) Nakamura, K. *et al.* CYP4F2 gene polymorphism as a contributor to warfarin maintenance dose in Japanese subjects. *Journal of clinical pharmacy and therapeutics* **37**, 481-5 (2012).
- (144) Liang, R., Wang, C., Zhao, H., Huang, J., Hu, D. & Sun, Y. Influence of CYP4F2 genotype on warfarin dose requirement—a systematic review and meta-analysis. *Thromb Res* **130**, 38-44 (2012).
- (145) Rusdiana, T., Araki, T., Nakamura, T., Subarnas, A. & Yamamoto, K. Responsiveness to low-dose warfarin associated with genetic variants of VKORC1, CYP2C9, CYP2C19, and CYP4F2 in an Indonesian population. *Eur J Clin Pharmacol* **69**, 395-405 (2013).
- (146) Wypasek, E., Branicka, A., Awsiuk, M., Sadowski, J. & Undas, A. Genetic determinants of acenocoumarol and warfarin maintenance dose requirements in Slavic population: a potential role of CYP4F2 and GGCX polymorphisms. *Thromb Res* **134**, 604-9 (2014).
- (147) Shendre, A. *et al.* Race-Specific Influence of CYP4F2 on Dose and Risk of Hemorrhage Among Warfarin Users. *Pharmacotherapy* **36**, 263-72 (2016).
- (148) Anderson, J.L. *et al.* Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. *Circulation* **116**, 2563-70 (2007).
- (149) International Warfarin Pharmacogenetics, C. *et al.* Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* **360**, 753-64 (2009).
- (150) Huang, S.W. *et al.* Validation of VKORC1 and CYP2C9 genotypes on interindividual warfarin maintenance dose: a prospective study in Chinese patients. *Pharmacogenet Genomics* **19**, 226-34 (2009).

- (151) Borgman, M.P. *et al.* Prospective pilot trial of PerMIT versus standard anticoagulation service management of patients initiating oral anticoagulation. *Thrombosis and haemostasis* **108**, 561-9 (2012).
- (152) Wang, M. *et al.* Clinical application of pharmacogenetic-based warfarin-dosing algorithm in patients of Han nationality after rheumatic valve replacement: a randomized and controlled trial. *Int J Med Sci* **9**, 472-9 (2012).
- (153) Anderson, J.L. *et al.* A randomized and clinical effectiveness trial comparing two pharmacogenetic algorithms and standard care for individualizing warfarin dosing (CoumaGen-II). *Circulation* **125**, 1997-2005 (2012).
- (154) Lenzini, P.A. *et al.* Laboratory and clinical outcomes of pharmacogenetic vs. clinical protocols for warfarin initiation in orthopedic patients. *J Thromb Haemost* **6**, 1655-62 (2008).
- (155) Burmester, J.K. *et al.* A randomized controlled trial of genotype-based Coumadin initiation. *Genetics in medicine : official journal of the American College of Medical Genetics* **13**, 509-18 (2011).
- (156) Kimmel, S.E. *et al.* A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med* **369**, 2283-93 (2013).
- (157) Jonas, D.E. *et al.* Impact of genotype-guided dosing on anticoagulation visits for adults starting warfarin: a randomized controlled trial. *Pharmacogenomics* **14**, 1593-603 (2013).
- (158) Avery, P.J. *et al.* A proposal for an individualized pharmacogenetics-based warfarin initiation dose regimen for patients commencing anticoagulation therapy. *Clin Pharmacol Ther* **90**, 701-6 (2011).
- (159) O'Brien, T.J. *et al.* First report of warfarin dose requirements in patients possessing the CYP2C9\*12 allele. *Clinica chimica acta; international journal of clinical chemistry* **424**, 73-5 (2013).
- (160) Nahar, R. *et al.* Implication of novel CYP2C9\*57 (p.Asn204His) variant in coumarin hypersensitivity. *Thrombosis research* **131**, 535-9 (2013).
- (161) Schelleman, H., Brensinger, C.M., Chen, J., Finkelman, B.S., Rieder, M.J. & Kimmel, S.E. New genetic variant that might improve warfarin dose prediction in African Americans. *Br J Clin Pharmacol* **70**, 393-9 (2010).
- (162) Zhang, J.E. *et al.* Effects of CYP4F2 genetic polymorphisms and haplotypes on clinical outcomes in patients initiated on warfarin therapy. *Pharmacogenet Genomics* **19**, 781-9 (2009).
- (163) Glurich, I., Berg, R.L. & Burmester, J.K. Does CALU SNP rs1043550 contribute variability to therapeutic warfarin dosing requirements? *Clinical medicine & research* **11**, 73-9 (2013).
- (164) Sun, Y. *et al.* Impact of gamma-glutamyl carboxylase gene polymorphisms on warfarin dose requirement: a systematic review and meta-analysis. *Thromb Res* **135**, 739-47 (2015).
- (165) Huang, S.W. *et al.* Influence of GGCX genotype on warfarin dose requirements in Chinese patients. *Thromb Res* **127**, 131-4 (2011).
- (166) Cavallari, L.H. *et al.* Association of apolipoprotein E genotype with duration of time to achieve a stable warfarin dose in African-American patients. *Pharmacotherapy* **31**, 785-92 (2011).

- (167) Jeong, E., Lee, K.E., Jeong, H., Chang, B.C. & Gwak, H.S. Impact of GATA4 variants on stable warfarin doses in patients with prosthetic heart valves. *Pharmacogenomics J* **15**, 33-7 (2015).
- (168) Nowak-Gottl, U. *et al.* In pediatric patients, age has more impact on dosing of vitamin K antagonists than VKORC1 or CYP2C9 genotypes. *Blood* **116**, 6101-5 (2010).
- (169) Shaw, K. *et al.* VKORC1 and CYP2C9 genotypes are predictors of warfarin-related outcomes in children. *Pediatric blood & cancer* **61**, 1055-62 (2014).
- (170) Hamberg, A.K., Wadelius, M., Friberg, L.E., Biss, T.T., Kamali, F. & Jonsson, E.N. Characterizing variability in warfarin dose requirements in children using modelling and simulation. *Br J Clin Pharmacol* **78**, 158-69 (2014).
- (171) Hawcutt, D.B. *et al.* Pharmacogenetics of warfarin in a paediatric population: time in therapeutic range, initial and stable dosing and adverse effects. *Pharmacogenomics J* **14**, 542-8 (2014).
- (172) Dilge Taskin, B. *et al.* The effect of CYP2C9 and VKORC1 genetic polymorphisms on warfarin dose requirements in a pediatric population. *Anatol J Cardiol*, (2016).
- (173) Nguyen, N., Anley, P., Yu, M.Y., Zhang, G., Thompson, A.A. & Jennings, L.J. Genetic and clinical determinants influencing warfarin dosing in children with heart disease. *Pediatric cardiology* **34**, 984-90 (2013).
- (174) Kamal El-Din, M.A., Farhan, M.S., El Shiha, R.I., El-Kaffas, R.M. & Mousa, S.M. Frequency of CYP2C9 and VKORC1 gene polymorphisms and their influence on warfarin dose in Egyptian pediatric patients. *Paediatric drugs* **16**, 337-41 (2014).
- (175) Biss, T.T., Avery, P.J., Williams, M.D., Brandao, L.R., Grainger, J.D. & Kamali, F. The VKORC1 and CYP2C9 genotypes are associated with over-anticoagulation during initiation of warfarin therapy in children. *J Thromb Haemost* **11**, 373-5 (2013).
- (176) Kato, Y. *et al.* Effect of the VKORC1 genotype on warfarin dose requirements in Japanese pediatric patients. *Drug Metab Pharmacokinet* **26**, 295-9 (2011).
- (177) Wakamiya, T. *et al.* Effect of VKORC1, CYP2C9, CYP4F2, and GGCX Gene Polymorphisms on Warfarin Dose in Japanese Pediatric Patients. *Mol Diagn Ther* **20**, 393-400 (2016).
- (178) Hirai, K. *et al.* Influence of CYP4F2 polymorphisms and plasma vitamin K levels on warfarin sensitivity in Japanese pediatric patients. *Drug Metab Pharmacokinet* **28**, 132-7 (2013).