

# Racial and Ethnic Differences in Warfarin Response

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**Background and aim of the study:** Variability of drug response among individuals is a well-recognized problem that may result in either under- or over-treatment of patients receiving similar drug concentrations. Patients with mechanical heart valves are dependent on adequate anticoagulation to prevent thrombosis development. 'Crystalline warfarin sodium' (warfarin) is the most common antithrombotic drug prescribed to control blood hemostasis in those patients, and also in those with indications such as stroke, myocardial infarction, pulmonary embolism and atrial fibrillation. Warfarin is a narrow therapeutic index agent; a small change in systemic concentration of the drug may lead to significant changes in pharmacodynamic response. Careful clinical management is required to balance the risks of bleeding (over-anticoagulation) with those of thrombosis (under-anticoagulation). The study aim was to summarize environmental, genetic and ethnic factors that affect a patient's response to warfarin and which must be considered for optimal patient outcome.

**Methods:** A Medline search was carried out to summarize various factors that influence a patient's response to warfarin.

Warfarin, as the most commonly used anticoagulation therapy, is indicated for the prophylaxis and/or treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement (1-3). It is also indicated for treatment and prophylaxis of deep vein thrombosis (4). Warfarin is defined as a narrow therapeutic index drug, which requires careful clinical management to balance the risks of bleeding with those of thrombosis (5,6). Similar doses of warfarin given to different individuals can

**Results:** Inter-ethnic differences may have profound implications for the efficacy and safety of warfarin. Ethnic differences can affect pharmacokinetic features such as bioavailability, protein binding and volume of distribution, as well as hepatic metabolism and renal elimination. Environmental factors and genetic variants in human enzymes that metabolize warfarin also contribute to interindividual variations and may render some patients more susceptible to serious or life-threatening adverse events.

**Conclusion:** Warfarin use is complicated by an unpredictable dose response that depends on factors such as demographics, diet, interacting drugs, genetic polymorphism and ethnic differences. The impact of racial differences on the kinetics of dose response or on drug efficacy is not well defined, as few clinical trials take ethnic variation into account. The use of the point of care and frequent patient self-testing may permit standardized warfarin monitoring across diverse geographical regions and facilitate analysis of ethnic variation among subpopulations.

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result in varied drug responses and overall patient outcome (7,8). Many foods and drugs are known to interfere with the anticoagulation effect of warfarin. Interactions occur through a variety of mechanisms, including interference with warfarin metabolism, displacement from protein binding sites, and disturbances of vitamin K absorption or metabolism (9). The goal of optimal warfarin therapy is to identify the daily dose which best maintains the desired therapeutic International Normalized Ratio (INR) range, thus reducing the risk of adverse events such as bleeding or thrombosis. The study aim was to summarize those environmental and genetic factors that might influence a patient's response to warfarin and which should be considered in dose management strategies.

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## Description and clinical pharmacology of warfarin

Warfarin, as administered to patients, is a racemic mixture of the *R*- and *S*-enantiomers. In humans, the *S*-enantiomer exhibits two to five times more anticoagulant activity than the *R*-enantiomer, but is generally cleared more rapidly (10). Warfarin acts by inhibiting the synthesis of vitamin K-dependent clotting factors, which include Factors II, VII, IX and X, and the anticoagulant proteins C and S. Vitamin K is an essential cofactor for the post-ribosomal synthesis of vitamin K-dependent clotting factors (11,12). The degree of inhibition is dependent upon the warfarin dosage administered, and the resultant *in vivo* effect is a sequential depression of the activities of Factors II, VII, IX and X. An anticoagulation effect generally occurs within 24 h after drug administration, though the peak anticoagulant effect may be delayed for 72-96 h. The duration of action of a single dose of racemic warfarin sodium is two to five days. The effects of warfarin may become more pronounced as the effects of daily maintenance doses overlap. The clearance of *R*-warfarin sodium is generally half that of *S*-warfarin sodium; thus, as the volumes of distribution are similar, the half-life of *R*-warfarin sodium is longer than that of *S*-warfarin sodium (37-89 h versus 21-43 h). Up to 92% of the orally administered dose is recovered in urine (13,14). There is no difference in the clearance of *S*-warfarin sodium in elderly versus young subjects, but there may be a slight decrease in the clearance of *R*-warfarin sodium in the elderly compared to the young (7,15). Older patients ( $\geq 60$  years) appear to exhibit a greater than expected prothrombin time (PT)-INR response to the anticoagulant effects of warfarin sodium. As patient age increases, less warfarin sodium is required to produce a therapeutic level of anticoagulation. The cause of the increased responsiveness to warfarin sodium is not known.

## Genetic variants affect warfarin metabolism

Pharmaceuticals are degraded via a number of metabolic pathways, primarily by the action of microsomal P-450 enzymes, which are localized in the liver and small intestine. The main cytochrome P-450 (CYP) subfamilies involved in drug metabolism are CYP3A4, CYP2D6 and CYP2C. Of these, CYP3A4 is the isozyme involved in the metabolism of 50% of most clinically useful drugs, while members of CYP2C gene products CYP2C9 and CYP2C19 are involved in the metabolism of 15% of drugs (16,17). The gene encoding the CYP2D6 enzyme is highly polymorphic. At least 70 CYP2D6 alleles are responsible for the 200-fold variability in the metabolism of 100 or more drugs (18,19).

In addition to the members of CYP3A4, CYP2D6 and CYP2C families, minor pathways are catalyzed by CYP2E1, CYP1A2, CYP2A6 and unidentified cytochrome P-450s (16).

Recent biogenetic studies have provided insights into the influence of genetic variants on warfarin metabolism. The principal enzyme involved in warfarin metabolism is CYP2C9 (20). The gene encoding CYP2C9 protein is localized on chromosome 10, has nine exons, and is ~55 kb in size. CYP2C9 cDNA encodes a protein of 490 amino acids (21). Two relatively common variant forms with reduced activity have been identified (22). The wild-type Arg144Ile359 is designated as *CYP2C9\*1*, and the two variants are Cys144Ile359 (exon 3, designated *CYP2C9\*2*), and Arg144Leu359 (exon 7, designated *CYP2C9\*3*). Patients with at least one of the two genetic variants have a significantly increased occurrence of a serious or life-threatening bleeding incident (23,24). In clinical studies, individuals heterozygous for *CYP2C9\*1/\*2* required a 20% lower mean maintenance dose of warfarin to sustain therapeutic anticoagulation than wild-type homozygotes (25). The *CYP2C9\*3* variant has been found to have a pronounced reduction in catalytic activity across all CYP2C9 substrates. A decreased metabolic clearance of *S*-warfarin was found in individuals heterozygous for *CYP2C9\*3* (17). Three more CYP2C9 variants have been recently identified, namely \*4, \*5 and \*6, but the metabolic consequences of individuals carrying those alleles remain to be evaluated (26). *In-vitro* data suggest that carriers of the *CYP2C9\*5* allele, which is expressed among African-Americans, would eliminate CYP2C9 substrates at slower rate relative to individuals expressing the wild-type protein (26). It has been suggested that screening for CYP2C9 variants may allow clinicians to develop dosing protocols and surveillance techniques to reduce the risk of adverse drug reactions in patients receiving warfarin.

## Daily dose variation in different geographical regions

A geographical variability of the warfarin dosing algorithm has been noted. Chinese patients require a smaller dose of warfarin than Caucasians for the same degree of anticoagulation (27). Yu et al. (28) have determined warfarin requirements for Chinese patients with mechanical heart valves to maintain an INR of 2.0-2.5. The mean daily warfarin dose required was  $3.3 \pm 1.4$  mg, whilst that reported for Caucasian patients was 6.1 mg. Thus, Chinese patients required approximately 50% lower average maintenance doses of warfarin than Caucasian patients to obtain comparable levels of anticoagulation (28). Iranian patients are

also reported to be more sensitive to warfarin than North Americans and Europeans, their response to a mean dose of  $3.79 \pm 1.02$  mg warfarin being similar to that of Asian Chinese patients (29). In a six-year follow up study on a rural Turkish patient population who underwent mitral and/or aortic valve replacement, a daily dose of 2.5 mg warfarin with 225 mg dipyridamole and 250 mg aspirin was sufficient for safe anticoagulation, without the need for serial PT-based adjustments (30,31). Similarly, the average maintenance dose of warfarin for Japanese patients with heart disease has also been shown to be much lower than that for American patients (3.3 mg/day) (32). A recent study suggested that African-American ethnicity is a newly identified predictor of higher warfarin dose requirements, and is independent of dietary vitamin K intake (33).

Since frequency analysis of CYP2C9 allelic variants in different ethnic groups revealed that white subjects have a significantly higher frequency of both CYP2C9\*2 and \*3 than Korean and Asians or black African subjects (20,25,30,34,35) and CYP2C9\*1 wild-type was the most prevalent allele in the Turkish study patient population (30), it appears that known CYP2C9 polymorphisms account for only part of the ethnic differences in sensitivity to warfarin.

### **Ethnic differences in drug transporters and plasma binding proteins**

Ethnic differences in drug response could be due to differences in drug transporters (e.g. p-glycoprotein; p-gp), drug receptors (adrenoreceptor) and functional binding proteins (36). P-gp plays an important role in drug absorption, distribution and excretion. It is expressed in the same tissues as CYP3A4, and shares substrate specificity, though evidence for ethnic variation in p-gp transporter activity for warfarin or other pharmaceuticals has not been determined (37).

Drug receptors comprise the alpha and beta-adrenergic receptor families. Three different subtypes of the beta-adrenergic receptor ( $\beta$ -AR) have been characterized ( $\beta_1$ ,  $\beta_2$  and  $\beta_3$ ). Ethnic differences in  $\beta$ -AR with regard to disease manifestations and responses to treatment have been extensively investigated. Two common polymorphisms of the human  $\beta_2$ -AR, Arg16→Gly and Gln27→Glu, that are associated with alterations in drug response have been identified (38). Although there is a marked ethnic difference in the frequency of these two common  $\beta_2$ -AR polymorphisms among African-American, Caucasian-American and Chinese individuals, there is no evidence that this allelic variation contributes to the observed differences in warfarin response.

GTP binding proteins (G proteins) include signal-

transducing proteins that participate in many intracellular signaling cascades and mediate the functional responses to numerous agonists (36,39,40). Some studies suggest that low doses of warfarin inhibit inflammatory signal transduction (i.e. interleukin-6 production and phosphorylation of I-kappaB) (41); however, there are no inter-ethnic data to support this finding. Inter-ethnic differences in protein binding do not seem to account for differences in drug disposition and drug responsiveness. In a study comparing Caucasian and Iranian patients, the unbound fractions of warfarin drug (acidic) and its major binding protein, albumin, were similar in the two groups. In contrast, levels of unbound lignocaine (basic) were significantly higher in Iranian subjects (42). Edeki et al. (43) reported no differences between African-Americans and white Americans in the protein binding of basic drugs.

### **Concurrent diseases alter warfarin effectiveness**

The effect of various disease states on response to warfarin has been reported. Hepatic and thyroid diseases are well documented as disorders that can alter the response to warfarin (44). Exaggerated responses to warfarin have been documented in patients with liver failure, this organ being the primary site of vitamin K-dependent clotting factor synthesis. Studies have shown that bleeding episodes correlated with evidence of worsening liver function, and that the presence of alcoholism and severe liver disease was associated with a high INR value (45). Hyperthyroidism is associated with an increased sensitivity to oral anticoagulants due to drug interactions. Thyroxine may increase the affinity of warfarin for receptor sites in the liver, leading to a decreased production of clotting factors. Another mechanism may be increased catabolism of vitamin K-dependent clotting factors. In hypothyroid states, decreased catabolism of vitamin K-dependent clotting factors is believed to cause the decreased response to oral anticoagulants (46-48). Other disease states such as heart failure, cancer and febrile illness may also influence anticoagulation control during warfarin therapy (49).

### **Drugs and dietary interactions with warfarin**

Warfarin is known to interact with approximately 250 different pharmaceuticals, and these interactions may either increase or decrease the INR value. Some medications alter platelet activity and modify the normal hemostatic pathway. In some instances, the INR may be unchanged despite an increased risk of bleeding. Dietary factors may also affect the action of war-

*Table I: Drugs that may increase the effect of warfarin.*

Acetaminophen (paracetamol) (high-dose)	Glucagon
Allopurinol (Zyloprim)	HMG CoA-reductase inhibitors
Amiodarone (Cordarone)	Isoniazid (INH)
Androgens	Itraconazole (Sporanox)
Aspirin and other NSAIDs	Ketoconazole (Nizoral)
Azithromycin (Zithromax)	Masna (Mesnex)
Bismuth subsalicylate (Pepto-Bismol)	Metronidazole (Flagyl)
Carbamazepine (Tegretol)	Miconazole (Nonistat)
Cephalosporins	Non-steroidal anti-inflammatory drugs
Chloral hydrate (Noctec)	Omeprazole (Prilosec)
Chloramphenicol (Chloromycetin)	Pravastatin (Pravachol)
Cimetidine (Tagamet)	Propranolol (Inderal)
Ciprofloxacin and other quinolone antibiotics	Quinidine (Quinaglute)
Cisapride (Propulsid)	Ranitidine (Zantac)
Clarithromycin (Biaxin)	Ritonavir (Norvir) and perhaps other protease inhibitors
Clofibrate (Atromids)	Salicylates (aspirin)
Cotrimoxazole (Bactrim)	Sertraline (Zoloft)
Dexrothyoxin	Simvastatin (Zocor)
Dirithromycin and other macrolide antibiotics	Streptokinase
Disopyramide (Norpace)	Sulfinpyrazone (Anturane)
Disulfiram (Antabuse)	Sulfonamide
Erythromycin	Tamoxifen (Nolvadex)
Felbamate (Felbatol)	Tetracyclines
Fluconazole (Diflucan)	Thyroid hormones
Fluoxetine (Prozac)	Tricyclic antidepressants
Fluvoxamine (Luvox)	Vancomycin (Vancoled)
Gemfibrozil (Lopid)	Vitamin E

farin and the resultant INR. A deficiency of vitamin K will increase the INR, while a diet high in vitamin K will decrease it. Dietary substances that affect the cytochrome P450 pathway may alter the metabolism of warfarin, thus increasing or decreasing its half-life (50,51). Drugs that are reported to either increase or decrease the anticoagulant effect of warfarin are listed in Tables I and II, respectively.

Nutritional supplements that include vitamin K, vitamin C and coenzyme Q10 have been associated with a decrease in INR, while vitamin E has been associated with increases in INR (52,53). A number of

herbal preparations have documented interactions with warfarin (54). In fact, herbs and herbal preparations may contain coumarin and therefore potentiate the activity of warfarin. Herbs which have been reported to either increase or decrease the anticoagulant effect of warfarin are listed in Table III (53,55-60). The mechanism of interaction leading to a decrease in the anticoagulation effect of warfarin is not always known, though it has been suggested that some medicinal plants increase warfarin metabolism through an action on the cytochrome P450 pathways, leading in turn to a lowering of the INR (61).

*Table II: Drugs that may decrease the effect of warfarin.*

Azathioprine (Imuran)	Griseofulvin (Gris-PEG)
Barbiturates	Phytonadione (Vitamin K)
Birth control pills (oral contraceptives)	Primidone (Mysoline)
Carbamazepine (Tegretol)	Some penicillins
Cholestyramine (Questran)	Spiroinolactone
Coenzyme Q (ubiquinone or ubidecarenone)	Sucralfate (Carafate)
Estrogens (possible)	Rifampin (Rifadin)
Ethchlorvynol (Placidyl)	Thiazide diuretics
Glutethimide (Doriden)	Vitamin K

Table III: Plants that may alter the effect of warfarin therapy.

Herbs which increase the effect of warfarin:

Alfalfa (*Medicago sativa*),  
Angelica (*Angelica archangelica*)  
Aniseed (*Pimpinella anisum*)  
Arnica (*Arnica montana*)  
Asafoetida (*Ferula* spp.)  
Celery (*Apium graveolens*)  
Danshen (*Salvia miltiorrhiza*)  
Devil's claw (*Harpagophytum procumbens*)  
Dong quai (*Angelica sinensis*)  
Fenugreek (*Trigonella foenum-graecum*)  
Garlic (*Allium sativum*)  
German chamomile (*Matricaria recutita*)  
Horse chestnut (*Aesculus hippocastanum*)  
Prickly ash (*Zanthoxylum americana*, *Z. clava-herculis*)  
Quassia (*Picrasma excelsa*)  
Red clover (*Trifolium pratense*)  
Roman chamomile (*Anthemis nobilis*)

Herbs which decrease the effect of warfarin:

Korean ginseng (*Panax ginseng*)  
Green tea (*Camellia sinensis*)  
Foods containing high levels of vitamin K: asparagus  
and leafy green vegetables

### Concluding remarks: ethnic diversity, warfarin dosing implications and point-of-care PT-INR testing

The human population is heterogeneous, and consists of subpopulations of immense ethnic diversity. Ethnic variations may result in differential warfarin responses with respect to the efficacy and/or the rate of adverse reactions. North American centers prescribe a higher mean dose of warfarin, while Asian physicians appear to prescribe a much lower dose than the rest of the world, although the intensity of their treatment as defined by target INR, is comparable. Ethnicity affects the average warfarin dose required to maintain therapeutic anticoagulation. The patient's enhanced sensitivity to warfarin may be due to a decreased clearance of warfarin secondary to genetic alteration of the gene encoding CYP2C9. The CYP2C9\*2 and CYP2C9\*3 polymorphisms (exons 3 and 7 respectively) are associated with an increased risk of bleeding events. However, in contrast to what would be predicted from ethnic differences in the frequency of the CYP2C9\*2 and CYP2C9\*3 alleles, white patients require higher warfarin doses than Asians to attain a comparable anticoagulant effect. The low frequency of the CYP2C9\*2 and CYP2C9\*3 allelic variants in Asian subjects does not contribute to the need for a low dose of warfarin in these populations. Unless other novel polymorphisms exist in the Asian populations, one

would not anticipate any CYP2C9 poor metabolizer subjects among this population. A recent report has demonstrated genetic polymorphisms of CYP2C9 at four positions in exon 4 in Hong Kong Chinese patients. At codon 208, heterozygous Leu208Val and homozygous Val208 appear to have a lower warfarin dose requirement than the homozygous Leu208 in those patients, but the significance of these CYP2C9 polymorphic alleles remains to be investigated (62).

Inter-ethnic differences in protein binding or beta-adrenergic receptor allelic variants do not seem to account for differences in warfarin responsiveness, but concurrent diseases such as cancer, hyperthyroidism and liver disease/failure may influence anticoagulation control during warfarin therapy. The patient's variable response to warfarin may be caused by other factors, which are strongly affected by ethnicity. Herbal remedies and nutritional supplements can alter the patient's response to warfarin, while many prescription drugs have been reported to interfere with warfarin if given concomitantly. Therefore, these practices must be evaluated in future studies of drug efficacy, and the optimal therapeutic ranges identified for each ethnic group in order to optimize individual patient care.

The development of small portable monitors designed for home use by patients makes patient self-testing and the adjustment of warfarin dosage an evolving strategy for the management of oral anticoagulation. Frequent PT-INR testing allows patients to be safely managed on warfarin without exposure to excessive dose adjustments that could increase the adverse event rate. In addition, point of care (POC) PT-INR testing has the advantage of being rapid, less subjective, and easily performed and therefore can be used to standardize INR measurement across a large clinical trial completed across diverse geographical regions. Future studies should be directed at using POC PT-INR testing for monitoring warfarin anticoagulation therapy to allow the analysis of ethnic variation in various subpopulations (63).

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