Regular Article

**Influence of CYP4F2 rs2108622 (V433M) on Warfarin Dose Requirement in Asian Patients**

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**Summary:** Warfarin exhibits wide interpatient variability in dosing requirements. Recent studies have shown a novel polymorphism (rs2108622, V433M) in the CYP4F2 gene to be associated with variability in warfarin requirements in Caucasians. The purpose of this study was to evaluate the impact of rs2108622 on warfarin dose requirements in the Asian population. The mean warfarin dose was found to be significantly lower in patients carrying homozygous wild-type allele CC when compared with patients carrying variant alleles CT and TT (CC vs CT+TT: 3.0 mg/day vs 3.75 mg/day, \(p = 0.033\)). In patients harboring VKORC1 diplotypes associated with low warfarin requirements, a linear regression model which included age, weight, CYP2C9 and CYP4F2 variants accounted for 38% of the variability in warfarin dose. Approximately 11% of the dose variation was explained by CYP4F2 rs2108622 (\(p = 0.004\)). The influence of rs2108622 in patients harboring VKORC1 diplotypes associated with high warfarin requirements was not significant. This study suggests that CYP4F2 rs2108622 may significantly affect warfarin dose requirements in carriers of VKORC1 low-dose-associated diplotypes.

**Keywords:** CYP4F2; warfarin; Asian; polymorphism; pharmacogenetics

**Introduction**

Warfarin is a widely prescribed anticoagulant for treatment and prevention of thromboembolic diseases such as deep vein thrombosis, atrial fibrillation, myocardial infarct and stroke. The narrow therapeutic range and wide interpatient variability in warfarin dose requirements causes its pharmacodynamic activity to be highly variable. Inter- and intraindividual variability of warfarin administration is attributed to several factors such as gender, age, body mass, vitamin-K supplements, drug interactions and genetic determinants.

Warfarin exists in two pharmacologically active enantiomeric forms, \(R\)-warfarin and \(S\)-warfarin, that are differentially metabolized by human cytochrome P450s (CYP450s). \(R\)-warfarin is primarily metabolized by CYP1A1, CYP1A2, CYP2C19, CYP3A4 and carbonyl reductases to several hydroxylated metabolites. \(S\)-warfarin is approximately 3- to 5-fold more active than \(R\)-warfarin and is metabolized primarily by CYP2C9 to 7-hydroxywarfarin.

Vitamin K epoxide reductase complex I (VKORC1) is the primary target of warfarin which catalyses the regeneration of the reduced hydroquinone form of vitamin \(K_1\) (vitamin \(K_1H_2\)) from its oxidized form (Vitamin \(K_1H_2\)). Vitamin \(K_1H_2\) is required for the gamma carboxylation of glutamyl acid residues on clotting factors II, VII, IX and X as well as proteins C, S and Z. This process is followed by the binding of the clotting factors to the phospholipid surface inside blood vessels. In view of the role of CYP2C9 and VKORC1 as an inactivating metabolism enzyme and the drug target of warfarin, respectively, many studies have looked into their pharmacogenetic profiles in an attempt to explain the wide interpatient variability in warfarin dose requirement.

CYP2C9*2 and CYP2C9*3 variants are associated with decreased metabolic capacity, and patients harboring these variant alleles require lower therapeutic doses of warfarin. The frequencies of CYP2C9*2 and *3 alleles vary...
across ethnic groups. Caucasians were reported to have the highest frequency (12% for CYP2C9*2 and 8% for CYP2C9*3), while African and Asian populations were reported to have low frequencies (1% to 4%). With regard to VKORC1, different haplotype variants have been found to affect a patient’s sensitivity to warfarin dosing.\(^{21,22}\) Haplotypes H1 and H2 are associated with low warfarin requirement and are highly prevalent in Chinese and Malay patients, but are uncommon in Indians, Caucasians and Africans.\(^{23–25}\) On the other hand, haplotypes H7, H8 and H9 are associated with higher warfarin requirements and occur at low to intermediate frequencies in Chinese and Malays (13% and 20%, respectively), but at higher frequencies in Indians, Caucasians, and African populations (86%, 58% and 49%, respectively).\(^{21,26}\) A recent report by Sandanaraj et al. in Asian patients receiving warfarin showed that the VKORC1 diplotype status and CYP2C9 genotype status explained approximately 59.1% and 7% of the total variability in warfarin dose requirements, respectively.\(^{27}\)

In addition to the above-mentioned polymorphisms, recent studies have identified a functional polymorphism in the CYP4F2 gene, rs2108622 (V433M), which was shown to affect the warfarin dose requirements in patients.\(^{28}\) CYP4F2 is a vitamin K₁ oxidase that catalyzes the metabolism of vitamin K (VK₁) to hydroxyvitamin K₁.\(^{29}\) The non-synonymous CYP4F2 variant V433M (rs2108622) is the result of a C>T nucleotide substitution at position 12 and encodes a protein with decreased catalytic activity. Caldwell et al. showed that Caucasian patients carrying the CYP4F2 433MM genotype required approximately 1 mg/day more warfarin compared with patients carrying the homozygous reference genotype (433VV).\(^{28}\) Furthermore, dosing models generated by including CYP4F2 rs2108622, in addition to functional polymorphic variants of CYP2C9, VKORC1 and demographic factors, showed an improvement in the overall warfarin dose predictability.\(^{30}\) The study by Borgiani et al. in Italian patients demonstrated that this CYP4F2 variant accounted for up to 7% of interpatient variability in warfarin dose requirement.\(^{31}\) Cen et al. found in Han Chinese patients that CYP4F2 rs2108622 T carriers required about 0.3 mg/day more warfarin than C homozygous patients.\(^{32}\) These recent findings suggest that the CYP4F2 rs2108622 polymorphism may contribute to overall warfarin dose variability and to different extents in patients of different ethnic origins.

To date, limited data are available regarding the influence of the CYP4F2 rs2108622 polymorphism on warfarin dose requirements in Asian populations.\(^{32,33}\) Although we have previously reported on the contributions of CYP2C9 and VKORC1 to the overall variability in warfarin dose requirements, the role of CYP4F2 has never been investigated in Asian patients. The aim of this project was two-fold: firstly, to investigate the genotype and allele frequencies of the CYP4F2 rs2108622 polymorphism in healthy Asian populations, and secondly to investigate the relative influence of this polymorphism on warfarin dose requirements in Asian patients.

**Materials and Methods**

**Healthy subjects and patients:** The healthy subjects enrolled in this study comprised African-Americans (N = 50) and Orientals belonging to three distinct ethnic groups, namely, Chinese (N = 88), Malays (N = 88) and Indians (N = 88). The ethnicity of the study subjects was confirmed verbally and verified against their National Registration Identification Card. A total of 124 patients [Chinese (N = 99), Malays (N = 12) and Indians (N = 13)] receiving anticoagulant therapy with warfarin were recruited at the Singapore General Hospital Anticoagulant Clinic. All patients were monitored to maintain their international normalized ratio (INR) between 2.0 and 3.0 with a stable maintenance dose of warfarin for at least a month. The indications for anticoagulant therapy were mainly for the prevention or treatment of thromboembolic diseases such as atrial fibrillation, deep vein thrombosis or prosthetic valve replacement. This study excluded patients with congestive heart failure (NYHA class 3 or greater), liver cirrhosis, thyroid disease or chronic gastrointestinal conditions. A subset of patients taking concurrent simvastatin (N = 18) and omeprazole (N = 19) were also included in this study. All patients received appropriate dietary advice. All healthy subjects and patients provided prior informed consent for the study. The study was approved by the ethics review board of the National Cancer Center, Singapore.

**Pharmacogenetic analysis of CYP4F2 rs2108622 polymorphism:** Approximately 5 mL of venous blood was drawn from patients 12 h after their last dose of warfarin during routine clinical visits. Purified genomic deoxyribonucleic acid (DNA) was extracted from mononuclear cells using the phenol-chloroform method and stored at -4°C. Pharmacogenetic analysis of CYP4F2 rs2108622 was carried out using CYP4F2-F, 5’-AGGACATTCGTGCCTCCCCAGC-3’, and CYP4F2-R, 5’-TGGACCTTCTCCTATTAAACTCTCAG-3’, as the forward and reverse primers, respectively. The amplified fragments were subjected to purification with exonuclease I and shrimp alkaline phosphatase, followed by sequencing using an Applied Biosystems 3730 DNA Analyzer (Applied Biosystems).

**Hepatic expression:** A total of 44 healthy, non-cancerous liver tissues belonging to Asian cancer patients (Chinese, N = 38; Malays, N = 1; Indians, N = 5) undergoing hepatectomy for metastasis from a colonic primary malignancy but otherwise pathologically certified to be free of malignant cells were available for investigation of hepatic CYP4F2 expression. Briefly, total RNA was extracted from the liver tissues using TRIzol reagent (Invitrogen Corp.), and reverse transcription was performed with 1 μg of DNase-treated total RNA using a high-capacity cDNA reverse-transcription kit (Applied Biosystems). Real-time PCR was carried out in a reaction volume of 20 μl in a 96-well plate.
with 100 ng cDNA and 1 µl (20×) of CYP4F2 Taqman assay probe (ABI). Reactions were performed in triplicate with GAPDH as the endogenous control and with appropriate negative (RT minus) controls.

**Western blotting**: Total protein was extracted using the TRIZol method (Invitrogen) and approximately 100 µg was used for the immuno-blot. Briefly, total protein was digested with 2× sample buffer in a boiling water bath for 7 minutes and the proteins were separated on 12% SDS-PAGE with tris-glycine buffer. Proteins were transferred to PVDF (Millipore) membrane by the Bio-Rad wet transfer system at 350 mA for 2 h at 4°C. The membrane was blocked for 2 h with 5% non-fat dried milk (Bio-Rad) and hybridized overnight with rabbit polyclonal anti-CYP4F2 primary antibody (Santa Cruz) at a dilution of 1:3000. Goat raised anti-rabbit IgG with HRP conjugate (Sigma) was used as the secondary antibody at a dilution of 1:7500. The bands were developed on X-ray film (Kodak) using West Pico Chemiluminescent (Pierce) detection system.

**Statistical analysis**: The Chi-squared and Fisher’s exact tests were used to analyze genotype and allele frequencies. The variability in warfarin dose requirement between the different CYP4F2 genotype groups was determined using the non-parametric Mann-Whitney U test. The level of statistical significance was set at \( p \leq 0.05 \) unless otherwise stated. Univariate linear regression analysis was performed to estimate the association of patient covariates to the warfarin dose. In addition to the CYP4F2 rs2108622 genotype, the other covariates included in the analysis were age, gender, weight, height, BMI, concurrent medication with simvastatin or omeprazole, VKORC1 diplotype and genotypes of CYP2C9 and CYP2C19. Covariates that were found to be significant (\( p \leq 0.05 \)) in univariate analysis were included in the multivariate regression model. The goodness-of-fit of the regression model was assessed by \( R^2 \). To control for the confounding effect of VKORC1, stratification based on VKORC1 diplotype was carried out and the above tests were repeated. All statistical analyses were performed using the SPSS program (SPSS Inc., IL, U.S.A.).

### Results

Table 1 summarizes the demographic information of patients in this study. A total of 124 patients were studied: 99 Chinese, 12 Malays and 13 Indians. The patients had a median age of 61 years and median body weight of 62.6 kg. Fifty six percent (\( N = 70 \)) of the patients were men. Patients were treated for various thromboembolic disorders: atrial fibrillation (32%), deep vein thrombosis (36%), prosthetic valve replacement (11%), pulmonary embolism (8%) and others (13%). All patients were maintained at an international normalized ratio (INR) between 2.0 and 3.0. The weekly mean warfarin dose for Chinese patients was 24.4 mg, Malays 24.9 mg and Indians 42.0 mg.

**CYP4F2 rs2108622 pharmacogenetics in healthy Asian and African-American populations, warfarin-treated Asian patients and healthy Asian liver tissues**: Table 2 depicts the CYP4F2 rs2108622 genotype and allele frequencies in Chinese, Malay, Indian, Caucasian

### Table 1. Demographic information of patients

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>N</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese</td>
<td>99</td>
<td>61 (29–87)</td>
<td>62.6 (36.2–147.6)</td>
<td>161.5 (142.5–185)</td>
<td>24.25 (12.67–48.6)</td>
</tr>
<tr>
<td>Malays</td>
<td>12</td>
<td>32</td>
<td>24.25</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Indians</td>
<td>13</td>
<td>36%</td>
<td>2.2</td>
<td>2.2</td>
<td>24.4</td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>36%</td>
<td>2.2</td>
<td>2.2</td>
<td>24.4</td>
</tr>
</tbody>
</table>

Data for age, weight, height and BMI are given as median (range).

### Table 2. Genotype and allele frequencies of CYP4F2 rs2108622 polymorphism among healthy Asians, African-Americans, liver tissue from Asians and warfarin-treated Asian and Caucasian patients

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>N</th>
<th>Genotype frequency, N (%)</th>
<th>Allele frequency (95% confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CC CT TT</td>
<td>C T</td>
</tr>
<tr>
<td>Chinese</td>
<td>88</td>
<td>59 (67.0) 25 (28.4) 4 (4.5)</td>
<td>0.81 (0.75–0.87) 0.19 (0.13–0.25)</td>
</tr>
<tr>
<td>Malays</td>
<td>88</td>
<td>65 (73.8) 21 (23.8) 2 (2.2)</td>
<td>0.86 (0.81–0.91) 0.14 (0.09–0.19)</td>
</tr>
<tr>
<td>Indians</td>
<td>88</td>
<td>29 (32.9) 40 (45.4) 19 (21.5)</td>
<td>0.56 (0.48–0.63) 0.44 (0.37–0.52)</td>
</tr>
<tr>
<td>African-Americans</td>
<td>50</td>
<td>42 (84) 8 (16) 0 (0)</td>
<td>0.92 (0.87–0.97) 0.08 (0.03–0.13)</td>
</tr>
<tr>
<td>Caucasians patients*</td>
<td>141</td>
<td>65 (46) 59 (42) 17 (12)</td>
<td>0.67 (0.61–0.72) 0.32 (0.27–0.38)</td>
</tr>
<tr>
<td>Liver tissue (Asian)</td>
<td>44</td>
<td>25 (56.8) 18 (40.9) 1 (2.3)</td>
<td>0.77 (0.69–0.86) 0.23 (0.14–0.31)</td>
</tr>
<tr>
<td>Asian patients</td>
<td>124</td>
<td>83 (66.9) 39 (31.5) 2 (1.6)</td>
<td>0.83 (0.78–0.87) 0.17 (0.13–0.22)</td>
</tr>
</tbody>
</table>

*From Borgiani et al., 2009 study.*

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and African-American populations, cancer patients and liver tissues. Fisher’s exact test validated the CYP4F2 rs2108622 frequencies to be in Hardy-Weinberg equilibrium in all studied samples. Significant interethnic variability was observed with regard to CYP4F2 rs2108622 allele frequency distribution across the Chinese, Malay, Indian, African-American and Caucasian populations \( (p < 0.0001) \). Pairwise interethnic comparisons showed the distribution of the 433M allele to be approximately 2-, 3- and 5.5-fold higher in the Indian population compared with Chinese \( (p < 0.0001) \), Malay \( (p < 0.0001) \) and African-American \( (p < 0.0001) \) populations, respectively (Table 2). The allele frequency of 433M in Asian patients \( (0.17) \) was similar to the frequency observed in the healthy Chinese \( (0.19) \) population, probably because the latter population was the predominant ethnic group in the Asian patient population.

**CYP4F2 rs2108622 effect on warfarin dose requirement:** Significant interindividual variations were observed in the warfarin dose requirement with respect to CYP4F2 rs2108622 polymorphic variants \( (p = 0.033) \). The mean weekly warfarin dose (MWWD) requirements for patients harboring the homozygous wild-type and variant allele were 21 and 26.25 mg, respectively (Fig. 1).

Univariate analysis on several covariates (age, weight, height, BMI, simvastatin co-administration, omeprazole co-administration, VKORC1 diplotype status and genotypes of CYP2C9, CYP2C19 and CYP4F2) revealed that the VKORC1 diplotype status \( (p < 0.0001) \), age \( (p < 0.0001) \) and CYP2C9 genotype status \( (p = 0.039) \) were significantly associated with warfarin dose requirements. The effect of CYP4F2 genotype status was modest and was not significantly associated with warfarin dose requirements. The percentage contributions to warfarin dose requirements by VKORC1 diplotypes, genotypes of CYP2C9 and CYP4F2 and age were 48%, 3.5%, 3% and 24%, respectively.

To further explore the contribution of CYP4F2 to dose variability, we performed two subset analyses based on VKORC1 diplotype status. We had previously shown that patients harboring the H1-H1 or H1-H\(^*\)_\text{a} diplotypes required a significantly lower MWWD compared to patients harboring the H1-H7 or H1-H\(^*\)_\text{b} diplotypes \( (p < 0.007) \). The patients in the present study were thus allocated to two distinct groups, namely, the low-dose diplotype (LDD) group comprising patients harboring the H1-H7 or H1-H\(^*\)_\text{b} diplotypes \( (N = 76) \) and the high-dose diplotype (HDD) group comprising patients harboring the H1-H1, H7-H7 or H1-H\(^*\)_\text{a} diplotypes \( (N = 48) \). Univariate analysis revealed age \( (p = 0.0001) \), CYP4F2 \( (p = 0.004) \), CYP2C9 status \( (p = 0.01) \) and weight \( (p = 0.02) \) to be significant cofactors in patients belonging to the LDD group, and these covariates accounted for 26%, 10.9%, 8.7% and 7.3% of variability in MWWD requirements, respectively. Age \( (p = 0.006) \) was the only significant covariate influencing the MWWD in patients belonging to the HDD group and accounted for 15% of variability in MWWD requirements. Subsequently, patients in the LDD group were selected for multiple linear regression analysis to predict the covariates responsible for the variation in dose requirements within this group.

Table 3 shows the results of a multiple linear regression (MLR) model with MWWD as the dependent variable and significant covariates including CYP4F2 genotypes as independent variables. The resulting MLR model accounted for 38% of variance in MWWD requirements in patients from the LDD group. The CYP4F2 variant alone accounted for 10.9% of variability and showed a significant role in MWWD requirement in patients from the LDD group.

**Effect of CYP4F2 rs2108622 on hepatic mRNA expression:** No significant associations were observed between CYP4F2 rs2108622 genotypes and hepatic mRNA or protein expression levels in 44 healthy liver tissues (data not shown).

**Discussion**

Warfarin therapeutic drug monitoring reveals great interindividual variability in dose requirement, and several studies have implicated VKORC1 and CYP2C9 polymorphisms.
as contributing significantly to the observed variability in warfarin dose requirements. The metabolic enzyme CYP4F2 is responsible for the synthesis of 20-hydroxyeicosatetraenoic acid (20-HETE) in human kidney, and CYP4F2 rs2108622 (C>T causing a V433M substitution) was demonstrated to decrease the synthesis of 20-HETE up to about 60% in human kidney. Therefore, the reduced function of CYP4F2 rs2108622 may explain the findings that individuals with the T allele are associated with decreased CYP4F2 enzymatic activity. CYP4F2 is a vitamin K1 (VK1) oxidase, and carriers of the CYP4F2 T allele have a reduced capacity to metabolize VK1, secondary to a rs2108622-dependent decrease in steady-state hepatic concentrations of the enzyme. Therefore, patients with the rs2108622 polymorphism are likely to have elevated hepatic levels of VK1, necessitating a higher warfarin dose to elicit a satisfactory anticoagulant response.

The present study compared CYP4F2 rs2108622 pharmacogenetics in healthy Asian, Caucasian and African-American populations and in Asian patients receiving warfarin anticoagulant therapy. Significant variability was observed in the frequency of CYP4F2 rs2108622 polymorphism in healthy subjects across different ethnic groups, \( p < 0.0001 \) (Table 2). The frequency of the T allele was higher in Indian and Caucasian populations than in Chinese, Malay and African-American populations, thereby suggesting that Indian and Caucasian ethnic groups are likely to have elevated levels of VK1, which may in turn necessitate a higher warfarin dose requirement in these populations. The low frequency of the rs2108622 T allele (0.17) in our studied patient population is probably due to a larger percentage of patients belonging to the Chinese ethnic group (\(-80\%\)). Our results for the frequency distribution of variant rs2108622 T allele among different ethnicities are comparable with recently published studies by Scott et al. and Ross et al. The main goal of these studies was to provide worldwide allele frequency information for the most commonly studied variants (including rs2108622) influencing warfarin dosing, and their results support inclusion of CYP4F2 rs2108622 into pharmacogenetic algorithms for improved prediction of warfarin dosing in major ethnic groups. However, none of the previous studies demonstrated phenotypic association of these polymorphisms on warfarin dosing.

Our findings demonstrated that there was a significant association between CYP4F2 genotype and weekly warfarin dose requirements among Asian patients (Fig. 1). The mean daily warfarin dose requirement in Asian patients harboring CYP4F2 variant allele T was 0.75 mg/day higher than patients harboring the reference genotype (3 mg/day). Similar trends of CYP4F2 association with warfarin dose requirement were established in other ethnic cohorts in previous reports. A study in an Italian population recommended that patients with CT and TT genotypes required 0.5 and 2.6 mg/day higher warfarin doses, respectively, than patients with the CC genotype. Caldwell et al. reported that the warfarin dose requirement in Caucasian patients harboring the T allele was 4–12% higher than that in patients carrying the reference genotype, and the dosing model incorporating CYP4F2 genotype status explained approximately 2% of the variability in warfarin dose requirement. Chen et al. and Harada et al. recently studied the effect of CYP4F2 rs2108622 on warfarin dosing in Han Chinese and Japanese patients, respectively. Chen et al. found that CYP4F2 rs2108622 T carriers required approximately 0.3 mg/day more warfarin than patients who were C homozygous; this polymorphism accounted for about 4% of interpatient variability in stable warfarin dose requirement. The study by Harada et al., on the other hand, did not demonstrate a positive association between CYP4F2 rs2108622 polymorphism and warfarin dose requirement in Japanese patients. The present study suggests that the T allele frequency of CYP4F2 is a critical factor influencing variation in warfarin dose requirement in different genotypic groups in Asian patients. Seventeen percent of patients harbored the low-activity-associated T allele, which accounted for approximately 3% of the interpatient variability in warfarin dose requirement, thus suggesting that the majority of Asian patients may require low doses of warfarin for effective anticoagulation. These observations may be particularly applicable to Chinese and Malay ethnic groups as they were found to have similar frequencies of the rs2108622 polymorphism (Table 2). A higher frequency of the rs2108622 polymorphism was noted in the healthy Indian population (44%), which may explain the higher warfarin dose often required to attain effective anticoagulation in this population, probably due to higher levels of CYP4F2 metabolizing capacity.

We had previously shown that warfarin dose requirements were significantly lower in patients carrying low-dose-associated VKORC1 diplotypes (H1-H1 and H1-H1*) compared with patients carrying the high-dose-associated VKORC1 diplotypes (H1-H7 and H1-H1*). Comparing these two diplotype groups based on stratification by CYP4F2 rs2108622 polymorphism status within each diplotype group suggested that warfarin dose requirements were significantly influenced by CYP4F2 rs2108622 in patients belonging to the LDD group, but not in patients belonging to the HDD group (Figs. 2A and 2B). Furthermore, both CYP4F2 and CYP2C9 accounted for similar degrees of interpatient variability in warfarin dose requirements (8–10%) within the LDD group, probably suggesting that these CYP enzymes may have similar contributory effects to overall variability in warfarin dose requirement in Asian patients belonging to the LDD group. No significant influence of CYP4F2 rs2108622 polymorphism was found when the analysis was restricted to the HDD group, probably suggesting that VKORC1 status, rather than the CYP4F2 rs2108622 polymorphism could be the major factor contributing to dose variability within this group.
The absence of CYP4F2 rs2108622 genotypic effects on hepatic mRNA or protein expression levels in healthy liver tissues and the absence of significant correlation between CYP4F2 mRNA and protein levels in the present study may be due to possible involvement of post-transcriptional regulation of CYP4F2. A previous report by McDonald et al. revealed that the enzymatic activity associated with CYP4F2 rs2108622 is probably due to a decrease in steady-state hepatic CYP4F2 levels. Further studies are needed to ascertain the mechanistic basis of these differences.

To the best of our knowledge, the effect of CYP4F2 rs2108622 in Asian patients has been investigated in a limited number of studies, and we explored its effect in detail with further adjustment for VKORC1 status. The VKORC1-dependent stratification approach revealed that CYP4F2 rs2108622 contributes to the warfarin dose variation in the VKORC1 LDD group but not in the HDD group. Consequently, the incorporation of CYP4F2 genotype status in dose prediction models might result in more accurate prediction of warfarin doses for patients in the low dose group. Further studies are warranted to evaluate the safety and efficacy of this model.

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References


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