Cytochrome P450 2C9 gene polymorphism and warfarin maintenance dosage in pediatric patients: A systematic review and meta-analysis

running title: CYP2C9 gene and warfarin maintenance dosage

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Abstract

**Aim:** To assess the effect of Cytochrome P450 2C9 (CYP2C9) gene polymorphism on pediatric warfarin maintenance dosage requirement.

**Methods:** A previously developed search strategy was conducted in PubMed, EMBASE, and the Cochrane Library. Eligible studies published prior to January 27, 2016, were identified and compared against strict inclusion/exclusion criteria. Required data were extracted, and researchers were consulted for additional data if needed. Review Manager Version 5.2.3 software was used to analyze the relationship between CYP2C9 polymorphisms and warfarin maintenance doses in pediatric patients. Eight articles with a combined total of 507 pediatric patients were included in the meta-analysis.

**Results:** Maintenance warfarin doses in patients with CYP2C9 *1/*2 genotype, CYP2C9 *1/*3 genotype, and CYP2C9 variant carriers which contain at least one variant allele (*2 or *3) were from 15% to 41% lower than doses in patients with the wild type allele (CYP2C9 *1/*1): all differences were significant with $P$-values <0.05. The Fontan procedure as a medical indication for anticoagulation was also associated with a lower warfarin maintenance dose; however, target INR range was not.
Conclusions: We found that CYP2C9 gene polymorphism (referring to the presence of *1/*2, *1/*3, and variant genotypes in the population in addition to the wild type) was significantly associated with decreased warfarin maintenance dose requirements. Additionally, a specific indication for warfarin, the Fontan procedure, was associated with a lower daily warfarin dose. However, the results of our study require confirmation from more research with larger numbers of pediatric patients.

Keywords: Warfarin, Pediatric patients, CYP2C9, Gene polymorphisms, Systematic review, Meta-analysis

Introduction

Warfarin, a vitamin K antagonist used as an oral anticoagulant, is widely prescribed for preventing the thrombosis. However, proper dosing can be clinically challenging due to its narrow therapeutic range as well as an almost twenty-fold difference in the dosages required for adequate anticoagulation. The prothrombin time (PT) and international normalized ratio (INR) should be monitored to ensure the desired antithrombotic effect while minimizing the risk of bleeding.

Over the past decade, researchers have proven that two genes, CYP2C9 and VKORC1, explain up to 40% of the variability seen in maintenance warfarin dosing requirements of adults. [1-3] CYP2C9 is highly polymorphic, which can lead to a significant influence on the metabolism of drugs. [4] In 1999, Aithal et al. have demonstrated that there is a strong association
between CYP2C9 variant alleles and warfarin dose requirement[5]. After that, many studies have certified the significant effect of CYP2C9 on warfarin doses in adult patients[6-11]. Moreover, a dosing algorithm for adult patients has been established by the US Food and Drug Administration and International Warfarin Pharmacogenetics Consortium[1,2]. However, due to several factors, the pharmacogenetic model for adults cannot be directly used for pediatric patients, and need for pediatric-focused pharmacogenomic studies[12,13]. One is that the maturation of metabolic enzymes, which is age-related, has a significant effect on warfarin dose requirements [14]. In addition, there are dietary differences in vitamin K intake among pediatric patients (e.g., breast milk vs. formula diets in infants), which affect warfarin activity[15]. Furthermore, clinical characteristics, such as indication for warfarin and the target INR range, cause great variability in the dose requirement for warfarin in children.

CYP2C9 is located on human chromosome 10q24.2 and is approximately 55kb in length. In adults, CYP2C9 mutant types require a 19.6 to 78.1% lower warfarin dose for proper anticoagulation[6]. There have also been studies that focused on CYP2C9 polymorphism and warfarin dosing in pediatric patients [16-23]. Questions about the effects of CYP2C9 polymorphism on pediatric warfarin dosing and about the possible development of a pharmacogenetic model for children remain unanswered. For this reason, it has been proposed that a meta-analysis be performed [4]. Therefore, we conducted a systematic review to analyze the relationship between warfarin maintenance dosage and gene polymorphism in pediatric patients.

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Methods and Materials

Search strategy

A comprehensive search was conducted in PubMed, EMBASE, and the Cochrane library for relevant English-language research articles published prior to January 27, 2016 (the date the search was completed). The search field strategy used was (CYP2C9 OR cytochromes OR Cytochrome-p-450 OR Cytochrome p-450 OR “Cytochrome P450”) OR (warfarin AND [gene OR genotype OR genetics OR alleles OR polymorphisms OR pharmacogenetics] AND (neonate OR infant OR child OR adolescents OR pediatrics OR pediatric). The included literature references were examined and the authors were consulted for any additional information.

Study inclusion criteria

A strict set of inclusion criteria was used to find eligible studies: (1) the focus was on the relationship between CYP2C9 polymorphism and warfarin maintenance dosing; (2) the sample size and mean warfarin maintenance dose and standard deviation [SD] for each CYP2C9 genotype group was provided; (3) data was given for patients in the pediatric age group (ages <19 years); (4) the mean age of subjects and information about their ethnicities were given. No restrictions were set for other clinical characteristics, such as possible interacting drugs, clinical indications for warfarin, or the sex ratio of patients.
**Study exclusion criteria**

Studies were excluded from the meta-analysis if (1) data were not provided, or could not be obtained, on the mean warfarin dose and SD, patient sample size, patient age, or patient ethnicity; (2) data were not provided specifically for a population of pediatric patients; (3) the data were already reported in a previous article; and (4) the publication type was an abstract, conference proceedings, review article, letter, or case report.

**Data extraction**

All required data were extracted independently by two researchers. To avoid potential data extraction errors, cross-checking was performed. If there was a question about any extracted data, there was discussion to reach a consensus regarding the data’s inclusion. Additional required data was obtained by consulting researchers when necessary. Information extracted included names of the first authors, publication years, target INR ranges, predominant patient ethnicities, mean ages, sex ratios, indications for warfarin use, sample sizes, allele frequencies, and warfarin maintenance doses (means with SDs) for single nucleotide polymorphism (SNP) genotypes.

**Quality assessment**

The criteria predefined by Lindh JD et al.[24] were used to conduct a Quality Score Assessment. The quality criteria were (1) analytical validity of genotyping (including sample types, time of sample collection, genotyping method, and quality control measures); (2) selection of study subjects (including geographic area(s), recruitment period, methods, exclusion criteria for cases and controls, sample size, mean age with SD or age range of study. This article is protected by copyright. All rights reserved.
subjects, and sex ratio); (3) population stratification (including identified potential correlates of the genotype and potential correlates taken into consideration for design or analysis); (4) statistical issues (including the number of subjects included in the analysis, analysis method, software used to perform the analysis, and confidence intervals [CIs]). Studies were graded as “++”, “+” or “-”, respectively, depending on whether most criteria, some criteria, or no criteria were fulfilled.

**Statistical analysis**

In our meta-analysis, we defined CYP2C9 *1/*1 genotype (the wild type) as the reference group, and included any genotype containing at least one variant allele (*2 or *3) in the variant group. To reduce the existence of any heterogeneity due to pharmacodynamic differences in warfarin sensitivity among study populations, warfarin maintenance doses (mean ± SD) for each genotype group (including the variant group) were normalized using the method of Lindh et al.[6] (dividing the mean maintenance dose of reference group). The normalized mean daily warfarin dose (MDWDs) of the genotype groups were compared with the MDWD of the reference group. However, due to the normalization procedure, results were not expressed as absolute difference, but as relative differences (e.g., a mean difference of 0.5 indicates a 50% increase in the MDWD).[6]

Meta-analysis was conducted using Review Manager Software version 5.2.3. The inverse variance method was used to weight each study, and the mean difference (MD) was employed to determine the effect of each CYP2C9 genotype on the MDWD. The Weighted Mean Difference (WMD) could be acquired by multiplying each MD by the relative weight...
of each study. The total WMD in each comparison was obtained by adding each WMD of the included studies, indicating the effect of each SNP on the MDWD. The influence of genotype polymorphism was considered statistically significant when the \( P \)-value was less than 0.05.

Heterogeneity among studies for each comparison group was tested by Cochran's Q test (Mantel-Haenszel chi-squared test), and expressed by the \( P_H \) value and \( I^2 \). A \( P_H \) value >0.1 or \( I^2 < 25\% \) was defined as negative for heterogeneity[6]. Then, a fixed effect model was used in the absence of heterogeneity; whereas, a random effect model was used if it was present.

Sensitivity analyses were performed using a one by one study elimination process. Publication bias was also assessed using tests from Begg[25] and Egger's test[26].

Results

Study identification and characteristics

A total of 210 articles were screened through the literature search. Use of strict inclusion/exclusion criteria resulted in only eight articles with a total of 507 pediatric patients remaining for meta-analysis [16-19,27-30]. The flow diagram for study selection is shown in Supplementary Figure S1. All studies are of high quality, being graded as “++”. Some studies were excluded for insufficient data [20-22,31]. All of the included remaining studies were published in English and primarily consisted of Caucasian patients, except for the one by Hirai et al[29]. Years of publication ranged from 2012 to 2015. Characteristics of selected studies are shown in Table 1.

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The frequency of *1/*1 (wild type), *1/*2, *1/*3, *2/*2, and *2/*3 was calculated as 70.4%, 13.8%, 10.7%, 3.6%, and 1.6, respectively. No pediatric patients in the remaining studies had the CYP2C9 *3/*3 genotype. Comparison of CYP2C9 genotype frequencies between adult and pediatric patients is shown in Supplementary Table S1.

**Meta-analysis**

**The relationship between CYP2C9 *1/*2 and warfarin maintenance dosage**

There were five studies investigating the impact of the CYP2C9 *1/*2 genotype on warfarin maintenance dosage [18,19,27,28,30]. The result of the meta-analysis is shown in Fig. 1. Analysis revealed that the CYP2C9 *1/*2 genotype was associated with a warfarin maintenance dose that was 15% lower than that found with CYP2C9*1/*1 (wild) genotype ($P = 0.03$, WMD = -0.15, 95% CI -0.29 to -0.01). (No heterogeneity was found in the meta-analysis [$I^2 = 0\%$, $P_{H} = 0.70$], so a fixed-model was used.) The effect of CYP2C9 *1/*2 on warfarin maintenance dosage in Caucasians pediatric patients was compared to adult patients, and is shown in Supplementary Table S1.

**The relationship between CYP2C9 *1/*3 and warfarin maintenance dosage**

There were also five studies included for meta-analysis which gave data for the CYP2C9 *1/*3 genotype [18,19,27-29]. Compared with the wild genotype, pediatric patients with CYP2C9 *1/*3 required a 41% lower warfarin maintenance dose ($P < 0.00001$, WMD = -0.41, 95% CI -0.51 to -0.31). (Again, the fixed-model was applied due to lack of
heterogeneity \( \Gamma^2 < 25\%, P_H = 0.26 \)). The result is presented in Fig. 2. A comparison of the CYP2C9 *1/*3 genotype between pediatric and adult patients in Caucasians is found in Supplementary Table S1.

**The relationship between CYP2C9 variant carriers and warfarin maintenance dosage**

Two studies focused on the relationship between the CYP2C9 variant genotype and warfarin maintenance dosage [16,17]. The results of meta-analysis are shown in Fig. 3, which indicate that pediatric patients with a variant carriers required significantly lower warfarin maintenance dosage than those with the wild-type \( (P = 0.004, \text{WMD} = -0.26, 95\% \text{ CI} -0.44 \) to \( -0.08 \)). (A fixed model method was used because analysis showed homogeneity \( [P_H = 0.12] \)).

**The effect of clinical characteristics on warfarin maintenance dosage**

Included studies provided data on the significance of only two clinical factors in pediatric patients—namely, indication for warfarin and target INR range [18,27]. For analyzing data, we divided target INR ranges into a 2–3 INR range group and a >2.5 INR group, as we had in a previous study [32]. Indications for warfarin were also divided into two groups, Fontan procedure vs. “others”. Meta-analysis revealed that the Fontan procedure indication was associated with a lower warfarin maintenance dose requirement (WMD = -1.50, 95% CI -2.46 to -0.54), while the target INR had no effect on the dose requirement (WMD = -0.12, 95% CI -1.19 to 0.96). The random effect model was used in the two meta-analyses \( (I^2 \geq 41\% \). The results were similar to those of our previous study [32] and are shown in Fig.4A and 4B.

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Sensitivity analysis and Publication bias

Sensitivity analysis was conducted using the method of eliminating studies one by one. There were no significant differences or revisal changes, which meant that the results of this analysis were stable. Both Begg’s[25] and Egger’s tests[26] were applied to detect publication bias in each analysis, and none was found. These analyses indicate that our results are stable and reliable.

Discussion

The results of meta-analysis showed that comparing to the CYP2C9 *1/*1 genotype, the CYP2C9 *1/*2 genotype required 15% lower warfarin maintain doses (95% CI -0.29 to -0.01), the CYP2C9*1/*3 genotype required 41% lower warfarin maintain doses (95% CI -0.51 to -0.31), and the CYP2C9 variant carriers were required 26% lower warfarin maintain doses (95% CI -0.44 to -0.08), respectively. The indication of Fontan procedure was also associated with a lower warfarin maintenance dose (WMD=-1.50, 95% CI -2.46 to -0.54), while the target INR range was not related to the dosage level (P > 0.05).

It is well known that gene polymorphisms affect warfarin maintenance dose requirements for adult patients, and that warfarin dosing algorithms should be used to address the presence of variant genotypes and other factors[2,6,11,33-35]. Taskın et al. have certified
that pediatric Patients with allelic variants (VKORC1 and CYP2C9) required lower warfarin
doses, and a 64.5% correlation could be found between their calculated ideal doses and
administered warfarin doses[36]. The effect of VKORC1 –1639 SNPs on pediatric warfarin
maintenance dosage has been examined[32], and the result was consistent with a previous
study in adult patients[37]. Many studies have indicated that CYP2C9 polymorphisms
significantly influence warfarin maintenance dose in pediatric patients[16,18,27]. The variant
genotypes CYP2C9 *1/*2 and *1/*3 are the most common and have been found to be
important factors related to warfarin dosage in adults [6]. Therefore, we chose to conduct a
meta-analysis examining these two genotypes (*1/*2 and *1/*3) and warfarin dosing in
pediatric patients, and obtained results similar to those found with adult patients[6].

In addition, we believe clinical factors should be taken into consideration in the
determination of warfarin maintenance doses. Sixteen years ago, Streif et
al.[38]demonstrated, based on data from 319 patients, that age and the clinical indication for
warfarin use was associated with the actual maintenance dose needed. Since then, more
studies have shown that various clinical factors (age, weight, indication for warfarin, and
target INR range) significantly affect the maintenance dose requirement[16,18,19,27]. In this
meta-analysis, the effect of two factors (target INR range and indication of warfarin) were
analyzed and results showed that pediatric patients on warfarin for a history of Fontan
procedure needed significantly lower warfarin doses, whereas the target INR range did not
influence dosage requirements.
We performed a comparison of the *CYP2C9* genotype frequency and the association between *CYP2C9* genotypes and warfarin maintenance dose for adult and pediatric patients in Caucasian. The results were similar (see Supplementary Table S1). However, due to the low frequencies of the *CYP2C9* *2/*2, *CYP2C9* *2/*3, and *CYP2C9* *3/*3 genotypes, and the small number of articles and pediatric sample sizes, the impact of these genotypes on warfarin maintenance dose requirement is uncertain.

Sensitivity analysis and other tests revealed no publication bias or heterogeneity, showing that the results of our meta-analysis are stable and reliable.

Considering the results of this study in combination with those from our previous study that focused on *VKORC1* polymorphism and pediatric warfarin maintenance dosing[32], we believe that gene polymorphisms do significantly affect warfarin maintenance dosage requirements in children. Although studies in pediatric patients to date are limited in terms of sample size and lack of ethnic diversity, considering the data from adult studies, we do feel that the addition of genotype to current warfarin dosing algorithms for pediatric patients would be beneficial. Genotyping should certainly be considered for all pediatric patients who are at high risk of bleeding complications, who are warfarin-resistant, or who suffer adverse events while receiving warfarin.

**Limitations and Perspectives**

Although sensitivity analysis reflected stable results without publication bias, the results of this meta-analysis should be considered with caution, due to the limited number of studies meeting selection criteria and overall low numbers of pediatric patients. Moreover, the effects of gene polymorphisms on warfarin maintenance dosage requirements require further investigation.
of the CYP2C9 *3/*3, *2/*2, and *2/*3 genotypes on warfarin maintenance dosage are still uncertain, because rare research mentioned them. In addition, all studies except for one study [29] involved in primarily Caucasian patients; therefore, the effect of CYP2C9 polymorphism on warfarin dose requirements in Asian and African pediatric patients is undefined. More studies looking at the relationship between CYP2C9 polymorphism and warfarin are necessary in the future. More research examining the impact of clinical factors, such as the medical indication for anticoagulation and age, are also needed and anticipated. Finally, future studies, which will update this meta-analysis, and pharmacogenetic dosing algorithms, which will be developed for pediatric patients as they have been for adults, were hope.

Conclusion

This meta-analysis firstly focused on the relationship between CYP2C9 polymorphism and warfarin maintenance dose in pediatric patients, and we found that the CYP2C9 *1/*2, CYP2C9 *1/*3, and CYP2C9 variant genotypes required significantly lower warfarin daily doses. It was also shown that pediatric patients needing anticoagulation after a Fontan procedure required significantly lower warfarin maintenance doses. A larger number of studies is required to ensure against publication bias and confirm generalizability. More data is also needed to build pharmacogenetic dosing algorithms for pediatric patients. Ideally, these algorithms will include both genotype data (CYP2C9 and VKORC1) and clinical factors (such as age, indication for warfarin, weight and possibly others).
Funding sources

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Conflict of Interest

The authors declared no conflict of interest.

References


Figure Legends

**Figure 1**: Forest plot showing the influence of CYP2C9 *1/*2 on warfarin maintenance dosage, compared with individuals with the CYP2C9 *1/*1 genotype (wild type). SD: standard deviation of normalized mean warfarin doses associated with each genotype. CI: confidence interval. Brackets denote 95% CIs.

**Figure 2**: Forest plot showing the influence of CYP2C9 *1/*3 on warfarin maintenance dosage, compared with individuals with the CYP2C9 *1/*1 genotype (wild type). SD: standard deviation of normalized mean warfarin doses associated with each genotype. CI: confidence interval. Brackets denote 95% CIs.

**Figure 3**: Forest plot showing the influence of CYP2C9 variant genotype (any genotype containing at least one variant allele) on warfarin maintenance dosage, compared with individuals with the CYP2C9 *1/*1 genotype (wild type). SD: standard deviation of normalized mean warfarin doses associated with each genotype. CI: confidence interval. Brackets denote 95% CIs.
**Figure. 4A and 4B:** Forest plot showing the influence of clinical characteristics on warfarin maintenance dosage. (A) The reduction in warfarin dose requirement associated with the indication of Fontan procedure; (B) The influence of target INR range on warfarin maintenance dosage. SD: standard deviation of normalized mean warfarin doses associated with each genotype. CI: confidence interval. Brackets denote 95% CIs.

**Supplementary Figure S1:** Flow diagram of the literature screening process.
<table>
<thead>
<tr>
<th>STUDY</th>
<th>INR target</th>
<th>Indication</th>
<th>num</th>
<th>male ratio</th>
<th>predominant</th>
<th>mean ages</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tabib, A. 2015[28]</td>
<td>2, 2.5</td>
<td>PHV, SVA</td>
<td>50</td>
<td>70</td>
<td>Caucasian</td>
<td>11.4 (5 – 17)</td>
<td>44 12 4 30 10 0 - -</td>
</tr>
<tr>
<td>Hirai, Keita2013[29]</td>
<td>-</td>
<td>TD</td>
<td>37</td>
<td>59.46</td>
<td>Asian</td>
<td>10.2 (1.9 – 16.5)</td>
<td>94 0 5.4 0 0 0 - -</td>
</tr>
<tr>
<td>Biss, T.T. 2012[27]</td>
<td>2-3, 2.5-3.5</td>
<td>FP, PHV, CA etc.</td>
<td>120</td>
<td>76.5</td>
<td>Caucasian</td>
<td>11 (1-18)</td>
<td>70 14.2 14.2 0.8 0.8 0 - -</td>
</tr>
<tr>
<td>Shaw, K. 2014[18]</td>
<td>&lt;2.5, 2-3, &gt;2.5</td>
<td>FP, PHV, DVT, E</td>
<td>93</td>
<td>55.9</td>
<td>Caucasian</td>
<td>4.8 (0.17-17.8)</td>
<td>69.9 15 12.9 2.2 0 0 - -</td>
</tr>
<tr>
<td>Lala, M. 2013[30]</td>
<td>#</td>
<td>PHV, FP, KD etc.</td>
<td>26</td>
<td>61</td>
<td>Caucasian</td>
<td>4.4 (0.33-18)</td>
<td>85 15 0 0 0 0 - -</td>
</tr>
<tr>
<td>Nguyen, N. 2013[19]</td>
<td>&amp;</td>
<td>FP, PHV</td>
<td>37</td>
<td>70.3</td>
<td>Caucasian</td>
<td>9.6 (1.8 – 18.6)</td>
<td>73 19 8 0 0 0 - -</td>
</tr>
</tbody>
</table>

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Table 1: Characteristics of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Age Range</th>
<th>Race</th>
<th>INR Range</th>
<th>Events</th>
<th>Controls</th>
<th>Target INR Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vear, S.I. 2014[16]</td>
<td>2-3</td>
<td>2.5-3.5</td>
<td>DVT, PHV</td>
<td>Caucasian</td>
<td>12.39 (1.01-19.85)</td>
<td>67</td>
<td>16</td>
</tr>
<tr>
<td>BISS, T.T. 2013[17]</td>
<td>2-3</td>
<td>2.5-3.5</td>
<td>FP, PHV, CA etc.</td>
<td>Caucasian</td>
<td>4 (1-17)</td>
<td>68.5</td>
<td>11.8</td>
</tr>
</tbody>
</table>

PHV = Prosthetic heart valve, DVT = deep venous thrombosis, FP = Fontan procedure, CA = Coronary aneurysm, TD = thromboembolic diseases, KD = Kawasaki disease, SVA = single ventricular approaches.

"-" means no data, "Wild" means wild type, "Mutant" means mutant type.

# means target INR range=1.5-2.5 (50%), 2.0-2.5 (19%), 2.5-3.5 (31%)

& means target INR range=1.5-2.5 (10.8%), 2-3 (51.4%), 2.5-3.5 (21.6%), 3-4 (16.2%).
Table 2 Comparison of the effect of variant CYP2C9 genotypes on warfarin dose requirements in pediatric and adult patients in Caucasians (data for adult patients from [6]). Data on the effect of variant CYP2C9 genotypes are expressed as weighted mean difference (WMD) [95% CI].

<table>
<thead>
<tr>
<th>CYP2C9 genotypes</th>
<th>frequency (%)</th>
<th>impact on MDWD</th>
<th>Adult</th>
<th>Pediatric</th>
<th>Adult</th>
<th>Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td>66.17</td>
<td>67.79</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*1/*2</td>
<td>19.81</td>
<td>14.74</td>
<td>19.9% (17.4, 22.4)</td>
<td>15% (1.0%, 29.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*1/*3</td>
<td>10.82</td>
<td>12.0</td>
<td>35.1% (29.6, 40.7)</td>
<td>43% (33.0%, 53.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*2/*2</td>
<td>1.34</td>
<td>3.79</td>
<td>36.8% (28.5, 45.1)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*2/*3</td>
<td>1.43</td>
<td>1.68</td>
<td>58.0% (50.0, 66.0)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*3/*3</td>
<td>0.42</td>
<td>0</td>
<td>78.1% (72.0, 84.3)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

"-" means no data; MDWD means Mean Daily Warfarin Dose.