Managing vitamin K antagonist (VKA) therapy is challenging in children because of a narrow therapeutic range and wide inter- and intra-individual variability in dose response. Only a few small studies have investigated the effect of nongenetic and genetic factors on the dose response to VKAs in children. In a cohort study including 118 children (median age 9 years; range, 3 months-18 years) mostly with cardiac disease, we evaluated by multivariate analysis the relative contribution of nongenetic factors and VKORC1/CYP2C9/CYP4F2 genotypes on warfarin dose (n = 83) or fluindione (n = 35) maintenance dose and the influence of these factors on the time spent within/above/ below the range. The results showed that height, target international normalized ratio and VKORC1 and CYP2C9 genotypes were the main determinants of warfarin dose requirement, accounting for 48.1%, 4.4%, 18.2%, and 2.0% of variability, respectively, and explaining 69.7% of the variability. Our model predicted the warfarin dose within 7 mg/wk in 86.7% of patients. None of the covariates was associated with the time spent above or below the international normalized ratio range. Whether this model predicts accurately the effective maintenance dose is currently being investigated. (Blood. 2012; 119(3):861-867)

Introduction

In pediatric patients, vitamin K antagonists (VKAs) are mainly used to prevent thromboembolism after cardiac valve replacement, total cavopulmonary connection, dilated cardiomyopathy, coronary aneurysms after Kawasaki disease, or, less frequently, extra-cardiac diseases.1-3 VKA therapy is challenging in children because VKAs have a narrow therapeutic range and considerable inter- and intra-individual variability.2 This variability is partly explained by age and other demographic, clinical, and environmental factors such as comedications. In the last decade, an increasing number of genetic variations affecting VKA pharmacodynamics and/or pharmacokinetics were found to have a major impact on the VKA dose in adults.4-15 These genetic variations are found in single nucleotide polymorphisms (SNPs) in VKORC1, CYP2C9, and CYP4F2.4-15 VKAs exert their anticoagulant effect by inhibiting the enzyme vitamin K epoxide reductase (VKORC1), thereby preventing vitamin K recycling and vitamin K-dependent carboxylation of the coagulation factors II, VII, IX, and X.16 SNPs located in the VKORC1 gene (VKORC1) have the largest effect on the response to VKAs. More specifically, patients carrying the −1639 G > A SNP (rs9923231) located in the functional promoter of VKORC1 require substantially lower doses than do wild-type patients, and a gene-dose effect has been reported for this genetic variant.5,17 The pharmacokinetics of warfarin and other coumarin derivatives depend mainly on the activity of cytochrome P450 2C9 (CYP2C9), a microsomal hepatic enzyme responsible for oxidation of these drugs to inactive metabolites. The effect of CYP2C9 on non-coumarin VKAs such as fluindione is unclear.18 Two common SNPs in the CYP2C9 gene, CYP2C9*2 (rs1799853) and CYP2C9*3 (rs1057910), are associated with decreased CYP2C9 catalytic activity compared with wild-type CYP2C9*1, and therefore, patients carrying at least one variant allele require lower doses of coumarin derivatives than do wild-type patients.19 More recently, an SNP (rs2108622) in the CYP4F2 gene encoding cytochrome 4F2 involved in vitamin K metabolism was shown to be associated with higher warfarin dose requirements.10,12,20 Overall, genetic factors accounted for 30%-40% of the dose variability in white adults.5,7,9,10,12,13,21-23

Many studies have assessed genetic variants influencing the VKA response in adults.4,15 In contrast, only a few small studies have investigated the effect of the VKORC1 and/or CYP2C9 genotype on VKA dose requirements in children.20-25 Moreover, no study evaluated the potential influence of pharmacogenetic variables on anticoagulation control.

Herein we report the results of a cohort study of 118 children (age 3 months to 18 years) who were followed in pediatric cardiology departments while receiving long-term VKA treatment.
Our primary objective was to determine the relative contributions of nongenetic and genetic factors (VKORC1, CYP2C9, and CYP4F2) on warfarin or fluindione dose requirements in this cohort. Our secondary objective was to evaluate the potential influence of these factors on the time spent within, above, and below the international normalized ratio (INR) range.

Methods

Study design

From September 2009 to December 2010, consecutive children on VKA therapy were recruited at the National Referral Center for Complex Congenital Heart Diseases (Necker-Enfants-Malades University Hospital, Paris, France). Inclusion criteria were as follows: age, birth to 18 years; VKA therapy for at least the past 2 months; and stable anticoagulation defined as results within the therapeutic range for 3 consecutive INR determinations at 2-week intervals.

Pediatric indications of VKA corresponded to 3 different target INRs: (1) 3.3 for patients with mitral valve replacement; (2) 2.5 for patients with aortic valve replacement, dilated cardiomyopathy, coronary aneurysms after Kawasaki disease, or extracardiac diseases; and (3) 2.2 for patients with total cavopulmonary connection.

Management of anticoagulant therapy in pediatric patients has been a concern at Necker Hospital for many years, with specific training given to all children receiving VKA and their parents. The training consists of information sessions on anticoagulant therapy. In most cases, the children and family members receive an education session on an INR self-measurement system. VKA initiation is performed according to the American College of Chest Physicians Antithrombotic and Thrombolytic Therapy recommendations. When stable INR is achieved, INR is measured at least every 15 days using an INR self-measurement system or at a licensed clinical laboratory. The INR value is given by phone to one of the referent physicians who adjusts the VKA dosage if needed. If a dosage adjustment is required, the INR is further determined at shorter intervals until stable anticoagulation is achieved again (defined in the previous paragraphs). In patients with INR values slightly above or under the therapeutic range, INRs are closely monitored before a dosage adjustment is required. Supratherapeutic INRs (>5) are managed according to expert recommendations. In the present study, INR values and the corresponding VKA dosages were prospectively recorded by physicians.

We also recorded demographic data (age, sex, height, and body weight) at the time of the maintenance dose, the indication for VKA therapy, and medications associated with the VKA once stable anticoagulation was achieved. The weekly maintenance dose was defined as the mean VKA dose (in milligrams) required to achieve stable anticoagulation (see previous paragraph). Body surface area (BSA) in square meters was computed as follows: BSA = [(4 × weight in kilograms + 7)/weight in kilograms + 90].

The times spent within, above, and below 3 prespecified INR ranges were determined using the Rosendaal method (ie, assuming a linear variation between 2 consecutive INR determinations). These ranges corresponded to INR values for which the physicians did not systematically perform a dosage adjustment. These 3 prespecified INR ranges were: 1.5-3.3 for the 2.2 INR target; 1.8-3.2 for the 2.5 INR target; and 2.5-4 for the 3.3 INR target.

The study was approved by the appropriate ethics committee (Comité de Protection des Personnes-Paris Ile de France IV). Written informed consent was obtained from each child’s parents or legal guardians in accordance with the Declaration of Helsinki.

Sample collection and genotyping

Blood or saliva samples were collected and analyzed at the biochemistry laboratory of the Georges Pompidou European University Hospital (Paris, France). Genomic DNA was extracted from peripheral blood leukocytes using the Blood DNA kit (QIAGEN) or from saliva using the Oragene Kit (Genotek) according to the manufacturers’ instructions. Genotyping was performed at the end of the study. Genotyping of the VKORC1-1639G > A promoter SNP (rs9923231) capturing most of the VKORC1 haplotypes was achieved using a real-time PCR allelic discrimination assay with a 7900HT Applied Biosystems thermal cycler. CYP2C9*2 (rs1799853, p.Arg144Cys), and CYP2C9*3 (rs1057910, p.Ile359Leu) alleles were identified using Taq Man Pre-Developed Assay Reagents (Applied Biosystems) for allelic discrimination. CYP4F2 rs2108622 genotyping (p.Val433Met) was also performed using an allelic discrimination assay with TaqMan technology (Applied Biosystems).

Statistical analysis

We coded CYP2C9 SNPs as follows: 0 in wild-type patients, 1 in patients heterozygous for CYP2C9*2 or CYP2C9*3, and 2 in patients homozygous for CYP2C9*2 or CYP2C9*3 or double heterozygous for both CYP2C9*2 and CYP2C9*3. This coding system allowed us to model additive allelic effects. Similarly, all other genotypes were coded 0 (wild-type), 1 (heterozygous), or 2 (mutant homozygous). Indications for VKA therapy were coded based on the 3 target INR groups. Finally, age, body weight, height, and BSA were handled as continuous variables.

Data were described as numbers and percentages for qualitative variables and mean (or median) and SD for quantitative variables. To assess relationships between the weekly maintenance VKA dose and covariates, we first performed a univariate analysis using the 2-sample Wilcoxon test or nonparametric ANOVA (Kruskal-Wallis test) for qualitative variables and the Spearman rank correlation coefficient for quantitative variables. Covariates with P values <.20 by univariate analysis were entered into a backward stepwise multiple linear regression model. Covariates with P values <.05 in this model were kept in the final model. The same statistical approach was used to evaluate times spent within, above, and below the INR range. Model accuracy was evaluated based on the proportion of individuals whose observed weekly warfarin dose differed by more than 7 mg from the weekly predicted dose. All tests were 2-sided, and P <.05 was considered significant. Computations were performed using the SAS Version 9 statistical package.

Results

Patient characteristics and maintenance dose

Between September 2009 and December 2010, we enrolled 120 unrelated patients. Two patients receiving acenocoumarol were not analyzed. The study population comprised 55 girls and 63 boys including more than 90% white and the median age was 9.0 years (range, 3 months-18 years). Of the 118 patients, 83 received warfarin and 35 received fluindione. Table 1 displays the mean VKA dose by age group and VKA type. In the 83 patients on
Table 2. Main characteristics of the 118 pediatric patients according to type of VKA and relationship between these characteristics and the VKA maintenance dose by univariate analysis

<table>
<thead>
<tr>
<th>Warfarin (n = 83)</th>
<th>Fludione (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N (%) or mean ± SD (range)</strong></td>
<td><strong>N (%) or mean ± SD (range)</strong></td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td><strong>P value</strong></td>
</tr>
<tr>
<td>Mean age, y, ± SD (range)</td>
<td>8.4 ± 5.6 (3 mo-18 y)</td>
</tr>
<tr>
<td>Sex, M/F, n</td>
<td>46/37</td>
</tr>
<tr>
<td>Weight, kg, mean ± SD (range)</td>
<td>29.5 ± 19.8 (3.5–81.5)</td>
</tr>
<tr>
<td>Height, cm, mean ± SD (range)</td>
<td>120.7 ± 33.4 (50–183)</td>
</tr>
<tr>
<td>Body surface area, m², mean ± SD (range)</td>
<td>0.97 ± 0.44 (0.22–1.94)</td>
</tr>
<tr>
<td>Associated medications, mean ± SD (range)</td>
<td>0.71 ± 1.54 (0–5)</td>
</tr>
<tr>
<td><strong>Target INR, n (%)†</strong></td>
<td><strong>&lt; .0001</strong></td>
</tr>
<tr>
<td>2.2</td>
<td>31 (37)</td>
</tr>
<tr>
<td>2.5</td>
<td>38 (46)</td>
</tr>
<tr>
<td>3.3</td>
<td>14 (17)</td>
</tr>
<tr>
<td><strong>VKORC1 genotype, n (%)</strong></td>
<td><strong>&lt; .0001</strong></td>
</tr>
<tr>
<td>GG</td>
<td>25 (30)</td>
</tr>
<tr>
<td>GA</td>
<td>43 (52)</td>
</tr>
<tr>
<td>AA</td>
<td>15 (18)</td>
</tr>
<tr>
<td><strong>CYP2C9 genotype, n (%)‡</strong></td>
<td><strong>.1582</strong></td>
</tr>
<tr>
<td>*1/*1</td>
<td>53 (64)</td>
</tr>
<tr>
<td>*1/x</td>
<td>25 (30)</td>
</tr>
<tr>
<td>*x/x</td>
<td>5 (6)</td>
</tr>
<tr>
<td><strong>CYP4F2 genotype, n (%)§</strong></td>
<td><strong>.5182</strong></td>
</tr>
<tr>
<td>CC</td>
<td>46 (57)</td>
</tr>
<tr>
<td>CT</td>
<td>26 (32)</td>
</tr>
<tr>
<td>TT</td>
<td>9 (11)</td>
</tr>
</tbody>
</table>

*By univariate analysis: association with the maintenance dose. Parameters with P values in bold were entered in the multivariate model.
†Target INR was 2.2 in patients with total cavopulmonary connection; 2.5 in those with aortic valve replacement, dilated cardiomyopathy, coronary aneurysms after Kawasaki disease, or extracardiac diseases; and 3.3 in those with mitral valve replacement.
‡CYP2C9 genotype: *1/*1, wild-type homozygotes; *1/x: CYP2C9*2 or CYP2C9*3 heterozygotes; and *x/x: CYP2C9*2 or CYP2C9*3 homozygotes or compound heterozygotes.
§NA indicates not applicable.

warfarin (median age, 9.0 years), the mean weekly maintenance dose was 23.2 ± 15.0 mg (range, 3.5-84 mg), which corresponded to 0.93 ± 0.55 mg/kg (range, 0.19-3.47 mg/kg). In the 35 patients on fludione (median age, 11.0 years), the mean weekly maintenance dose was 123.1 ± 52.2 mg (range, 45-250 mg), corresponding to 4.07 ± 2.68 mg/kg (range, 1.15-12.19 mg/kg). When the VKA dose was expressed relative to body weight (mg/kg), we found that very young patients, especially those younger than 3 years, required higher weekly doses than older patients (Table 1). Two patients were younger than 1 year of age (12 and 15 weeks).

The main characteristics of the 118 patients receiving warfarin or fludione are shown in Table 2. Overall, 38 patients had total cavopulmonary connection with a target INR of 2.2. Forty-nine patients had a target INR of 2.5; 16 had dilated cardiomyopathy, 6 had coronary aneurysms after Kawasaki disease, and 12 had extracardiac diseases (2 strokes with cyanotic congenital heart disease, 2 pulmonary arterial hypertension, 4 cardiac arrhythmias, 1 lupus, 1 antiphospholipid syndrome, 1 thrombosis with deepanocytosis, and 1 thrombosis with histiocytosis); 31 patients had mitral valve replacement with a target INR of 3.3.

The distribution of the VKORC1, CYP2C9, and CYP4F2 genotypes is shown on Table 2. The VKORC1 and CYP2C9 allele frequencies did not differ from those found in the general white population (Table 2).10 No significant deviation from the Hardy-Weinberg equilibrium was observed for any of the SNPs (P > .05; Table 2). The allele frequency of the CYP4F2 gene was as expected in the warfarin-treated group, with no significant deviation from Hardy-Weinberg equilibrium. In the fludione-treated group, allele frequency differed from that in the general population and there was a significant deviation from Hardy-Weinberg equilibrium, probably because of the small sample size (n = 35).

All patients receiving VKA for dilated cardiomyopathy were treated with β-blockers, conversion enzyme inhibitor, and spironolactone; in addition, some of them received furosemide or and digoxin if necessary. All patients treated for coronary aneurysms after Kawasaki disease received low doses of acetylsaliclic acid. No patient had amiodarine or antibiotics at the time of stable anticoagulation as defined above. In the overall cohort (n = 118), the mean number of medications per patient was 0.65 ± 1.46 (range, 0-5).

**Influence of nongenetic and genetic variables on maintenance dose in warfarin-treated patients**

**Univariate analysis.** By univariate analysis, the weekly warfarin maintenance dose (in milligrams) was strongly associated with age, weight, height, and BSA (P < .0001; Table 2). The relationship between dose in milligrams and height is shown in the supplemental Figure 1 (available on the Blood Web site; see the Supplemental Materials link at the top of the online article). Sex was significantly associated with the weekly warfarin maintenance dose (P = .0082; Table 2). Girls required significantly lower doses (mean, 19.3 ± 1.9 mg) than boys (mean, 27.1 ± 2.5 mg; P = .0246). Among warfarin-treated patients, those with a target INR of 2.2 (n = 31) had significantly lower mean weekly doses (18.5 ± 9.6 mg) than those in the other 2 INR targets (target INR of 2.5, n = 38, 26.1 ± 17.2 mg; and target INR of 3.3, n = 14, 27.5 ± 17.1 mg; Figure 1). Children carrying at least 1 VKORC1 variant allele required significantly lower doses than wild-type patients. A gene-dose
effect was observed: the weekly maintenance dose was 32.0/11006 3.6 in wild-type patients (GG), 23.0/11006 1.9 mg (28%) in heterozygotes (GA), and 10.6/11006 0.9 mg (67%) in mutant homozygotes (AA; *P*/11021 .0001; Figure 2A). There was a trend for an association (*P*/11005 .16) between the presence of 1 or 2 CYP2C9 variant alleles and a decrease in warfarin dose requirements (Figure 2B).

Multivariate analysis. By multivariate analysis, after statistical adjustment for potential confounding variables, *P*/11021 .05 for height, VKORC1 genotype, target INR, and CYP2C9 genotype (Table 3). The final model explained 69.7% of the overall interindividual variability in the warfarin dose (Table 3). Height accounted for 48.1% of the variability, VKORC1 genotype for 18.2%, target INR for 4.4%, and CYP2C9 genotype for 2.0%.

Stepwise linear multiple regression resulted in the following final model:

Dose in milligrams per week = (−10.77 + 0.28) × (height in centimeters − 5.44) × (number of VKORC1 variant allele) + 7.83 if target INR is 2.5 or 11.52 if target INR is 3.3−3.29 × (number of CYP2C9 variant alleles).

Accuracy of the model. Figure 3 shows the patient distribution according to the difference between the observed weekly maintenance dose and the maintenance dose predicted individually by the model. The difference was ≤ 7 mg/wk in 86.7% of patients; 8% of patients had observed doses at least 7 mg/wk higher than predicted and 5.3% had observed doses at least 7 mg/wk lower than predicted. Given the small number of patients younger than 1 year in our study, this model is probably not applicable in this age group.

Influence of genetic and nongenetic variables on maintenance dose in fluindione-treated patients

The VKORC1 genotype was the only variable significantly associated with the weekly fluindione maintenance dose (*P*/110363; Table 2). Because the CYP4F2 allele frequency differed from that in the general population, this variable was not entered into the statistical analysis. None of the nongenetic factors was significantly associated with the weekly fluindione maintenance dose (Table 2).

Times spent within, above, and below the prespecified INR ranges depending on INR target

Of the 118 patients, 92 had INR values collected routinely during the study period and the mean follow-up was 388 ± 229 days (29-776). Among them, the warfarin-treated patients (n = 61) spent 83.0% ± 14.6% (range, 45.9%-100%) of the time within the INR range for which no dosage adjustment was systematically performed, 9.6% ± 10.5% (range, 0%-34.3%) above this INR range, and 7.1% ± 8.9% (range, 0%-36.0%) below this INR range (Table 4). By univariate analysis, the only variable significantly associated with the time spent within the range was the target INR (*P*/110001). Patients for whom the target INR was of 2.2 spent significantly more time within the INR range than those with the other 2 INR targets (*P*/11001). Neither the univariate nor the multivariate analysis identified genetic or nongenetic factors associated with the time spent above or below the INR range.

The fluindione-treated patients (n = 31) spent 81.4% ± 15.7% (range, 36.5%-100%) of the time within the INR range,

![Figure 2](https://www.bloodjournal.org/pic/moreau_2012/f2a.png)

**Figure 2.** Weekly warfarin dose requirement (mg) by genotype. (A) VKORC1 genotype: GG wild-type homozygotes, GA heterozygotes, and AA homozygotes. (B) CYP2C9 genotype: *1/*1, wild-type homozygotes; *1/*x: CYP2C9*2 or CYP2C9*3 heterozygotes; and *x/*x: CYP2C9*2 or CYP2C9*3 homozygotes or compound heterozygotes. NS indicates nonsignificant.
Table 3. Final multivariate regression model for predicting the weekly warfarin maintenance dose

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient</th>
<th>SE</th>
<th>P</th>
<th>Univariate $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-10.77</td>
<td>4.44</td>
<td>&lt;.0001</td>
<td>0.481</td>
</tr>
<tr>
<td>Height, cm</td>
<td>0.28</td>
<td>0.028</td>
<td>&lt;.0001</td>
<td>0.182</td>
</tr>
<tr>
<td>Number of VKORC1 variant allele(s)</td>
<td>-5.44</td>
<td>1.41</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Target INR 2.2</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Target INR 2.5</td>
<td>7.83</td>
<td>2.08</td>
<td>&lt;.0001</td>
<td>0.019</td>
</tr>
<tr>
<td>Target INR 3.3</td>
<td>11.52</td>
<td>2.74</td>
<td>&lt;.0001</td>
<td>0.025</td>
</tr>
<tr>
<td>Number of CYP2C9 variant allele(s)</td>
<td>-3.29</td>
<td>1.55</td>
<td>.0370</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Target INR was 2.2 in patients with total cavopulmonary connection; 2.5 in those with aortic valve replacement, dilated cardiomyopathy, coronary aneurysms after Kawasaki disease, or extracardiac diseases; and 3.3 in those with mitral valve replacement.

Dose (mg/wk) = –10.77 + 0.28 × height (cm) – 5.44 × number of VKORC1 variant allele(s) + 7.83 (if target INR of 2.5) or 11.52 (if target INR of 3.3) – 3.29 × number of CYP2C9 variant alleles.

11.4% ± 11.6% (range, 0%-36.7%) above the INR range, and 7.7% ± 11.6% (range, 0%-61.7%) below the INR range. Neither the univariate nor the multivariate analysis identified genetic or nongenetic factors associated with the time spent within, above, or below the INR range.

Discussion

This study is one of the largest cohort studies assessing the impact of genetic and nongenetic factors on VKA dose requirements in pediatric patients with cardiac disease. Our study comprised 118 patients of median age 9 years who were receiving long-term VKA therapy mostly for cardiac disease. In the warfarin-treated patients, we showed that height, target INR, and the VKORC1 and CYP2C9 genotypes were significantly associated with dose requirements and explained 69.7% of the overall dose variability in the final model. In our model, nongenetic factors explained most of the variability, with height being the major contributor (48.1%).

To date, only the cohort study of Nowak-Göttl et al in white children assessed the relative impact of the VKORC1 and CYP2C9 genotypes in addition to age on VKA dose requirements.27 In this study, in which the main indication for warfarin therapy was venous thrombosis (INR range, 2-3), the multiple linear regression model of daily warfarin dose requirements (in milligrams/kilogram) explained 34% of the dose variability in the warfarin-treated group (n = 34; median age, 15 years).27 Age was by far the main factor (31.2%), with the VKORC1 and CYP2C9 genotypes accounting for only approximately 4% of the variability.27 In our study, age was strongly associated with the warfarin dose by univariate analysis, but was not significant in the final model, in which height explained most of the variability (48.1%). This apparent discrepancy may be related to the hypothesis made by Nowak-Göttl et al that age would be the single most important factor in VKA. Because age correlates strongly with weight and height in pediatric patients, Nowak-Göttl et al entered neither weight nor height into their model. However, weight and height can vary widely across children of the same age, depending on the combination of genetics, sex, cardiovascular disease, nutrition, physical activity, environmental factors, hormones, and lifestyle in each individual.1,2,31 Further, these variations in morphology are particularly frequent in the setting of congenital heart diseases with various physiologies. Therefore, we investigated not only age, but also weight and height. When we used the dose in milligrams/kilogram to build the final prediction model, height remained the main determinant of dose variability (data not shown). Finally, both the study by Nowak-Göttl et al and our study showed that the most important contributors to variations in warfarin dose requirements in pediatric patients are age or developmental changes related to age. Conversely, in middle-aged adults, demographic data such as age and body mass index explained less than 20% of the dose variability.6,7,9,13,32

In our cohort, the VKORC1 and CYP2C9 genotypes accounted for 18.2% and 2.0% of the warfarin dose variability, respectively. Interestingly, 2 small studies in Japanese patients also found a significant influence of VKORC1 on warfarin dose requirements.25,33 In 31 Japanese patients older than 12 years (median age, 22 years; body weight > 40 kg), Kosaki et al found that VKORC1 heterozygotes required higher warfarin doses (in milligrams) than VKORC1 mutant homozygotes after adjustment for the INR value (P = .003).25 In 48 Japanese children (mean age, 6.6 years), Kato et al reported that age and the VKORC1 genotype were the main factors affecting the relationship between the weight-normalized warfarin dose and the INR value.33 Nevertheless, the influence of the CYP2C9 genotype could not be evaluated in these Japanese studies because of the very low allelic frequency of CYP2C9 variants in this ethnic group.34 In the white pediatric sample studied by Nowak-Göttl et al, the VKORC1 and CYP2C9 genotypes explained only a very small part of the warfarin dose variability.

Table 4. Follow-up and percentage of time spent within, below, and above the INR range depending on INR target in warfarin-treated patients

<table>
<thead>
<tr>
<th>INR range</th>
<th>Follow-up, d, mean ± SD (min-max)</th>
<th>Time spent within the INR range, %, mean ± SD (min-max)</th>
<th>Time spent below the INR range, %, mean ± SD (min-max)</th>
<th>Time spent above the INR range, %, mean ± SD (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5-3.3 (n = 18)</td>
<td>285 ± 203 (29-571)</td>
<td>93.0 ± 9.5 (75.4-1)</td>
<td>4.2 ± 9.0 (0-34.5)</td>
<td>2.8 ± 3.9 (0-12.5)</td>
</tr>
<tr>
<td>1.8-3.2 (n = 14)</td>
<td>323 ± 220 (32-768)</td>
<td>83.5 ± 11.6 (56.4-1)</td>
<td>8.0 ± 8.1 (0-24.1)</td>
<td>8.5 ± 9.1 (0-28.7)</td>
</tr>
<tr>
<td>2.5-4.0 (n = 29)</td>
<td>511 ± 207 (80-776)</td>
<td>69.8 ± 13.6 (45.9-97.7)</td>
<td>9.3 ± 9.2 (0-35.9)</td>
<td>21.0 ± 10.1 (23.3-34.3)</td>
</tr>
<tr>
<td>Total (n = 61)</td>
<td>354 ± 226</td>
<td>83.3 ± 14.6</td>
<td>7.1 ± 8.9</td>
<td>9.6 ± 10.5</td>
</tr>
</tbody>
</table>
A limitation of our study is that most of the patients were whites and therefore our results may not apply to non-white children, because the allele frequencies of SNPs associated with warfarin dose requirements vary across ethnic groups. Another limitation is that the small number of fluindione-treated patients, which did not allow us to build a dose prediction model for fluindione. Finally, the patients spent more than 80% of the time within the INR range. This may have impaired our ability to identify factors that significantly influenced the times spent within, above, or below the INR range.

In conclusion, our study provides new information on the contribution of the VKORC1 and CYP2C9 genotypes to variations in warfarin response among children with cardiac disease. Our dosing model based on height, target INR, and VKORC1 and CYP2C9 genotypes predicted the warfarin dose within 7 mg/wk (1 mg/d) in 86.7% of patients. We are currently validating this model in a prospective cohort of children receiving warfarin therapy. Further work is needed to determine whether this model could minimize the risk of over- and under-anticoagulation, especially at the start of treatment and thus could improve the management of these patients.

Acknowledgments

The authors, particularly F.B., thank the French Federation of Cardiology and the French Society of Cardiology for financial support by the award “Bourse Épidémiologie-Prévention et Éducation Thérapeutique.”

Authorship

Contribution: C.M., F.B., D.L., D.B., and M.-A.L. designed and performed the research, analyzed the data, and wrote the manuscript; and V.S., J.-L.G., C.E., P.B., and R.C. analyzed the data and wrote the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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