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ORIGINAL ARTICLE

The impact of child-specific characteristics on warfarin dosing requirements

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Abstract

Background: The influence of child characteristics on warfarin dosing has been reported; however, there is no consensus on the nature and extent of this effect.

Objectives: To investigate the impacts of the demographic and clinical characteristics of children on the warfarin dose required to achieve a therapeutic international normalization ratio (INR).

Methods: This retrospective cohort study included children aged 3 months to 14 years old who were prescribed warfarin for 3 months or longer with a "stable INR." The primary outcome was the total daily dose (TDD) and total weekly dose of warfarin required to achieve a therapeutic INR target.

Results: We included 127 patients with a mean age of 7.7 ± 3.7 years and a median weight of 22 (IQR, 16-33) kg. Of the sample, 55 patients (43.3%) required a TDD of ≤0.1 mg/kg. The TDD for children younger than 5 years, 5 to 10 years, and older than 10 years were 0.14 ± 0.06 mg/kg, 0.12 ± 0.05 mg/kg, and 0.096 ± 0.04 mg/kg, respectively (P = .002). Overweight and obese children required a smaller TDD than normal-weight children: 0.09 ± 0.05 vs 0.13 ± 0.05 mg/kg (P = .004), which was similar for underweight children. A lower body surface area (<0.5 m^2) required a higher dose. All the other variables did not affect warfarin doses. The incidence of a subtherapeutic or supratherapeutic INR was independent of demographic or clinical variables.

Conclusion: The study confirmed that the patient demographics affect the daily warfarin dose required to achieve the INR target. However, they do not have any predictive value for the incidence of out-of-range-INR.

KEYWORDS
anticoagulation, characteristics, children, international normalized ratio, pediatric obesity, warfarin

Essentials

- We know little about how a child's characteristics affect how much warfarin they need.
- Children who were taking warfarin and whose laboratory tests were stable were studied.
- Younger and smaller children need more warfarin per bodyweight than older and larger children.
- Overweight and obese children need less warfarin than children of normal weight.

1 | INTRODUCTION

Warfarin, an oral anticoagulant, is a racemic mixture of 2 isomers: R-isomer and the more potent S-isomer. It exerts its effect by inhibiting vitamin K activation, which results in the production of partially decarboxylated and diminished efficacy of clotting factors II, VII, IX, and X by the liver. After oral administration, warfarin is absorbed from the gastrointestinal tract immediately and completely, thus yielding a high serum bioavailability. S-warfarin is a substrate of cytochrome P450 2C9 (CYP2C9) isoenzyme and is transformed into inactive metabolites [1–3].

Bleeding is the main concern associated with the use of warfarin. The risk of major bleeding is reported as 0.5% per patient-year, with a higher risk (3.2% per person-year) reported when a higher international normalization ratio (INR) is targeted. Other side effects include skin necrosis, osteoporosis, cholestatic jaundice, hepatitis, vasculitis, nausea and vomiting, and hair loss [2,3].

The effect of the CYP2C9 and vitamin K epoxide reductase (VKORC1) polymorphisms on interpatient warfarin dosing variability is well-documented [4–7]. However, the pharmacogenomic dosing of warfarin is not widely used despite the addition of pharmacogenomic-based dosing to the product labeling after approval in 2010 by the U.S. Food and Drug Administration [8]. This may be due to the high cost and limited availability of genetic testing, in addition to equivocal data regarding this issue [9]. The actual bodyweight is currently used for warfarin dosing in children despite the lack of an established relationship between the weight and amount of warfarin required to achieve the INR target. In practice, warfarin is used for the prevention and treatment of thromboembolic disorders at a standardized pediatric dose of 0.1 mg/kg/d. Some clinicians start with a loading dose of 0.2 mg/kg; however, these strategies may not always be appropriate in the case of liver and renal insufficiency or with a high baseline INR [10].

The influence of other demographic characteristics, including gender, height, body mass index (BMI), and body surface area (BSA), are described in the literature. However, there is no consensus on the nature and magnitude of these effects. In a prospective study, age was the most important factor influencing warfarin dosing in pediatrics [11,12]. Children younger than 1 year required a higher warfarin dose, a longer time to achieve a therapeutic INR, and more dose adjustments than older children. In addition, the warfarin doses of pediatric patients with a BSA < 1 m^2 were higher than in those with a BSA > 1 m^2 (0.16 ± 0.08 mg/kg vs 0.09 ± 0.04 mg/kg) [11]. In a review of 32 studies that included pediatric and adult patients, 29 reported a correlation between bodyweight or BSA and the warfarin dose requirement [13]. In Japanese adult patients, multivariate analysis revealed that bodyweight and age had independent and significant contributions to the overall variability in warfarin dosing [14]. Another retrospective study reported that in addition to age, genetic factors could explain 53% of the variability in the stable dose of warfarin [8]. In contrast to earlier findings, however, a prospective study observed a negative correlation between a stable warfarin dose and gender, age, weight, height, and BSA [15].

Although many studies examined the effect of patient characteristics on the warfarin dose required to achieve the INR target, the findings are inconsistent. We performed a retrospective study to investigate the effect of the child-specific demographic and clinical characteristics on the warfarin dose required to achieve the therapeutic INR target, determine the optimum maintenance warfarin dose for different age groups, and predict factors associated with out-of-range-INR (ORI). We hypothesized that child-specific characteristics determine the amount of warfarin required and affect the incidence of ORI.

2 | METHODS

2.1 | Design and settings

We conducted a retrospective cohort study of children who received long-term warfarin at the pediatric Anticoagulation Clinic (ACC), King Abdulaziz Medical City in Riyadh, an academic, tertiary, and Joint Commission International-accredited health care center. The pediatric ACC is located within the Cardiac Ambulatory Care Center and is managed by pediatric anticoagulation-trained clinical pharmacists. The clinic provides services to patients younger than 15 years old who are referred for anticoagulation follow-up and management. Coagulation testing can be performed in the main hospital laboratory or the clinic using point-of-care monitoring. The clinic visit is usually 20 minutes, during which the clinical pharmacist manages the anticoagulant medication, screens for noncompliance and complications, provides education, and refers the patient to any specialty whenever needed. All interventions are based on the institutional anticoagulation guidelines and documented in a built-in ACC note template in the hospital's electronic health information system.

2.2 | Ethical considerations

The study was approved by the institutional review board of the King Abdullah International Medical Research Center, Riyadh, Saudi Arabia

(RC17/135/R). Patient consent was not required since this was a retrospective study.

2.3 | Participants

Eligibility criteria included age from 3 months to 14 years, warfarin use for any indication, and a "stable INR," defined as an INR within the therapeutic range (INR ranges 2-3 or 2.5-3.5) for at least 3 consecutive visits, with 1 to 12 weeks between visits, without a dose change. If the last INR reading was not within the therapeutic range, the data collector could go back and identify a therapeutic INR reading within the study period that met the definition of "stable INR."

We excluded participants without documented routine pediatric ACC follow-up due to noncompliance, no "stable INR," used medication with a known effect on the INR, or a condition affecting the INR or warfarin action (eg, liver or kidney failure and hypo- or hyperthyroidism).

2.4 | Sample size

Considering the warfarin total daily dose (TDD) a continuous variable, a multivariate linear regression model could be used to determine the independent effect of each of the factors in terms of the outcome. In this case, the minimum required sample size for the multiple linear regression was 84. This was calculated based on an anticipated medium effect size of 0.15, number of predictors = 4, statistical power of 0.8, and probability of type I error of 0.05.

2.5 | Outcome measures

Once a "stable INR" reading was identified, the data were retrospectively collected. Demographic data (ie, gender, age, weight, height, BSA, and BMI), comorbid diseases, and concomitant medications affecting INR were recorded. The variables related to the warfarin therapy included primary indication, dosing regimen (daily vs alternating), TDD, the stable INR reading, and the ORI of ≤1.7 or ≥3.3 and ≤2.2 or ≥3.7 for the target INR of 2 to 3 and 2.5 to 3.5, respectively. We also collected complications (eg, thrombosis or bleeding) recorded during the year preceding the stable INR. The primary outcome was the TDD and total weekly dose (TWD) of warfarin required to achieve the therapeutic INR target. The secondary outcomes were to predict the appropriate warfarin dose in relation to the demographic and clinical characteristics and to determine the factors associated with ORI.

2.6 | Statistical analysis

We used SPSS statistics software version 21 (IBM) for analysis. The data are presented as frequency and percentage for the categorical variables and as mean ± SD for the continuous variables. Data without a normal distribution are expressed as median and IQR. The continuous variables were compared using a paired Student's *t*-test or Mann–Whitney U-test for the nonparametric variables whenever needed, and the categorical variables were compared using a chi-squared test or Fisher's exact test as appropriate. A 1-way analysis of variance was used to identify the significant difference in the means between more than 2 groups. A *P* value of ≤.05 was considered statistically significant.

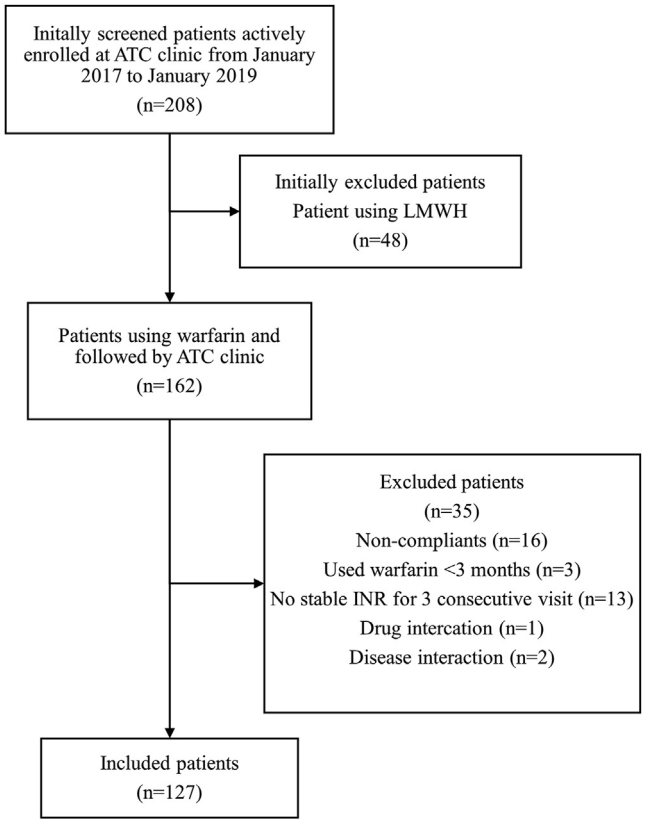

FIGURE 1 Patient enrollment flow diagram. ATC, anticoagulation; INR, international normalization ratio; LMWH, low-molecular-weight heparin.

3 | RESULTS

After excluding noneligible participants (*n* = 35), 127 patients were included (Figure 1). The baseline characteristics are summarized in Table 1. The mean age was 7.7 ± 3.7 years. Based on the weight categories, 75 patients (59.1%) had a normal weight, 30 (24%) were underweight, and 22 (17%) were overweight or obese. The primary indication for warfarin was thromboprophylaxis post total cavopulmonary connection (TCPC; "Fontan") procedure in 83 (65%) patients and post mechanical heart valve replacement in 28 (22%) children. Other indications are listed in Table 1. Thirty-six (28%) of the patients experienced a supratherapeutic INR, and 52 (41%) had a subtherapeutic INR during the year preceding the date of enrollment.

The INR target range was between 2 and 3 for 110 (87%) patients and 2.5 and 3.5 for 17 (13%) patients. Eighty-two (65%) patients were

TABLE 1 Characteristics of the study sample.

	Mean ± SD/median (IQR)/*n* (%)
Demographics	
Age (y)	7.7 ± 3.7
Weight (kg)	22 (16-33)
Height (cm)	123 ± 22
BMI (kg/m^2)	16 (14-17)
BMI percentile (%)	41 ± 35
BSA (m^2)	0.87 (0.7-1.14)
Gender	
Male	72 (57)
Female	55 (43)
Weight category[a]	
Underweight	30 (24)
Healthy weight	75 (59)
Overweight	10 (8)
Obese	12 (9)
Indication of warfarin	
Nonfenestrated Fontan	47 (37)
Fenestrated Fontan	36 (28)
High-risk Glenn	8 (6)
Mechanical mitral valve	17 (13)
Mechanical aortic valve	11 (9)
Others[b]	8 (6)
Aspirin use	3 (2.4)
History of ORI during the last year	
Supratherapeutic INR (≥3.3)	36 (28)
One event	20 (56)
2-3 events	12 (33)
>3 events	4 (11)
Subtherapeutic INR (≤1.7)	52 (41)
1 event	26 (50)
2-3 events	17 (33)
>3 events	9 (17)

BMI, body mass index; BSA, body surface area; INR, international normalization ratio; ORI, out-of-range-INR.
[a]Weight category is based on the Centers for Disease Control and Prevention chart: Weight-for-length percentiles for children ≤24 months (<5th: underweight; 5th to <95th: healthy weight; ≥95th: overweight) and BMI percentiles for children >24 months (<5th: underweight; 5th to <85th: healthy weight; ≥85th to < 95th: overweight; ≥95th: obese).
[b]Includes Kawasaki disease (*n* = 3), venous thromboembolism (*n* = 3), stroke, and intracardiac thrombi (*n* = 3).

on an equal daily regimen, and the rest on an alternating regimen during the week. The highest proportion (43.3%, *n* = 55) required a total daily maintenance warfarin dose of 0.1 mg per bodyweight or less to achieve their INR targets. A small proportion (9%, *n* = 12) required a maintenance dose of more than 0.2 mg/kg/d. Almost half (48%, *n* = 60) required a total daily maintenance warfarin dose of 0.1 to 0.2 mg/kg/d. The TWD of warfarin was 20 ± 10.25 mg (range, 6-49). More data on dosing requirements are presented in Table 2.

TABLE 2 Warfarin therapy.

	N (%)
INR target	
2-3	110 (87)
2.5-3.5	17 (13)
Regimen	
Daily regimen	82 (65)
Alternating regimen	45 (35)
Dose (mg/kg/d)	
≤0.1	55 (43)
>0.1-0.15	34 (27)
>0.15-0.2	26 (21)
>0.2	12 (9)
Daily dose (mg)	**Mean ± SD**
TDD	2.86 ± 1.48
per BW (kg)	0.12 ± 0.05
per BMI	0.18 ± 0.09
per BSA	3.11 ± 1.29
Weekly dose (mg)	
TWD	19.99 ± 10.25
per BW (kg)	0.83 ± 0.38
per BMI	1.23 ± 0.6
per BSA	21.75 ± 9

BMI, body mass index; BSA, body surface area; BW, bodyweight; INR, international normalization ratio; TDD, total daily dose; TWD, total weekly dose.

Patient-specific characteristics and the TDD of warfarin are displayed in Figure 2. The maintenance TDD of warfarin was higher in younger and smaller children. The TDD for the groups younger than 5 years, 5 to 10 years, and older than 10 years were 0.14 ± 0.06, 0.12 ± 0.05, and 0.096 ± 0.04 mg/kg/d, respectively (P = .002). The dose for patients weighing <20 kg was 0.14 ± 0.05 mg/kg/d compared with 0.06 ± 0.02 mg/kg/d in the group weighing >60 kg (P = .001). Overweight and obese children required a smaller dose than normal-weight children (0.09 ± 0.05 vs 0.13 ± 0.05 mg/kg/d, P = .004), with underweight children requiring the same dose as normal-weight children (0.127 ± 0.05 vs 0.13 ± 0.05 mg/kg/d, P = .9). Furthermore, children with a BSA < 0.5 m^2 required a higher maintenance TDD than those with a BSA between 0.5 to 1 m^2 or >1 m^2 (0.20 ± 0.04, 0.12 ± 0.05, and 0.09 ± 0.04 mg/kg/d, respectively; P = .0001). Compared to patients with non-Fontan circulation, the Fontan group required a

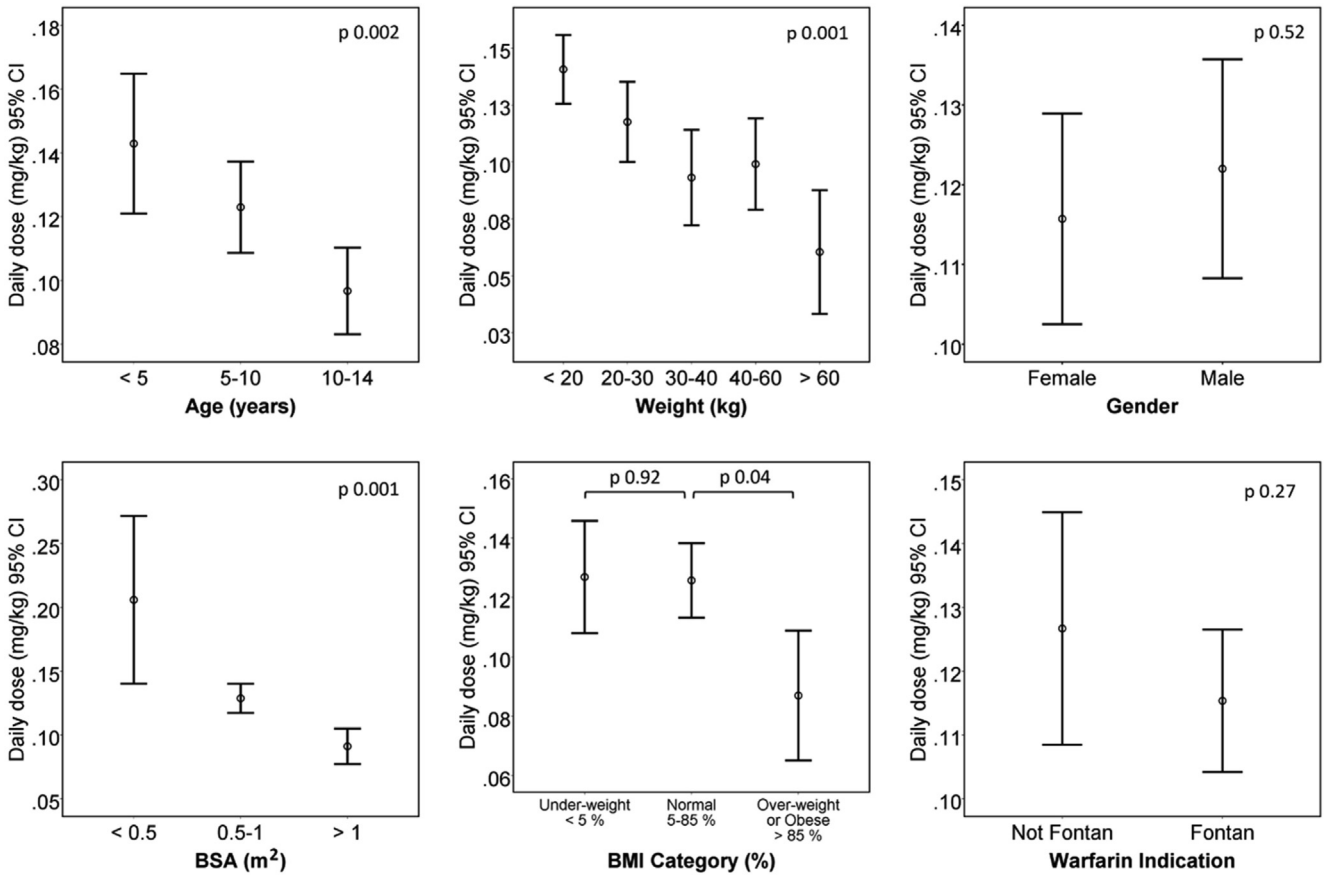

FIGURE 2 Patient-specific characteristics and total daily dose of warfarin. BMI, body mass index; BSA, body surface area.

similar amount of warfarin to achieve the INR targets (0.12 ± 0.05 vs 0.13 ± 0.06 mg/kg/d, P = .27).

Patient-specific characteristics and the TWD are summarized in Figure 3. The older and heavier the children, the more TWD they required. Underweight patients required lower TWD than normal-weight children (16 ± 8 vs 21 ± 10 mg/wk; P = .018); however, obese and normal-weight children had a similar TWD. There was no difference in warfarin doses for children with lower INR (2-3) and higher INR (2.5-3.5) targets (TDD 0.12 ± 0.05 vs 0.11 ± 0.06 mg/kg/d; P = .64 and TWD 20 ± 10 vs 21 ± 12 mg/wk; P = .65).

To identify the predictors of ORI, we compared the demographic and clinical characteristics of the group with at least 1 ORI to the no-ORI group in the year preceding enrollment (Supplementary Table). Neither demographic nor clinical characteristics had any statistically significant predictive value on the incidence of ORI. The occurrence of ORI was independent of gender, age, weight, obesity, underweight, alternating or daily regimen, TDD, and TWD.

Major bleeding was reported in 3 patients who were taking an average daily dose of 0.14 mg per total bodyweight (mean TWD was 24.8 ± 15.6 mg). Of this group, 2 children were underweight, and the bleeding events occurred with an INR at the target level. A stroke was reported in 1 obese child who had her warfarin discontinued after completing 2 years of thromboprophylaxis.

4 | DISCUSSION

The variability in patient demographics and genetics modulates warfarin dosing requirements in adults; however, less is known about their effect on children. This is the first study to concomitantly shed light on the impact of major demographic and clinical variables in children related to warfarin dosing. In this study, the effect of the demographic variables (ie, gender, age, weight, BSA, BMI percentile, and being a patient with Fontan circulation) on the warfarin TDD and TWD required to achieve therapeutic INR targets and the incidence of ORI was studied. Age, weight, and BSA significantly modulated the daily requirements of warfarin, but the TWD was only affected by age and weight. The occurrence of ORI was independent of the studied variables.

Warfarin is the preferred agent for long-term (>3 months) anti-coagulation in children after therapy initiation with heparinoids [16]. Several factors increase the odds of a supratherapeutic INR, including the length of hospital stay, cardiac surgery, elevated baseline INR, obesity, and Asian ethnicity [17,18]. However, none of these variables affected the occurrence of ORI in the present study. Similarly, in the study by Moffet and Bomgaars [19], no difference in the occurrence of a supratherapeutic INR was reported between obese and nonobese children. The recommended initial dose of warfarin for infants and

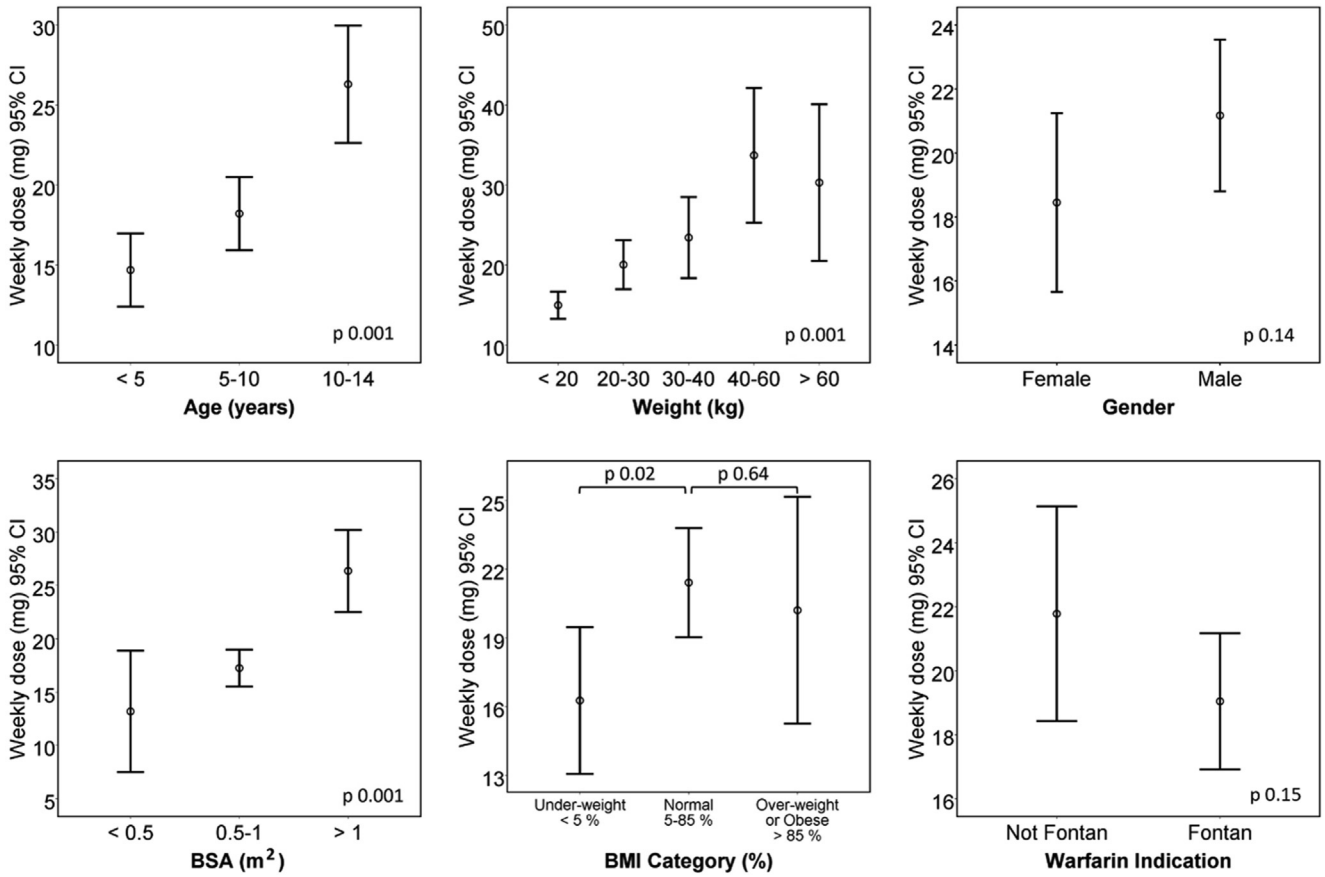

FIGURE 3 Patient-specific characteristics and total weekly dose of warfarin. BMI, body mass index; BSA, body surface area.

children to provide adequate anticoagulation, free of significant adverse effects, is 0.1 mg/kg/d [20]. In this study, the mean provided dose was 0.12 ± 0.05 mg/kg/d, which is in line with the stated recommendations; however, 12% of the patients required a dose greater than 0.2 mg/kg/d.

In the cohort study by Streif et al. [11], the required warfarin doses were inversely correlated with age, though no clear mechanisms were established. Similarly, according to Bonduel [21], increased warfarin doses were required for infants younger than 12 months to attain the therapeutic target INR. Although the mean plasma concentrations of unbound S-warfarin were comparable between prepuberty (1-11 years) and postpuberty (12-17 years), significantly higher INR levels were reported in prepubertal patients who may be more sensitive to the effects of warfarin [22]. Similarly, in the Absher et al. [23] study, males required higher doses. Gender, however, had no significant effect on the TWD in the Khoury and Taha [24] and Whitley et al. [25] studies (P = .281), similar to the findings of our study. Kendrick et al. [26] reported that obese children required lower doses of warfarin per kilogram than normal-weight children. In the Moffet et al. [19] study, obese children required lower empiric and adjusted warfarin doses but a longer time to therapeutic INR compared with normal-weight children. One suggested mechanism is that the weight increase in obese patients is associated with an increase in the volume of distribution and clearance of warfarin, mandating increased doses [11].

Other variables with a potential impact on the TWD in the Whitley et al. [25] study were the use of a CYP450 inducer and the patient's height and ethnicity, all of which would necessitate a higher TWD. Negative correlations were also observed between the required warfarin dose and age, weight, height, and BSA in the Nguyen et al. [15] study. However, factors that did not affect warfarin dose comprised CYP2C9 polymorphism, gender, race, congenital heart disease, and Fontan physiology.

Crone et al. [27] reported that pediatric patients required significantly lower doses of warfarin following the Fontan procedure compared with the recommendations in clinical practice guidelines. One factor that can explain this discrepant finding is the use of maintenance fluids and patient immobility. However, our study indicated that patients with Fontan circulation should be dosed with warfarin the same as others. It is worth mentioning that the alternating regimen doses did not affect patients' compliance, instruction comprehension, or the dynamics of warfarin. The group receiving alternating regimen doses did not significantly differ from those receiving a daily regimen.

Bleeding is the most frequent side effect associated with the use of warfarin. The risk of bleeding is increased by a patient's genetic

profile, drug interactions, and indications that mandate higher target INR values [18]. Moffett et al. [18] reported the Asian race, mitral valve replacement, levofloxacin or lansoprazole use at discharge, and length of hospital stay as significant predictors for bleeding. In this study, however, major bleeding was independent of any of these factors; notably, it was reported in patients taking an average daily dose of 0.14 mg/kg. Yet, despite the risk of bleeding, warfarin is considered the preferred option for long-term anticoagulation.

4.1 | Limitations

The primary limitation of our study is that the majority of the sample are children with cardiac issues, mainly postcardiac surgery. This was expected since warfarin in pediatric patients, unlike adult patients, is mainly indicated for the prevention of thrombosis after various cardiac surgeries. In addition, all our participants were from a single tertiary care center in a high-income country with comprehensive governmental health care services and a predominantly Middle Eastern population. Thus, detailed information on race and ethnicity was not collected. Although this might have advantages of increasing the homogeneity of the data and ensuring equal care for all participants, this may limit the generalizability of the study finding. In our study, we did not include CYP2C9 or VKORC1 polymorphism as a factor affecting the warfarin requirements, although the mutations in these genes were proven to influence the patient's sensitivity to vitamin K antagonists. Therefore, it was difficult to comprehensively address the interindividual differences in warfarin doses associated with pharmacogenomic variability. Because of the retrospective nature of our study and its focus on certain demographic and clinical data, only a subset of INR was collected. Consequently, the time within the therapeutic range that needs serial INR reading could not be calculated. Finally, incomplete documentation limited our ability to collect data on some factors known to influence warfarin response that may be potential confounders, including INR testing methods, food-warfarin interactions, and vitamin K intake.

5 | CONCLUSIONS

The most appropriate maintenance dose for general pediatrics was 0.1 mg/kg/d or less. Younger and smaller children and the group with a lower BSA required a higher maintenance daily dose of warfarin per bodyweight. Overweight and obese children required a lower dose of warfarin than normal-weight children. These observations suggest that doses for the general pediatric population are not always appropriate for an overweight or obese child, which can be reduced by approximately 30% to 40% to avoid overanticoagulation.

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ETHICS STATEMENT

This study was approved by the institutional review board of the King Abdullah International Medical Research Center, Riyadh, Saudi Arabia (RC17/135/R). Patient consent was not required since this was a retrospective study.

AUTHOR CONTRIBUTIONS

Y.S.A and A.M.Z.J. conceptualized and designed the study and analyzed and interpreted the data. N.S.B. and M.F.A. generated the data and drafted the manuscript. N.A.A., J.A.G., and M.A.A. reviewed the manuscript. All authors contributed to the final version of the article. The authors read and approved the final manuscript.

RELATIONSHIP DISCLOSURE

The authors have no conflicts of interest to declare with respect to the research, authorship, and/or publication of this article.

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SUPPLEMENTARY MATERIAL

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