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Effect of chronic kidney disease on warfarin responsiveness among Thai patients

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ABSTRACT

This study aims to determine the effect of chronic kidney disease on warfarin response, including initial doses, maintenance doses, time in therapeutic range (TTR), and international normalized ratio (INR) variability. This is a retrospective cohort study at Rajavithi Hospital from 2015 to 2018. A total of 189 patients were included and divided into five groups based on estimated glomerular filtration rate (eGFR) (G1, eGFR ≥ 60 mL/min/1.73 m^2; G2, 30–59 mL/min/1.73 m^2; G3, 15–29 mL/min/1.73 m^2; G4, ≤ 15 mL/min/1.73 m^2; and G5, ≤ 15 mL/min/1.73 m^2 with dialysis). The median age was 65.00 years, and 60.9% of patients were female. The median (interquartile range) of initial warfarin doses were 17.50 (14.0, 21.0) mg/week, and average doses for achieved target INR were 19.00 (14.0, 25.0) mg/week in all groups. The initial warfarin doses were not different among groups but the maintenance doses were significantly different (P = 0.001). The median of INR variability was 0.16, which was not significantly different and TTR was 69.00%. Patients with CKD used lower average targeted doses of warfarin and had lower TTR than those with normal renal function. Interestingly, this study revealed that eGFR ≥60 ml/min/1.73 m^2 and female sex affected TTR by more than 60%.

Keywords: International normalized ratio variability, international normalized ratio, renal impairment, time in therapeutic range, Warfarin

INTRODUCTION

Warfarin is an oral anticoagulant that has been used for the primary and secondary prevention of systemic thromboembolism in various indications, including atrial fibrillation (AF), prosthetic valve replacement, venous thromboembolism (VTE), and protein C or protein S deficiency.[1] Several factors can affect an individual's response to warfarin, such as genetic polymorphisms, weight, various diseases or conditions (e.g., liver disease, congestive heart failure, hypoalbuminemia, thyroid dysfunction, and malignancy), high Vitamin K consumption, and drug-drug or drug-herb interactions. Unfortunately, studies on the effects of interaction in chronic kidney disease (CKD) on warfarin response are limited since several studies excluded patients with CKD.[2]

The previous studies suggested that kidney function is associated with warfarin response.[3,4] Most patients with CKD used initial and maintenance doses of warfarin less than those without CKD.[3] Reduced kidney function is classified by estimated glomerular filtration rate (eGFR) correlated with bleeding and lower warfarin doses.[3,4] Thus, the trend of time in the therapeutic range (TTR) was low in patients with CKD.[2,4] CKD had risks of hemostatic disorders that can cause abnormal bleeding. Because renal insufficiency causes platelet dysfunction, glycoprotein IIb/IIIa receptors' expression is decreased on the platelet surface that may cause abnormal hemostasis. Furthermore, patients with CKD who undergo hemodialysis (HD) often receive heparin to prevent blood clotting during dialysis and accumulation of drugs due to insufficient clearance in end-stage renal disease (ESRD patients.[5,6] Furthermore, ESRD may decrease warfarin metabolism because cytochrome P450 (CYP450) through 2C9 has reduced expression.[7] However, CKD increases the risk of thrombotic events.[8]

Thailand is a developing country in Asia with many patients with CKD.[9] Almost 18% of Thai people have been diagnosed with CKD, 8.6% of those have been identified CKD

Stages 3–5, and over 0.1 million require dialysis, including HD or peritoneal dialysis (PD).[10,11] At present, warfarin is generally prescribed in patients with CKD, similar to those without CKD. The previous studies reported the effect of CKD or dialysis on warfarin response among the Caucasian population, but data are in Asian countries, including Thailand, is still limited.[4,12,13] This descriptive study aims to determine the initial and maintenance doses of warfarin in patients with CKD, including the relationship between the international normalized ratio (INR) variability and TTR in patients with CKD using warfarin.

MATERIALS AND METHODS

Study Design and Population

This retrospective and cohort study was conducted in patients who received warfarin to prevent thromboembolic events for various indications at the Rajavithi Hospital, a tertiary care hospital in Bangkok, Thailand, between January 2016 and January 2018. Patient data were retrieved from an electronic medical database at the study hospital. Eligibility requirements at the screening included age ≥18 years and follow-up at Rajavithi Hospital for at least two continuous years. Patients were excluded if they were transferred to other hospitals and did not undergo INR monitoring. Included patients were classified into CKD stages by eGFR at the first visit or eGFR at the time close to warfarin initiation. After that, we followed up whether INR values were still within the INR target ranges. The present study was approved by the Ethics Committee of Rajavithi Hospital (reference number: 058/2562).

Data Collection and Definitions

Patient demographic data were collected for each patient: Age, sex, comorbidities, a warfarin indication, initiated doses of warfarin, INR values, and laboratory data. CKD was diagnosed using the International Classification of Diseases Thai modification 10 ([N181; CKD Stage 1], [N182; CKD Stage 2], [N183; CKD Stage 3], [N184; CKD Stage 4], and [N185; CKD Stage 5]). Patient profiles were available from the central laboratory department's electronic reports and linked to other patient data by the patient unique identification number. TTR was calculated using the Rosendaal method, which uses linear interpolation to assign an INR value to each day between successive observed INR values.[14] We calculated the percentage of time during which the interpolated INR values between 2.0 and 3.0.[15,16] The INR variability was calculated by Fihn's method, reflecting the degree of instability of the INR control from TTR.[17] This formula is provided in Figure 1.[18]

The CKD epidemiology collaboration equation was used to calculate eGFR. We categorized the patients into five groups based on eGFR at the first doses of warfarin, which were classified as G1, eGFR ≥ 60 mL/min/1.73 m^2; G2, eGFR = 30–59 mL/min/1.73 m^2; G3, eGFR = 15–29 mL/min/1.73 m^2; G4, eGFR < 15 mL/min/1.73 m^2; and G5, eGFR < 15 mL/min/1.73 m^2 with HD or PD.[2]

$$\text{INR variability} = \frac{1}{n}\sum_{i=1}^{n}\frac{\left(INR_i - \ average\ INR\right)^2}{\left(time\ in\ week\ between\ INR\ measurements\right)_i}$$

Figure 1: Fihn's method formula[18] (n, number of all INR measurements when the course of therapy was terminated, average INR, 2.5 if INR target 2.0–3.0 and 3.0 if INR target 2.5–3.5)

Statistical Analyses

Descriptive statistics were used in the present study. The data were analyzed using the Statistical Package for the Social Sciences statistics version 27.0. (IBM Corp, Armonk, NY). All variables were analyzed using descriptive statistics to determine the frequencies with percentages for categorical variables. In contrast, continuous variables were expressed in mean ± standard deviation or median with interquartile range (IQR). Comparisons of initial doses of warfarin, maintenance doses of warfarin, INR variability, and TTR between each stage of CKD were performed using the Kruskal-Wallis test or one-way ANOVA depending on the data distribution. Logistic regression was used to determine the relationship between TTR and INR variability in each stage of CKD.

RESULTS

Between January 2016 and January 2018, a total of the 189 eligible participants were included in this study; 43.9% (83/189) in the G1 group, 45.5% (86/189) in the G2 group, 4.2% (8/189) in the G3 group, 2.1% (4/189) in the G4 group, and 4.2% (8/189) in the G5 group. All patients in the G5 group needed HD. The G1 to G5 groups comprised patients whose ages ranged from 19 to 99 years, the median (IQR) of age was 65.00 (IQR 52.75) years, and 60.9% of patients were female. Non-valvular AF, VTE, mechanical valve replacement, and valvular AF were indications for warfarin use in 51.9%, 22.8%, 21.7%, and 3.7%, respectively. The target range of INR is 2.5–3.5 for mechanical valve replacement in the mitral position and the aortic position with conditions (e.g., AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions or an older generation mechanical AVR (such as ball-in-cage) and 2.0–3.0 for AF, VTE, and mechanical valve replacement in an aortic replacement position without a condition.[1,19,20]

Hypertension (47.1%), dyslipidemia (21.5%), and diabetes mellitus (18.2%) were the three most common comorbidities. The patients' baseline characteristics who used warfarin in each stage of CKD are provided in Table 1.

The initial warfarin dose, referring to the first dose that was started at Ratvithi Hospital, was 17.5 (IQR 14.0, 21.0) mg/week. However, there was no significant difference (P = 0.094) in each stage. The maintenance dose that led to therapeutic INR achievement was 19.0 (IQR 14.0–25.0) mg/week [Table 2].

The INR variability was calculated using Fihn's method, which was 0.16 (IQR 0.04, 0.3). Therefore, the TTR in our study was 69.00% (IQR 43.5, 87.0), which was calculated using the Rosendaal method. The TTR in patients in the G1 group and G2 group was statistically significant (P = 0.006). INR variability and TTR in each stage of CKD are provided [Table 2].

Although the use of TTR might have some limitations, this parameter is still used to evaluate the efficacy of warfarin. Thus, we tested the factors related to TTR ≥ 60%. The results from the relationship of factors and TTR ≥ 60% in the multivariate analysis are shown in Table 3. eGFR ≥ 60 ml/min/1.73 m^2 (odds ratio [OR], 3.44: 95% confidence interval [CI] 1.35–8.73, P = 0.009) and female (OR, 0.32: 95% CI, 0.13–0.76: P < 0.011).

Table 1: Demographic data of patients (n=189)

Variable	Overall; *n* (%)	Classified by eGFR; *n* (%)				
		G1	G2	G3	G4	G5
Number of patient (%)	189 (100)	83 (43.9)	86 (45.5)	8 (4.2)	4 (2.1)	8 (4.2)
Age (median (IQR); year	65 (52.0, 75.0)	53 (44.0,63.0)	73 (65.8, 81.0)	76.50 (70.3,82.5)	65.5 (55.8, 83.5)	51.5 (44.3, 65.8)
Gender (%)						
Male	74 (39.2)	32 (16.9)	33 (17.5)	5 (2.7)	1 (0.5)	3 (1.6)
Female	115 (60.9)	51 (26.9)	53 (28.0)	3 (1.6)	3 (1.6)	5 (2.7)
Indication of warfarin (%)						
Non-valvular AF	98 (51.9)	24 (12.7)	57 (30.2)	7 (3.7)	4 (2.1)	6 (3.2)
Valvular AF	(3.7)	4 (2.1)	3 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Mechanical valve replacement	41 (21.7)	28 (14.8)	12 (6.4)	0 (0.0)	0 (0.0)	1 (0.5)
VTE	43 (22.8)	27 (14.3)	14 (7.4)	1 (0.5)	0 (0.0)	1 (0.5)
Comorbidities (%)						
Hypertension	57 (47.1)	11 (9.1)	36 (29.8)	6 (4.9)	2 (1.7)	2 (1.7)
Diabetes mellitus type 2	22 (18.2)	4 (3.3)	13 (10.7)	2 (1.7)	2 (1.7)	1 (0.8)
Dyslipidemia	26 (21.5)	3 (2.5)	16 (13.2)	3 (2.5)	2 (1.7)	2 (1.7)
Congestive heart failure	16 (13.2)	7 (5.8)	8 (6.1)	1 (0.8)	0 (0.0)	0 (0.0)

G1: eGFR≥60 ml/min/1.73 m^2, G2: eGFR 30–59 ml/min/1.73 m^2, G3: eGFR 15–29 ml/min/1.73 m^2, G4: eGFR<15 ml/min/1.73 m^2, G5: eGFR<15 ml/min/1.73 m^2 with dialysis, eGFR: Estimated glomerular filtration rate; AF: Atrial fibrillation, VTE: Venous thromboembolism, IQR: Interquartile range

Table 2: Initial doses of warfarin, maintenance doses of warfarin, INR variability, and TTR classified by eGFR

Parameters	Overall	eGFR (1.73/min/m^2)					*P*-value
		G1	G2	G3	G4	G5	
Initial doses (mg/week)	17.5 (14.0, 21.0)	18.0 (14.0, 21.0)	14.0 (10.0, 21.0)	16.0 (10.5, 21.0)	21.0 (12.8, 21.0)	21.0 (15.8, 31.5)	0.094
Maintenance doses (mg/week)	19.0 (14.0, 25.0)	21.0 (16.0, 28.0)	16.0 (13.3, 23.0)	18.4 (11.9, 23.3)	17.5 (8.8, 22.5)	21.0 (17.6, 23.6)	0.001
INR variability	0.16 (0.04, 0.3)	0.13 (0.03, 0.3)	0.18 (0.06, 0.3)	0.15 (0.02, 0.2)	0.18 (0.15, 0.2)	0.08 (0.03, 0.2)	0.313
TTR (%)	69.0 (43.5, 87.0)	78.9 (61.0, 92.5)	59.5 (30.0, 83.5)	81.5 (63.5, 92.5)	34.5*	56.0 (22.8, 94.5)	0.025

*Could not calculated interquartile, TTR: Time in therapeutic range, INR: International normalized ratio. Maintenance doses; doses of warfarin achieved INR in target range on at least two consecutive.

Table 3: Relationship of factors and TTR>60% in the logistic regression

Factors	Univariate analysis	Multivariate analysis		
	OR (95%CI)	*P*-value	OR (95% CI)	*P*-value
eGFR ≥60 ml/min/1.73 m^2	3.08 (1.36–6.96)	0.007*	3.44 (1.35–8.73)	0.009**
Maintenance doses ≥21 mg/week	1.81 (0.80–4.07)	0.155	1.18 (0.48–2.93)	0.719
Female	0.37 (0.16–0.83)	0.016*	0.32 (0.13–0.76)	0.011**
Age ≥75 years	1.93 (0.77–4.83)	0.160	1.06 (0.37–3.04)	0.908

*P<0.1 for statistical significance, **P<0.05 for statistical significance, TTR: Time in therapeutic range. Multivariable analysis was adjusted for the following variables: eGFR≥60 ml/min/1.73 m^2, maintenance doses≥21 mg/week, female and age≥75 years compared with eGFR≤60 ml/min/1.73 m^2, maintenance doses≤21 mg/week, male and age≤75 years

DISCUSSION

Warfarin is metabolized through the CYP450 in the liver.[1] However, the correlation between kidney function is controversial, including initial doses of warfarin, maintenance doses of warfarin, TTR, and INR variability in patients with CKD.

The previous studies reported that the CKD group used warfarin doses lower than the normal renal function group. One reason is that patients with ESRD had a downregulation of CYP450 activity of approximately 40%–85% and decreased expression of proteins and mRNA of many CYP450 enzymes, resulting in reduced warfarin metabolism.[21,22] Sakaan *et al*.

revealed that the average daily doses to maintain an INR target were 4.3 ± 1.6, 4.6 ± 1.9, and 4.8 ± 1.9 mg in CKD Stage 3, CKD Stage 4/5, and ESRD groups, respectively, compared with 5.6 ± 1.7 mg in the normal kidney function group.[23] Similar to the results from Japan, creatinine clearance was positively related to warfarin dose. There was a significant difference in warfarin doses in patients with different stages of eGFR ($P < 0.01$). Patients in the G3a/G3b and G4/G5 groups showed significantly lower warfarin doses than those in the G1/G2 groups (2.9 ± 1.4 and 2.3 ± 1.0 mg/day vs. 3.5 ± 1.4 mg/day, $P < 0.05$).[2]

The present study found that the initial dose of warfarin in the G4 and G5 groups (21.00 mg/week) was higher than in the G1–G3 groups (18.0, 14.0, and 16.0 mg/week, respectively). This may be due to the smaller number of patients in the G4 and G5 groups. Thus, initial doses were calculated with the upper estimate. Therefore, initial warfarin doses in the Thai population were 3–5 mg/day because polymorphism in the Thai population was haplotype AA (low-dose haplotype) in 95% and CYP2C9 *1*1 in 65%.[24] The warfarin maintenance doses to achieve INR target in the G2, G3, and G4 groups were lower than that in the G1 group, which was similar to the results of the previous studies.[2,23] However, the warfarin maintenance doses to achieve INR target in the G5 group was more than that in the G1 group. We hypothesized that warfarin can pass through HD.[25] Approximately 99% of warfarin is bound to the protein albumin in plasma and has a high molecular weight (308.3 g/mole). Ifudu and Dulin reported that plasma warfarin levels were 1.95 ± 0.15 mcg/mL and 1.4 ± 0.5 mcg/mL before and after HD, respectively. A patient with HD received warfarin 10 mg daily. The warfarin level decreased by approximately 31.0% after HD.[26] However, the Nephrology Pharmacy Associates suggested to unnecessarily add warfarin doses in HD with a coefficient of ultrafiltration (Kuf) of dialyzer <12 mL/h/mmHg. Unfortunately, the data in a high flux dialyzer with Kuf >12 mL/h/mmHg were unclear.[27] In this study, the overall patients in the G5 group were HD patients. Therefore, the data about warfarin in PD, including continuous ambulatory peritoneal dialysis (CAPD) patients, were less evidenced. As shown in the previous study, CAPD patients who were treated with a fixed low-dose (2 mg/day for 12 months) warfarin for stroke prevention had an INR above the target range, but did not have major bleeding.[28] However, one case report showed that ocular and periocular hemorrhages were present in a CAPD patient who received warfarin (2.5 mg once daily). Uremia and uncontrolled blood pressure that were reported in this case might affect platelet function and increase the risk of bleeding.[29]

INR variability is a value used to evaluate the efficacy and safety of warfarin therapy that is calculated using Fihn's method. Furthermore, the INR variability is an equal predictor of TTR in predicting thromboembolism and bleeding in patients using warfarin.[16,30] The results showed that the INR variability in the G1–G5 groups was not different. However, the G5 group had lower INR variability than the G1–G4 groups. This indicated that the INR in the G5 group could be more controlled than those in the other groups. These results were not related to those of the previous studies.[16,18,30,31] We hypothesized that the physician more frequently followed patients in this group than those in the other groups. The previous studies have not reported on INR variability in CKD.

The present study reported that the G4–G5 groups had a lower TTR than the G1–G3 groups, indicating decreased eGFR related to poor INR control. As described previously, the percentage of TTR in the G1 group and G2 group was found significantly difference while other groups were not found to be significant because the sample size was not adequate for distinguishing differences of TTR between eGFR categories. These results were consistent with those of the previous studies.[2] Kleinow *et al*. divided patients into two groups according to estimated creatinine clearance (eCrCl): Group 1, patients with CKD (eCrCl < 60 mL/min) and Group 2, patients without CKD (eCrCl ≥ 60 mL/min). It was found that patients with CKD had lower TTR than patients without CKD (62% and 74%, respectively; $P = 0.021$).[4] However, the Rosendaal method cannot be precisely calculated for patients whose INR values were largely outside the target range, or intervals between each visit for monitored INR were different.[32]

In our study, eCrCl ≥ 60 mL/min and female sex were associated with TTR > 60%, while maintenance doses ≥21 mg/week and age <75 years old were conversely associated with TTR > 60% on logistic regression. Similar to the study of Proietti *et al*., CKD was associated low quality control of warfarin used because the result from this study showed that TTR was higher in patients with normal renal function compared with CKD.[33] However, the effect of other factors such as gender, age, and maintenance doses of warfarin on TTR is still controversial.[33,34]

This study had several limitations. Since this was a retrospective cohort study, some data could not be completely collected, for example, Vitamin K consumption, history of alcohol consumption, history of smoking, compliance, concomitant medications, and genetic polymorphism. These are factors that affect INR values. Therefore, the small sample size, especially in CKD G4 and G5, is the reason for the absence in difference in results in each group. Furthermore, the present study did not gather data on outcomes, including thromboembolism and bleeding. Hence, the future study should evaluate the effect of warfarin use in patients with CKD and be conducted in a multicenter setting to increase the sample size.

CONCLUSION

Patients with CKD required lower warfarin doses, including the starting and maintenance doses than those who have normal renal function. TTR, well known to estimate the efficacy of warfarin, was not related to INR values to achieve the target in CKD, especially the G4 and G5 groups. Hence, INR variability may be useful in this groups. Furthermore, health-care professionals have to monitor INR values in CKD patients carefully when they are receiving warfarin to ensure their safety and have better efficacy.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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