Original Article

Correlation between Time in Therapeutic Range and Glomerular Filtration Rate in Chronic Kidney Disease Patients with Atrial Fibrillation

Apisit Leedumrongwattanakul MD[1,3], Kesinee Leedumrongwattanakul MD[2,3]

[1] Cardiology Unit, Department of Medicine, Pranangklao Hospital, Nonthaburi, Thailand

[2] Nephrology Unit, Department of Medicine, Pranangklao Hospital, Nonthaburi, Thailand

[3] Faculty of Medicine, Siam University, Bangkok, Thailand

Background: Chronic kidney disease is associated with an increased risk of atrial fibrillation and cerebrovascular disease. Acceptable levels of time in the therapeutic range (TTR) are associated with better treatment outcomes.

Objective: To correlate between time in therapeutic range and glomerular filtration rate in Thai chronic kidney disease patients with atrial fibrillation.

Materials and Methods: The present study was retrospectively collected from 312 medical records of patients with atrial fibrillation aged 18 years or over at Pranangklao Hospital between January 2018 and December 2020.

Results: The average age of patients was 67.8±12.6 years and 44.9% were male. The average CHA_2DS_2-VASc scores were 3.6±1.5 and the average follow-up duration was 883.5 ± 398.4 days. Most patients had hypertension and dyslipidemia, and have been prescribed statins, proton pump inhibitors, and aspirin. Most patients had TTR of less than 65%. The present study showed patients with low estimate glomerular filtration rate (eGFR) were significantly correlated with having low TTR. A reduction of eGFR by 1 correlated with a decrease in TTR by 0.33. An equation that predicted the relationship between the eGFR and the TTR could be expressed as TTR=26.95+0.33 multiply eGFR.

Conclusion: Decreased glomerular filtration was associated with poorer anticoagulation control.

Keywords: Time in therapeutic range; Atrial fibrillation; Chronic kidney disease

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Chronic kidney disease (CKD) is associated with an increased risk of atrial fibrillation (AF) and stroke. AF is a common disease in cardiology clinics[1,2]. The prevalence of AF was found to be as high as 2% to 4% of adults[3,4]. The prevalence of CKD coexisting with AF was 16 to 21%[5-7] in non-dialysis patients and 14 to 50% in patients on dialysis[8]. The international normalized ratio (INR) should be 2 to 3 during the treatment program and does not fluctuate[9,10]. Patients on warfarin can be followed up with the INR treatment level for extended treatment intervals[11]. When the time in therapeutic range (TTR) was less than 60%, it increased fatal and severe bleeding. However, when the TTR level was greater than 75%, the severity of bleeding and high mortality was significantly reduced[12]. The use of anticoagulation and other medications resulted in platelet dysfunction such as platelet abnormalities and impaired platelet-vessel wall interaction, in CKD and due to this, developed hemostatic disorders[13]. Therefore, the combined increased risk of stroke and bleeding in warfarin-treated patients with CKD may be due to poor quality control of the INR.

The present study aimed to demonstrate the correlation between TTR and glomerular filtration rate in CKD Thai patients with AF.

Materials and Methods

The present study was conducted retrospectively in Pranangklao Hospital. Between January 1, 2018

Correspondence to:

Leedumrongwattanakul A.

Cardiology Unit, Department of Medicine, Pranangklao Hospital, Muang Nonthaburi, Nonthaburi 10705, Thailand.

Phone: +66-2-5284567

Email: apisit_lee@hotmail.com

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and December 31, 2020, patients aged 18 years and older, diagnosed with AF who taken warfarin for more than a year were included in the present study. The data collection was conducted from 2021 onward.

The following patients were excluded, (i) patients who needed to stop taking warfarin during the treatment program for less than or equal to four months, (ii) patients with a history of replacement of a diseased heart valve with a mechanical prosthetic valve and (iii) patients who discontinued warfarin for more than four months. A sample size of 124 subjects was estimated based on the infinite population mean calculation technique, based on previous data by Reid et al[14] with the standard deviation and the error approximating 17 and 3, and Type I & II error set at 0.05, 0.2, respectively.

The labile INR was defined as TTR by Rosendalls linear interpolation method of patients having less than 60% of the follow-up period[15]. It showed that the occurrence of the ischemic stroke appeared when INR was less than 2, and the bleeding event appeared when INR was more than 3. In addition, the estimated glomerular filtration rate of eGFR as mL/minute/1.73 m^2 was calculated using the chronic kidney disease epidemiology collaboration formula (CKD-EPI)[16]

The present study protocol was approved by the Institutional Review Board No EC32/2564. and complied with the Declaration of Helsinki. CIOMS Guidelines and International Conference on Harmonization in Good Clinical Practice (ICH-GCP).

Statistical analysis

Descriptive statistics, including frequency and percentage, were used for categorical variables. Continuous variables were reported as mean and standard deviation (SD). The distribution of variables was examined by the Kolmogorov-Smirnov test. Analysis of variance (ANOVA) was used for the comparison of normally distributed continuous variables between three groups and the chi-square test was used for categorical data. The correlation and regression analyses were conducted to assess the correlation between TTR and eGFR by the IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). A p-value of less than 0.05 was considered to be statistically significant.

Results

According to the Pranangklao Hospital database, 312 patients were diagnosed with AF and prescribed warfarin between January 1, 2016 and December 31, 2020.

Baseline characteristics are shown in Table 1. The average age was 67.81±12.57 years, and 140 (44.9%) were male. The average CHA_2DS_2-VASc score was 3.62±1.54. The average CHA_2DS_2-VASc score was higher in patients with eGFR of less than 30 mL/minute/1.73 m^2. Of the patients included in the present study, 91.3% had hypertension, 53.5% had diabetes mellitus, 14.1% had percutaneous coronary intervention, 3.8% had coronary artery bypass surgery, and 17.9% had previous stroke/TIA. Most patients had hypertension and dyslipidemia. Most patients were prescribed beta-blockers. Most patients had TTR of less than 65%.

Patients with lower eGFR also had a higher prevalence of percutaneous coronary intervention, diabetes mellitus, and congestive heart failure. Patients with lower eGFR also had a high prevalence of using aspirin, clopidogrel, and statins.

For patients with low eGFR, there was a shorter period of follow-up and a smaller number of tests compared to patients with high eGFR.

The proportions of Thai AF patients with average TTR between eGFR of less than 30, 30 to 59, and 60 or more mL/minute/1.73 m^2 groups are shown in Figure 1. The present study showed that the proportion of AF patients with low average TTR were also found in patients with eGFR of less than 30 mL/minute/1.73 m^2. This finding was of statistical significance ($p<0.001$). The average TTR in patients with different eGFR were 28.2±24.37, 48.25±22.42, and 53.33±22.06 in patients with eGFR of less than 30, 30 to 59, and 60 or more mL/minute/1.73 m^2, respectively.

The distribution of correlation between TTR and eGFR are shown in Figure 2. Further analysis in Figure 2 shows a significant correlation between TTR and eGFR with R=0.416 When writing an equation that predicts the relationship between the eGFR and the TTR, it could be expressed as TTR=26.95+0.33 multiply eGFR, R^2 linear=0.173. It was found that when the eGFR decreased by 1, the TTR also decreased by 0.33.

Discussion

TTR is the percentage of the duration of treatment. Past studies have shown the TTR for AF in CKD to be in the range of 58% to 65%[17-22]. The present study highlighted the correlation of eGFR and TTR of AF patients with CKD. The present study further added to the current knowledge that there is a significant association between low eGFR and low TTR levels, which can be seen even when the GFR

Table 1. Baseline characteristics of the patients

Factors	Total (n=312)	GFR (mL/minute/1.73 m^2)			p-value
		<30 (n=107)	30 to 59 (n=103)	≥60 (n=102)	
GFR (mL/minute/1.73 m^2); mean±SD	48.5±31.7	14.8±8.2	45.1±7.9	86.9±16.4	<0.001
Age (years); mean±SD	67.8±12.6	68.8±13	72.5±9.6	61.9±12.5	<0.001
Sex (male); mean (%)	140 (44.9)	47 (43.9)	55 (53.4)	38 (37.3)	0.065
CHA_2DS_2-VASC; mean±SD	3.6±1.5	4.0±1.5	3.8±1.4	3.1±1.5	<0.001
TTR (%); mean±SD	43.0±25.4	28.2±24.4	48.2±22.4	53.3±22.1	<0.001
Total days; mean±SD	883.5±398.4	649.4±388.5	929.6±371.2	1082.4±301.7	<0.001
Total test; mean±SD	12.8±6.3	11.0±6.9	13.58±5.7	14.1±5.9	0.001
Test in range (%); mean±SD	39.7±22.4	25.4±21.3	44.8±19.5	49.6±18.4	<0.001
Comorbid history; n (%)					
Percutaneous coronary intervention	44 (14.1)	19 (17.8)	18 (17.5)	7 (6.9)	0.038
Coronary artery bypass surgery	12 (3.8)	4 (3.7)	3 (2.9%)	5 (4.9)	0.758
Hypertension	285 (91.3)	101 (94.4)	96 (93.2)	88 (86.3)	0.081
Diabetes mellitus	167 (53.5)	70 (65.4)	48 (46.6)	49 (48.0)	0.01
Heart failure	37 (11.9)	20 (18.7)	12 (11.7)	5 (4.9)	0.009
Biological valve	7 (2.2)	1 (0.9)	2 (1.9)	4 (3.9)	0.335
Pacemaker/ICD	12 (3.8)	3 (2.8)	6 (5.8)	3 (2.9)	0.442
Liver disease	7 (2.2)	1 (0.9)	4 (3.9)	2 (2.0)	0.344
COPD	13 (4.2)	3 (2.8)	4 (3.9)	6 (5.9)	0.53
Cancer	5 (1.6)	4 (3.7)	1 (1.0)	0 (0.0)	0.081
Ischemic stroke	56 (17.9)	24 (22.4)	15 (14.6)	17 (16.7)	0.305
Pulmonary embolism	6 (1.9)	1 (0.9)	1 (1.0)	4 (3.9)	0.201
Deep vein thrombosis	12 (3.8)	4 (3.7)	5 (4.9)	3 (2.9)	0.774
Medication history (last 6 months); n (%)					
Aspirin	70 (22.4)	42 (39.3)	18 (17.5)	10 (9.8)	<0.001
Clopidogrel	17 (5.4)	10 (9.3)	6 (5.8)	1 (1.0)	0.028
NSAIDs	3 (1.0)	0 (0.0)	2 (1.9)	1 (1.0)	0.354
Acetaminophen	11 (3.5)	3 (2.8)	4 (3.9)	4 (3.9)	0.883
Statin	252 (80.8)	92 (86.0)	87 (84.5)	73 (71.6)	0.015
Proton pump Inhibitors	80 (25.6)	46 (43.0)	22 (21.4)	12 (11.8)	<0.001
Amiodarone	15 (4.8)	5 (4.7)	7 (6.8)	3 (2.9)	0.434

GFR=glomerular filtration rate; TTR=time in therapeutic range; ICD=intracardiac defibrillation; COPD=chronic obstructive pulmonary disease; NSAIDs=non-steroidal anti-inflammatory drugs; SD=standard deviation

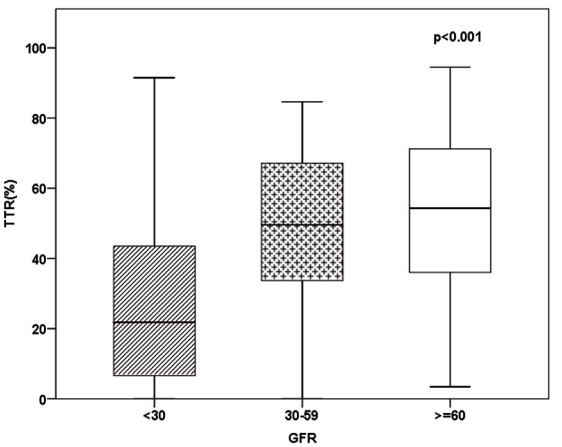

Figure 1. Box plot represented the proportion of Thai AF patients with TTR between eGFR <30, 30 to 59, ≥60 groups.

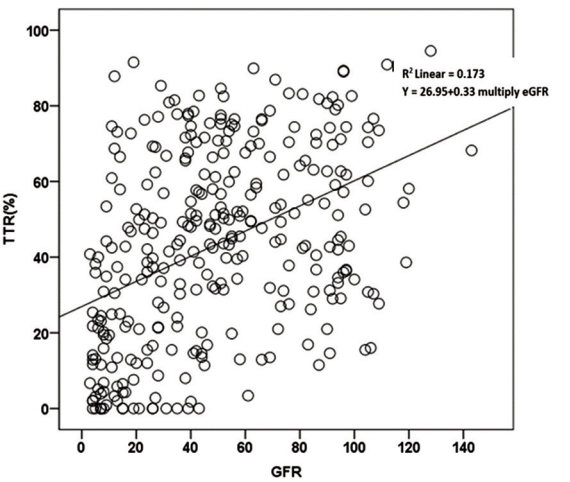

Figure 2. The relationship between TTR and eGFR.

was less than 30 mL/minute/1.73 m².

The present study further added evidence that a significant correlation between TTR and eGFR was found with R=0.416. When writing an equation that predicts the relationship between the eGFR and the TTR, it can be expressed as TTR=26.95+0.33 multiply eGFR. It was found that when the eGFR decreased by 1, the TTR decreased by 0.33.

Mechanisms by which CKD affects INR levels also affect subsequent important clinical outcomes, which have not been thoroughly studied. Impaired renal function can significantly reduce the dialysis and absorption of warfarin. The non-renal warfarin clearance is decreased and the therapeutic value of INR is reduced. Therefore, in patients with CKD, the willingness to sub-treatment INR, which translates to low TTR in patients with major CKD, needs careful consideration[21,22].

There are limitations to the present study. First, there may be an influence of time-dependent changes during CKD. Renal function may deteriorate over time or during follow-up. However, CKD status was classified only at the time of registration. Secondly, in addition to the factors described in the present study, other factors may still not be accounted for, such as weakness, accidental drug use, and daily dietary patterns. These factors may be unknown and may result in variable TTR and worsening renal function. Third, the study population was recruited from a single-center, and subsequently, the study may not be generalized. Fourth, the study was retrospective and had a minimum sample size. The study may not be effective. In conclusion, the present study was conducted on few Thai patients. Therefore, data from further studies with larger population, and from multi-centers are needed to cover all aspects.

Conclusion

The quality of blood coagulation control is reduced in Thai patients with CKD, and it decreased glomerular filtration in Thai patients taking warfarin for AF.

What is already known on this topic?

Patients taking warfarin are indicated for AF with CKD. Decreased glomerular filtration results in a decrease in the quality of blood coagulation control.

What does this study add?

The study found that for patients taking warfarin from AF with a chronic renal disease that each incremental decrease in GFR by 1 mL/minute/1.73 m² results in a decreased TTR of 3%.

Conflicts of interest

The authors declare no conflicts of interest.

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