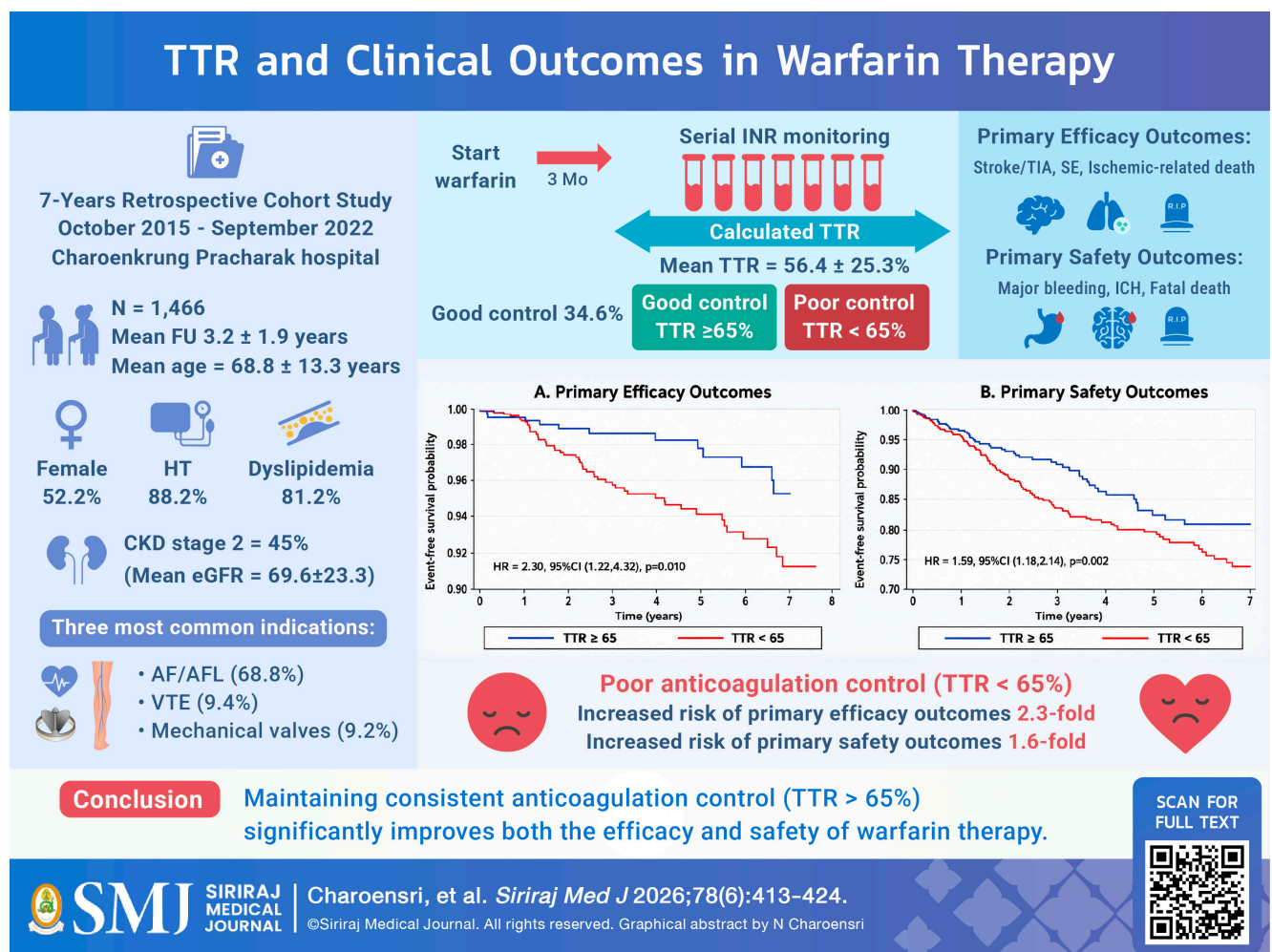


Association between Time in Therapeutic Range (TTR) and Clinical Outcomes in Patients on Warfarin: A 7-year Retrospective Cohort Study

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ABSTRACT

Objective: To evaluate the relationship between TTR and long-term clinical outcomes, focusing on the efficacy and safety of warfarin therapy.

Materials and Methods: A retrospective cohort study (2015–2022) of 1,466 patients at Charoenkrung Pracharak Hospital. TTR was calculated using the Rosendaal method. Patients were categorized into two groups: good control (TTR $\geq$ 65%) and poor control (TTR < 65%). Efficacy outcomes included ischemic stroke or transient ischemic attack (TIA), systemic embolism (SE), and ischemic-related death. Safety outcomes included major bleeding, intracranial hemorrhage (ICH), and fatal bleeding. Cox proportional hazards regression was used to determine the association between TTR and clinical outcomes.

Results: Mean age was 68.8 ± 13.3 years (52.2% female). Mean follow-up duration was 3.2 ± 1.9 years, with a mean TTR of $56.36 \pm 25.34\%$. Three most common indications were atrial fibrillation/flutter (AF/AFL) (68.8%), venous thromboembolism (VTE) (9.4%), and mechanical heart valves (9.2%). Compared to the good control group, patients with poor control (TTR < 65%) had significantly higher incidence rates of both efficacy (1.29 vs. 0.56 per 100 person-years) and safety outcomes (4.69 vs. 2.92 per 100 person-years). After adjusting for potential confounders, poor control was independently associated with an increased risk of primary efficacy outcomes (aHR 2.30; 95% CI 1.22–4.32; $p=0.01$) and primary safety outcomes (aHR 1.59; 95% CI 1.18–2.14; $p=0.01$).

Conclusion: Poor anticoagulation control (TTR < 65%) is strongly associated with an increased risk of both thromboembolic and hemorrhagic complications. Maintaining a TTR $\geq$ 65% remains a critical therapeutic target consistently linked to better clinical outcomes in real-world practice.

Keywords: Warfarin; time in therapeutic range; international normalized ratio; therapeutic efficacy; patient safety (Siriraj Med J 2026;78(6):413–424)

INTRODUCTION

Vitamin K antagonists (VKAs), primarily warfarin, remain the cornerstone of thromboembolic prophylaxis in Thailand for patients with atrial fibrillation/flutter (AF/AFL), mechanical heart valves, rheumatic mitral stenosis, venous thromboembolism (VTE) and various hypercoagulable states.^{1–5} Warfarin prevents blood clotting by inhibiting the synthesis of vitamin K-dependent clotting factors.^{1,6} Despite its established efficacy in preventing ischemic stroke/ transient ischemic attack (TIA), and systemic embolism (SE),^{7,8} the clinical utility of warfarin is constrained by high bioavailability, narrow therapeutic range, significant inter-individual pharmacokinetic variability, and complex drug-drug and drug-food interactions.^{1,6} Due to this narrow therapeutic window, dosages must be carefully titrated based on the International Normalized Ratio (INR).¹ Frequent INR fluctuations create a persistent clinical dilemma:⁷ sub-therapeutic levels increase the risk of thromboembolic events, whereas supra-therapeutic levels markedly elevate the risk of bleeding. Consequently, anticoagulation quality is best quantified by the Time in Therapeutic Range (TTR),^{9–13} which measures the percentage of time a patient's INR remains within the target range. Current evidence suggests that a TTR $\geq 65\%$ is the optimal threshold for balancing clinical

efficacy and safety.^{14–18} This retrospective study aims to evaluate the relationship between TTR and long-term clinical outcomes—specifically efficacy and safety—at the Anticoagulation Clinic, Charoenkrung Pracharak Hospital.

MATERIALS AND METHODS

Study design

This retrospective cohort study was conducted at the Anticoagulation Clinic, Cardiac Center, Charoenkrung Pracharak Hospital, covering the period from October 2015 to September 2022. The study protocol was approved by the Bangkok Metropolitan Administration Human Research Ethics Committee (BMAHREC) (Protocol No. S003h/65_EXP), and patient confidentiality was strictly maintained. Data were collected from electronic medical records for patients aged ≥ 18 years who had received warfarin for at least three months. Eligible patients required ≥ 2 INR measurements and a valid indication for long-term anticoagulation, such as AF/AFL,^{2,3} mechanical heart valves,⁴ or VTE.^{1,5} Exclusion criteria included pregnancy, stage 5 chronic kidney disease (eGFR < 15 mL/min/1.73 m²) as defined by KDIGO 2021¹⁹ or the requirement for renal replacement therapy,¹⁹ advanced liver cirrhosis (Child-Pugh class

B or C),²⁰ baseline platelet count below 100,000/mm³, baseline INR greater than 1.7, and a recent history (<3 months) of ischemic stroke/TIA²¹ or SE.^{7,8}

Patient Selection

A standardized data collection form was utilized to extract information from electronic medical records. The recorded data included demographic characteristics (age, gender, and BMI); baseline clinical parameters (blood pressure, heart rate, and hemoglobin levels); comorbidities (diabetes mellitus, hypertension, chronic liver disease, ischemic heart disease,²² heart failure,^{23,24} and chronic kidney disease¹⁹); echocardiographic findings²⁵ (such as left ventricular ejection fraction [LVEF]); concurrent medications; and serial INR values. For patients with AF/AFL, CHA₂DS₂-VASc and HAS-BLED scores were specifically calculated.^{2,3} TTR was determined using the Rosendaal method, representing the percentage of time that the INR was maintained within the therapeutic range of 2.0–3.0.^{9–13} Patients were categorized into two groups based on anticoagulation quality: good control (TTR ≥ 65%) and poor control (TTR < 65%).^{14–18} To ensure data accuracy, inpatient periods involving warfarin discontinuation were excluded from TTR calculation. This minimizes the impact of INR instability, as the timing of drug interruption and resumption significantly affects anticoagulation control.²⁶ Assessment was resumed at least two weeks post-discharge to ensure the restoration of a steady-state anticoagulant effect. Patients were censored at the date of their last documented contact in cases of loss to follow-up, failure to complete the study period, a treatment gap exceeding six months between consecutive INR measurements, or switching from warfarin to direct oral anticoagulants (DOACs).

Outcome measures

Primary clinical outcomes were categorized into two categories: efficacy outcomes and safety outcomes. Efficacy outcomes included: (1) ischemic stroke,²¹ diagnosed through clinical assessment and confirmed by radiographic findings (Computed Tomography [CT] or Magnetic Resonance Imaging [MRI]) of cerebral ischemia; (2) transient ischemic attack (TIA),²¹ characterized by stroke-like symptoms resolving within 24 hours; (3) systemic embolism (SE),^{7,8} identified by clinical symptoms alongside objective radiographic evidence of thromboembolism; and (4) ischemic-related death, defined as any death resulting from a documented ischemic event, including fatal ischemic stroke, fatal systemic embolism, or death occurring within 30 days of an acute ischemic complication. Safety outcomes included (1) major bleeding, defined

according to the International Society on Thrombosis and Haemostasis (ISTH) criteria;^{7,15,16} (2) intracranial hemorrhage (ICH), including subarachnoid hemorrhage, subdural hematoma, or epidural hematoma, confirmed by radiographic findings (CT or MRI); and (3) fatal bleeding, defined as any death directly attributed to a bleeding event, including both intracranial and extracranial causes within 30 days. Mortality data were obtained from medical records and cross-referenced with the National Death Registry, facilitated by the Bangkoklaem District Office, Bangkok Metropolitan Administration.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for non-normally distributed data. Categorical variables were presented as frequencies and percentages (n, %). Clinical outcome incidence rates were calculated as events per 100 person-years. Baseline characteristics were compared between the good control (TTR ≥ 65%) and the poor control (TTR < 65%) groups using the chi-square test for categorical variables, and the independent t-test for continuous variables. The association between TTR and time-to-event clinical outcomes was evaluated using Kaplan-Meier survival curves and the log-rank test. Multivariable Cox proportional hazards regression models were constructed to estimate adjusted hazard ratios (aHR) with 95% confidence intervals (CI). The proportional hazards (PH) assumption for all multivariable Cox regression models was rigorously validated using Schoenfeld residuals and visual inspection of log-minus-log survival plots. Variables with a *p*-value < 0.05 in univariable analysis, alongside established clinical predictors, were included in the multivariable models. Potential confounders adjusted for in the models included age, comorbidities, HAS-BLED score, hemoglobin level, kidney function (eGFR), left ventricular function (LVEF), and concurrent medications. Statistical significance was defined as a two-tailed *p* < 0.05. All statistical analyses were conducted using SPSS version 26.0 (Concurrent license, Medical Research and Education Center, Medical Service Department, Bangkok Metropolitan Administration).

RESULTS

Demographic and clinical data

A total of 1,466 patients were included in the study, with a mean age of 68.8 ± 13.3 years, and 52.2% were female. The mean follow-up duration was 3.2 ± 1.9 years. The three most common indications for warfarin therapy were AF/AFL (68.8%), VTE (9.4%), and mechanical heart valves (9.2%). The mean TTR for the overall study

population was $56.36 \pm 25.34\%$. Patients were categorized into two groups based on the quality of anticoagulation control: the good control group (TTR $\geq 65\%$; $n = 507$; 34.6%) and the poor control group (TTR $< 65\%$; $n = 959$; 65.4%). Baseline characteristics of the study population, stratified by TTR levels, are presented in Table 1.

Comparison of good control (TTR $\geq 65\%$) and poor control (TTR $< 65\%$) groups

Table 1 summarizes and compares baseline characteristics stratified by TTR status. Patients in the poor control group were generally older (particularly those aged >75 years) and showed a higher burden of comorbidities, including type 2 diabetes mellitus, chronic lung disease and coronary artery disease. Furthermore, the poor control group showed significantly lower kidney function (as measured by eGFR), a higher prevalence of severely reduced left ventricular ejection fraction (LVEF

$\leq 40\%$), and a greater frequency of concomitant dual antiplatelet therapy (DAPT). Other baseline characteristics, comorbidities, and medications were comparable between the two groups.

Multivariable Cox proportional hazards analysis

After adjusting for potential confounders, multivariable Cox proportional hazards analysis revealed that age was an independent predictor of safety outcomes. Compared with patients aged < 65 years, those aged ≥ 75 years had a 1.6-fold higher risk of safety events (aHR 1.58; 95% CI 1.08-2.32; $p=0.02$). Furthermore, declining kidney function (eGFR < 60 mL/min/1.73 m²) was strongly associated with efficacy failure, demonstrating a 2.9-fold increased risk of primary efficacy outcomes (aHR 2.87; 95% CI 1.09-7.56; $p=0.03$) compared to patients with preserved kidney function (eGFR ≥ 60 mL/min/1.73 m²).

TABLE 1. Baseline characteristics of the study population stratified by Time in Therapeutic Range (TTR) levels ($\geq 65\%$ vs. $< 65\%$).

Variables	Total (n = 1466)	TTR $\geq 65\%$ (n = 507)	TTR $< 65\%$ (n = 959)	p-value
Age (years); Mean $\pm$ SD	68.8 $\pm$ 13.3	68.6 $\pm$ 12.7	69.0 $\pm$ 13.7	0.59 ^t
< 65 years	484 (33.0)	163 (32.2)	321 (33.5)	0.02 ^{c*}
65-74 years	451 (30.8)	179 (35.3)	272 (28.4)	
≥ 75 years	531 (36.2)	165 (32.5)	366 (38.2)	
Female	765 (52.2)	272 (53.7)	493 (51.4)	0.41 ^c
BMI (kg/m ²); Mean $\pm$ SD	24.7 $\pm$ 5.4	24.6 $\pm$ 5.1	24.8 $\pm$ 5.6	0.47 ^t
Mean SBP (mmHg); Mean $\pm$ SD	128.9 $\pm$ 19.2	129.0 $\pm$ 18.5	128.9 $\pm$ 19.6	0.93 ^t
Heart Rate (BPM); Mean $\pm$ SD	79.3 $\pm$ 15.3	79.1 $\pm$ 14.9	79.4 $\pm$ 15.5	0.70
Hemoglobin (g/dl); Mean $\pm$ SD	12.6 $\pm$ 2.0	12.8 $\pm$ 1.9	12.4 $\pm$ 2.0	0.001 ^{t*}
Indications for anticoagulation				
1. Atrial fibrillation/ flutter (AF/AFL)	1009 (68.8)	341 (67.3)	668 (69.7)	-
CHA2DS2-VASc scores; (n=1009)	4.1 $\pm$ 1.5	4.0 $\pm$ 1.6	4.1 $\pm$ 1.5	0.25 ^t
CHA2DS2-VASc ≤ 1	40 (4.0)	15 (4.4)	25 (3.7)	0.32 ^c
CHA2DS2-VASc 2-4	579 (57.4)	205 (60.1)	374 (56.0)	
CHA2DS2-VASc ≥ 5	390 (38.6)	121 (35.5)	269 (40.3)	
HAS-BLED scores; (n=1009)	2.4 $\pm$ 0.9	2.4 $\pm$ 0.9	2.5 $\pm$ 0.9	0.04 ^{t*}
HAS-BLED 0	24 (2.4)	11 (3.2)	13 (1.9)	0.03 ^{c*}
HAS-BLED 1-2	484 (47.9)	179 (52.5)	305 (45.6)	
HAS-BLED ≥ 3	502 (49.7)	151 (44.3)	351 (52.5)	
2. Venous thromboembolism (VTE)	137 (9.4)	43 (8.5)	94 (9.8)	-
3. Mechanical heart valve	135 (9.2)	64 (12.6)	71 (7.4)	-
4. Cardiomyopathy	108 (7.3)	32 (6.3)	76 (7.9)	-
5. Rheumatic heart disease	37 (2.5)	14 (2.8)	23 (2.4)	-

TABLE 1. Baseline characteristics of the study population stratified by Time in Therapeutic Range (TTR) levels ($\geq 65\%$ vs. $< 65\%$). (Continued)

Variables	Total (n = 1466)	TTR $\geq 65\%$ (n = 507)	TTR $< 65\%$ (n = 959)	p-value
6. Hypercoagulable state	27 (1.8)	8 (1.6)	19 (2.0)	-
7. Vascular disease	13 (0.9)	5 (1.0)	8 (0.8)	-
Echocardiographic findings				
LVEF (%); Mean $\pm$ SD	58.3 $\pm$ 15.1	60.4 $\pm$ 14.0	57.1 $\pm$ 15.6	<0.001 ^{†*}
LVEF $\leq 40\%$	171 (14.5)	43 (10.3)	128 (16.9)	0.01 ^{c*}
LVEF 41-49%	94 (8.0)	32 (7.7)	62 (8.1)	
LVEF $\geq 50\%$	912 (77.5)	343 (80.0)	569 (75.0)	
LAVI (mL/m ²); Mean $\pm$ SD	54.7 $\pm$ 38.6	54.5 $\pm$ 34.5	54.9 $\pm$ 40.6	0.87 ^t
LVEDV (mL); Mean $\pm$ SD	89.2 $\pm$ 54.8	83.8 $\pm$ 40.8	92.3 $\pm$ 61.1	0.01 ^{†*}
Comorbidities				
Hypertension	1293 (88.2)	446 (88.0)	847 (88.3)	0.84 ^c
Dyslipidemia	1191 (81.2)	413 (81.5)	778 (81.1)	0.88 ^c
Type 2 Diabetes Mellitus	522 (35.6)	161 (31.5)	361 (37.6)	0.03 ^{c*}
History of heart failure	449 (30.6)	143 (28.2)	306 (31.9)	0.14 ^c
History of ischemic stroke/TIA	323 (22.0)	121 (23.9)	202 (21.0)	0.22 ^c
History of coronary artery disease	288 (19.7)	83 (16.4)	205 (21.4)	0.02 ^{c*}
History of chronic lung disease	151 (10.3)	38 (7.6)	113 (11.8)	0.01 ^{c*}
History of thyroid disease	108 (7.4)	42 (8.3)	66 (6.9)	0.33 ^c
History of CIED	98 (7.0)	34 (7.0)	64 (7.0)	0.99 ^c
History of other brain disease	79 (5.4)	31 (6.1)	48 (5.0)	0.37 ^c
History of liver disease	63(4.3)	21 (4.1)	42 (4.4)	0.83 ^c
Kidney function; eGFR (mL/min/1.73m ²); Mean $\pm$ SD	69.6 $\pm$ 23.3	71.6 $\pm$ 21.3	68.5 $\pm$ 24.3	0.02 ^{†*}
Stage 1 (eGFR ≥ 90)	293 (20.0)	103 (20.3)	190 (19.8)	0.01 ^{c*}
Stage 2 (eGFR 60-89)	652 (44.5)	249 (49.1)	403 (42.0)	
Stage 3A or higher (eGFR < 60)	521 (35.5)	155 (30.6)	366 (38.2)	
Medications				
Dual Antiplatelet Therapy (DAPT)	252 (17.2)	66 (13.0)	186 (19.4)	0.01 ^{c*}
Statin	1074 (73.3)	379 (74.8)	695 (72.5)	0.35 ^c
Beta-blocker	1027 (70.1)	360 (71.0)	667 (69.6)	0.56 ^c
RAAS blocker	766 (52.3)	280 (55.2)	486 (50.7)	0.10 ^c
Dihydropyridine CCB	446(30.4)	166 (32.7)	280 (29.2)	0.16 ^c
Diuretic	395 (26.9)	132 (26.0)	263 (27.4)	0.57 ^c
Digitalis	239 (16.3)	94 (18.5)	145 (15.1)	0.09 ^c
Spironolactone	183 (12.5)	56 (11.1)	127 (13.2)	0.23 ^c
Alpha-blocker	56 (3.8)	17 (3.4)	39 (4.1)	0.50 ^c
Non-dihydropyridine CCB	37 (2.5)	14 (2.8)	23 (2.4)	0.67 ^c
Amiodarone	35 (2.4)	8 (1.6)	27 (2.8)	0.14 ^c

Data are presented as mean $\pm$ SD, n (%).

Abbreviations: BMI, body mass index; CCB, calcium channel blocker; CIED, cardiac implantable electronic device; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; RAAS, renin-angiotensin-aldosterone system; TIA, transient ischemic attack; TTR, time in therapeutic range. ^t Independent t-test; ^c Chi-square test; ^{*} Statistical significance at $p < 0.05$.

Comparison of clinical outcomes between good (TTR $\geq$ 65%) and poor (TTR < 65%) anticoagulation control groups

Table 2 illustrates the clinical outcomes stratified by TTR status. A total of 61 patients (1.03 per 100 person-years) reached the primary efficacy endpoint. This included 41 cases of ischemic stroke/TIA (0.69 per 100 person-years), 4 cases of systemic embolism (SE; 0.07 per 100 person-years), and 16 cases of ischemic-related death (0.27 per 100 person-years). The composite outcome of stroke/TIA and ischemic-related death occurred in 57 patients (0.96 per 100 person-years). Regarding primary safety outcomes, 224 events were documented (4.05 per 100 person-years), comprising 159 cases of major bleeding defined by ISTH criteria (2.81 per 100 person-years), 32 cases of intracranial hemorrhage (ICH; 0.53 per 100 person-years), and 33 cases of fatal bleeding (0.55 per 100 person-years).

Patients with poor anticoagulation control (TTR < 65%) demonstrated significantly higher incidence rates for both primary efficacy (1.29 vs. 0.56 per 100 person-years) and primary safety outcomes (4.69 vs. 2.92 per 100 person-years) compared to those with good control (TTR $\geq$ 65%). After adjusting for potential confounders, poor TTR was independently associated with a 2.3-fold increased risk of primary efficacy failure (aHR 2.30; 95% CI 1.22–4.32; $p=0.01$). This disparity was primarily driven by the incidence of ischemic stroke/TIA, which exhibited a 2.3-fold increased risk (aHR 2.28; 95% CI 1.05–4.93; $p=0.04$). In contrast, no statistically significant difference in the incidence of systemic embolism was observed between the two groups ($p=0.57$). While the incidence

of ischemic-related death appeared higher in the poor control group, it did not reach statistical significance ($p=0.07$). Notably, the composite outcome of stroke/TIA and ischemic-related death was 2.6-fold higher in patients with poor anticoagulation control (aHR 2.64; 95% CI 1.34–5.23; $p=0.01$).

Regarding safety outcomes, poor anticoagulation control was associated with a 1.6-fold increased risk of adverse events (aHR 1.59; 95% CI 1.18–2.14; $p=0.01$). This finding was primarily driven by major bleeding, which occurred with a 1.6-fold increased risk (aHR 1.56; 95% CI 1.10–2.23; $p=0.01$). Although the incidences of intracranial hemorrhage and fatal bleeding were higher in the poor control group, these differences did not reach statistical significance ($p=0.06$ and $p=0.09$, respectively).

Survival analysis

The cumulative incidence of clinical events stratified by TTR status is presented in Fig 1. Kaplan-Meier survival analysis demonstrated a significant difference in event-free survival between the two groups.

As shown in Fig 1A, patients with poor anticoagulation control (TTR < 65%) exhibited a significantly lower cumulative event-free survival rate for the composite efficacy outcomes —comprising ischemic stroke/TIA, SE, and ischemic-related death—compared to those with good control (TTR $\geq$ 65%) (log-rank $p=0.01$). Correspondingly, the safety analysis (Fig 1B) revealed a significant difference in the cumulative incidence of primary safety outcomes between the poor and good control groups (including major bleeding, ICH, and fatal bleeding; log-rank $p=0.002$).

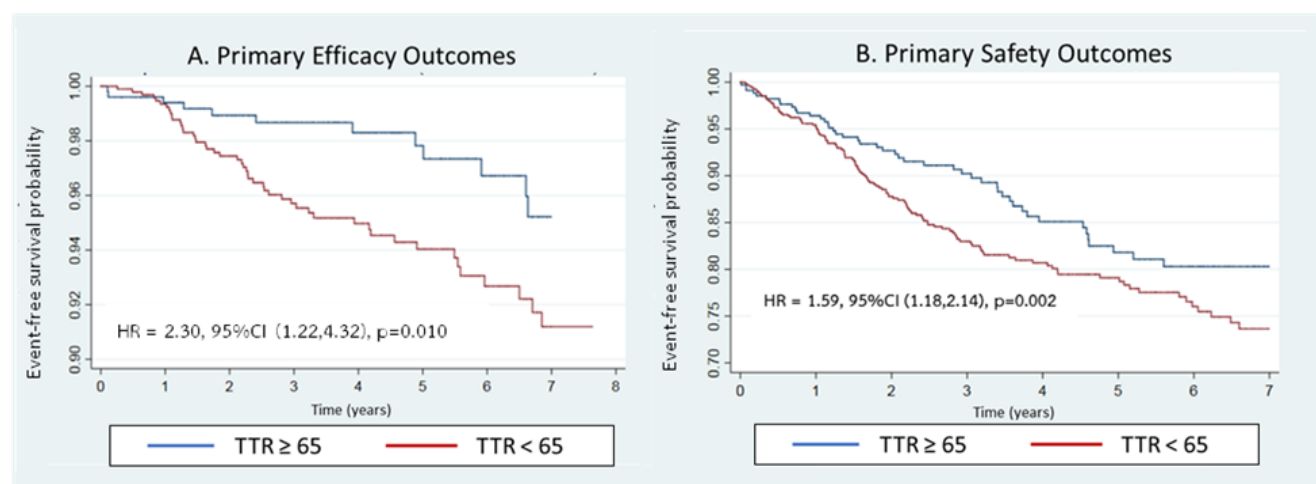


Fig 1. Kaplan-Meier curves for event-free survival stratified by anticoagulation control (TTR $\geq$ 65% vs. < 65%). (A) Primary clinical efficacy outcomes, comprising the composite of stroke/TIA, SE, and ischemic-related death. (B) Primary clinical safety outcomes, including major bleeding, ICH, and fatal bleeding.

Notes: The blue line represents the good control group (TTR $\geq$ 65%), and the red line represents the poor control group (TTR < 65%). P-values were calculated using the log-rank test.

Abbreviations: ICH, intracranial hemorrhage; SE, systemic embolism; TIA, transient ischemic attack; TTR, time in therapeutic range.

TABLE 2. Comparison of clinical efficacy and safety outcomes stratified by Time in Therapeutic Range (TTR) levels ($\geq 65\%$ vs. $< 65\%$).

Variables	Total (n=1466)		TTR $\geq 65\%$ (n=507)		TTR $< 65\%$ (n=959)		Adjusted Hazard Rate (aHR)	95% CI	p-value
	Incidence (n, %)	Incidence Rate	Incidence (n, %)	Incidence Rate	Incidence (n, %)	Incidence Ratio			
Primary efficacy outcomes[†]	61 (4.2)	1.03	12 (2.4)	0.56	49 (5.1)	1.29	2.30	1.22-4.32	0.01*
Stroke/TIA	41 (2.8)	0.69	8 (1.6)	0.38	33 (3.4)	0.86	2.28	1.05-4.93	0.04*
Systemic embolism (SE)	4 (0.3)	0.07	2 (0.4)	0.09	2 (0.2)	0.05	0.57	0.08-4.05	0.57
Ischemic-related death	16 (1.1)	0.27	2 (0.4)	0.09	14 (1.5)	0.36	4.03	0.92-17.74	0.07
Stroke/TIA and Ischemic-related death	57 (3.9)	0.96	10 (2.0)	0.47	47 (4.9)	1.24	2.64	1.34-5.23	0.01*
Primary safety outcome[‡]	224 (15.3)	4.05	59 (11.6)	2.92	165 (17.2)	4.69	1.59	1.18-2.14	0.01*
Major bleeding	159 (10.9)	2.81	42 (8.3)	2.04	117 (12.3)	3.25	1.56	1.10-2.23	0.01*
Intracranial hemorrhage (ICH)	32 (2.2)	0.53	10 (2.0)	0.47	22 (2.3)	0.57	1.20	0.57-2.54	0.06
Fatal bleeding	33 (2.3)	0.55	7 (1.4)	0.33	26 (2.7)	0.67	2.06	0.89-4.75	0.09

Data are presented as n (%), incidence rates are expressed as events per 100 person-years unless otherwise indicated.

[†]Composite of stroke/TIA, SE, and ischemic-related death.

[‡]Composite of ISTH-defined major bleeding, ICH, and fatal bleeding.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; ICH, intracranial hemorrhage; SE, systemic embolism; TIA, transient ischemic attack; TTR, time in therapeutic range, *Statistically significant at $p < 0.05$.

Notes: aHR was adjusted for age, comorbidities, HAS-BLED score, hemoglobin level, eGFR, LVEF, and concurrent medications.

Causes of mortality unrelated to ischemic events or fatal bleeding

Of the 345 recorded deaths, 246 (71.3%) occurred in the poor TTR control group (TTR < 65%), while 99 (28.7%) occurred in the good control group (TTR ≥ 65%). Causes of mortality unrelated to ischemic events or fatal bleeding are summarized in Table 3. There was no significant difference in the distribution of cardiac versus non-cardiac causes of death between the two groups ($p=0.45$).

Non-cardiac causes accounted for 80.3% of total mortalities ($n=277$). Within this category, infection was the leading cause of death ($n=100$, 36.1%). The proportion of deaths attributed to infection was significantly higher in the poor control group compared to the good control group (41.5% vs. 23.2%, $p=0.01$). Conversely, mortality due to COVID-19 was significantly higher in the good control group (24.4% vs. 10.8%, $p=0.01$). No statistically significant intergroup differences were observed regarding malignancy, senescence, or other etiologies.

Subgroup analysis

The largest subgroup consisted of 1,009 patients with atrial fibrillation or atrial flutter (AF/AFL). The mean age of this cohort was 72.4 ± 10.9 years, with a slight female predominance (52.3%). The mean CHA₂DS₂-VASc and HAS-BLED scores were 4.1 ± 1.5 and 2.4 ± 0.9 , respectively. The mean LVEF was $59.8 \pm 13.7\%$, and the mean TTR was $56.1 \pm 20.0\%$. Within this subgroup, 341 patients (33.8%) were classified into the good control group and 668 (66.2%) into the poor control group.

Regarding clinical outcomes within the AF/AFL cohort, the primary efficacy outcome occurred in 47 patients (1.18 per 100 person-years). This composite endpoint comprised ischemic stroke/TIA ($n=32$, 0.8 per 100 person-years), systemic embolism (SE; $n=2$, 0.05 per 100 person-years), and ischemic-related death ($n=13$, 0.32 per 100 person-years).

In terms of safety, primary safety outcomes were documented in 168 patients (4.53 per 100 person-years), consisting of major bleeding ($n=120$, 3.16 per 100 person-years), intracranial hemorrhage (ICH; $n=24$, 0.59 per 100 person-years), and fatal bleeding ($n=24$, 0.59 per 100 person-years). Consistent with the findings in the overall cohort, patients with poor anticoagulation control (TTR < 65%) demonstrated a significantly higher risk for both primary efficacy (aHR 2.31; 95% CI 1.08-4.62; $p=0.03$) and primary safety outcomes (aHR 1.42; 95% CI 1.01-1.99; $p=0.04$) compared to those with good control.

DISCUSSION

In Thailand, warfarin remains a critical therapeutic option for preventing thromboembolism in various conditions. The primary therapeutic objective remains the optimization of efficacy¹⁻³—reducing ischemic stroke/TIA, systemic embolism and ischemic-related death—while ensuring safety¹⁻³ by mitigating major bleeding, intracranial hemorrhage (ICH), and fatal bleeding. Current clinical guidelines emphasize that a TTR ≥ 65% is the benchmark for high-quality anticoagulation.^{2,3,15-18}

Our findings demonstrate that TTR is a critical determinant of clinical outcomes. Patients achieving a

TABLE 3. Causes of mortality unrelated to ischemic-related death or fatal bleeding, stratified by TTR levels (≥ 65% vs. < 65%).

Causes of mortality	Total (n=345)	TTR ≥ 65% (n=99)	TTR < 65% (n=246)	p-value
Cardiac causes	68 (19.7)	17 (17.2)	51 (20.7)	0.45
Non-cardiac causes; (n=277)	277 (80.3)	82 (82.8)	195 (79.3)	0.45
Infection	100 (36.1)	19 (23.2)	81 (41.5)	0.01*
Senescence	86 (31.1)	31 (37.8)	55 (28.2)	0.12
COVID-19 infection	41 (14.8)	20 (24.4)	21 (10.8)	0.01*
Malignancy	27 (9.8)	8 (9.8)	19 (9.7)	0.99
Other causes	23 (8.3)	4 (4.9)	19 (9.7)	0.18

Data are presented as n (%).

Abbreviations: COVID-19, corona virus disease 2019; TTR, time in therapeutic range. * Statistically significant at $p < 0.05$.

Note: P-values were calculated using the Chi-square test or Fisher's exact test, as appropriate.

TTR $\geq 65\%$ demonstrated significantly lower rates of both thrombotic and hemorrhagic complications. These results align with international registries, including GARFIELD-AF,¹⁵ Connolly et al.,¹⁶ and the COOL-AF registry (Krittayaphong et al.)¹⁸ which established that a lower TTR is consistently associated with increased thromboembolic and bleeding events.

The mean TTR in our cohort was $56.36 \pm 25.34\%$, mirroring the $53.56 \pm 26.37\%$ previously documented in the COOL-AF study¹⁸ thereby reinforcing the persistent challenges in achieving optimal anticoagulation control in Thailand. This suboptimal TTR aligns with the incidence of clinical outcomes observed in our cohort, which parallels the incidence rates established by the national registry. Specifically, incidence rates for major bleeding (2.81 vs. 2.48 per 100 person-years) and intracranial hemorrhage (0.53 vs. 0.76 per 100 person-years) are consistent with national trends. Our incidence rate for ischemic stroke/TIA was also lower than that reported in the COOL-AF registry (0.69 vs. 1.33 per 100 person-years). Furthermore, mortality outcomes in our study—specifically ischemic-related death (0.27 per 100 person-years) and fatal bleeding (0.55 per 100 person-years)—were lower than the all-cause mortality reported in the COOL-AF cohort (3.3 per 100 person-years). These variations likely reflect differences in study design, cohort size, and clinical settings between our single-center study and the national registry. Within our AF/AFL subgroup, which shares a similar patient profile to the COOL-AF registry,¹⁸ incidence rates and clinical outcomes were consistent with our overall cohort and corresponded to the general trends reported in the national registry. However, the sample sizes and event rates for patients with other indications for warfarin—such as venous thromboembolism (VTE), mechanical heart valves, cardiomyopathy, rheumatic heart disease, and various hypercoagulable states—were insufficient to achieve statistical significance regarding efficacy and safety outcomes.

Consistent with the GARFIELD study¹⁵ Asian populations frequently exhibit lower TTR compared to Western cohorts.²⁷⁻²⁹ This disparity is likely multifactorial, involving genetic polymorphisms (e.g., *CYP2C9* and *VKORC1*),^{30,31} high dietary intake of vitamin K-rich foods, a higher prevalence of small vessel disease and challenges in monitoring consistency.²⁷⁻²⁹ Additionally, our study identified age ≥ 75 years and declining kidney function ($\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$) as significant independent predictors of adverse clinical outcomes. These findings align with established literature indicating that older patients undergo cognitive and physiological changes,³²⁻³⁵ such as diminished synthesis of vitamin K-dependent

clotting factors and increased vascular fragility, which complicate warfarin therapy. In patients with declining kidney function, platelet dysfunction and fluctuating coagulation factor levels render anticoagulation control inherently more challenging, thereby escalating the risk of adverse outcomes compared to patients with preserved kidney function.^{36,37} These results underscore that patients aged ≥ 75 years and those with compromised kidney function require closer clinical supervision. Consequently, maintaining a stable TTR through meticulous dosage titration is imperative for these vulnerable populations.

In this study, INR monitoring relied on conventional laboratory testing. However, point-of-care testing (POCT) has demonstrated high reliability and accuracy relative to standard methods.³⁸ Implementing POCT in clinical practice could facilitate more frequent INR monitoring, improving patient compliance and facilitating precise dosage adjustments, potentially leading to higher TTR and improved clinical outcomes.

Additionally, although a standardized INR range of 2.0–3.0 was utilized to ensure a consistent TTR analysis, we recognize the clinical diversity within our cohort. Specifically, 135 patients (9.2%) had mechanical heart valves, including 75 with prosthetic mitral valve replacements for whom a higher intensity INR target is typically indicated.⁴ Nevertheless, the application of a uniform range facilitated a comprehensive evaluation of anticoagulation stability across the entire study population.

A notable observation was the higher incidence of infection-related mortality in the poor control group. This association likely involves complex mechanisms,³⁹ including antimicrobial drug-drug interactions,³⁹ sepsis-induced coagulopathy (SIC),⁴⁰ and sepsis-induced multiorgan dysfunction,⁴¹ all of which critically destabilize INR levels. Conversely, poor anticoagulation control and the inherent frailty of these patients may further predispose them to severe infectious complications and poor clinical outcomes.

As data collection coincided with the COVID-19 pandemic, a substantial mortality rate was observed across both cohorts. This reflects the severity of the outbreak in Thailand, where epidemiological data from the Department of Disease Control (Ministry of Public Health) reported 33,669 COVID-19-related fatalities between 2019 and 2022.⁴² Patients on warfarin therapy were particularly vulnerable during COVID-19 infection due to marked INR volatility, which significantly elevated the risks of both thrombosis and hemorrhage.⁴³ The instability of INR during infection is multifactorial, precipitated by malnutrition-related vitamin K deficiency, hepatic dysfunction, and systemic inflammation.⁴⁴ Furthermore,

significant drug-drug interactions involving antivirals, antibiotics, and corticosteroids further complicated anticoagulation management.⁴⁴ Interestingly, the substantial mortality observed in our good-control group suggests that clinical outcomes were primarily dictated by the inherent virulence of COVID-19 rather than anticoagulation quality. Severe COVID-19 infection is characterized by profound cytokine storms, vascular inflammation, and a pro-thrombotic state, which collectively lead to acute respiratory distress syndrome (ARDS) and multiorgan failure. This COVID-19-induced hypercoagulable state manifests as widespread microvascular thrombosis that may bypass the protective threshold of conventional anticoagulation; consequently, even strictly maintained INR levels were often insufficient to counteract the resulting systemic collapse.⁴⁵⁻⁴⁷

Strengths and limitations

This study provides a comprehensive overview of warfarin therapy in real-world clinical practice, encompassing diverse clinical indications. Furthermore, the follow-up duration in this cohort is among the longest recorded in the Thai literature, offering robust longitudinal data on both the long-term efficacy and safety profiles of warfarin.

However, several limitations must be acknowledged. As a retrospective, single-center study, our findings are subject to potential selection bias and incomplete data, which may limit their generalizability. Furthermore, anticoagulation therapy for AF/AFL patients was initiated based on the CHA₂DS₂-VASc score,^{2,3} whereas current guidelines have transitioned to the CHA₂DS₂-VA score;⁴⁸ this shift in clinical criteria may limit the direct application of our results to contemporary practice. Additionally, the overlap with the COVID-19 pandemic acted as a major confounder. The impact of lockdowns on follow-up and the high volume of pandemic-related fatalities may have obscured the true incidence of warfarin-specific adverse events, potentially leading to outcomes that deviate from non-pandemic settings.

Future directions

Future research should focus on multicenter, prospective registries to validate these findings on a larger scale. Expanding the sample size would increase the statistical power to detect differences in rare events, such as systemic embolism, and provide a more nuanced analysis of efficacy and safety outcomes across diverse patient populations and varied clinical contexts.

CONCLUSION

In conclusion, poor anticoagulation control (TTR < 65%) is strongly associated with an increased risk of both thromboembolic and hemorrhagic complications. Maintaining an optimal TTR ≥ 65% remains a critical therapeutic target consistently linked to better clinical outcomes in real-world practice.

Data Availability Statement

The datasets generated and analyzed during the current study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request.

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DECLARATIONS

Grants and Funding Information

None.

Conflict of Interest

The authors declare that they have no competing interests.

Registration Number of Clinical Trial

Not applicable. This was a retrospective study and was not registered as a clinical trial.

Author Contributions

Conceptualization and methodology: N.C.; Investigation and data collection: N.C.; Data analysis: N.C.; Writing—original draft preparation: N.C.; Writing—review and editing: N.C. and R.K.; Supervision: R.K. All authors have read and approved the final manuscript.

Use of Artificial Intelligence

During the preparation of this manuscript, the authors used Grammarly and Gemini 3 Flash to assist in refining grammar, improving clarity, and enhancing readability. Following the use of these tools, the authors reviewed and edited the content to ensure accuracy and accept full responsibility for the final text.

Ethics Approval and Consent to Participate

This study was approved by the Bangkok Metropolitan

Administration Human Research Ethics Committee (BMAHREC), Charoenkrung Pracharak Hospital (Protocol No. S003h/65_EXP). Given the retrospective nature of the study, the requirement for informed consent was waived by the BMAHREC.

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