Comparison of the real-life clinical outcomes of warfarin with effective time in therapeutic range and non-vitamin K antagonist oral anticoagulants: Insight from the AFTER-2 trial

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ABSTRACT

Background: It is unclear whether warfarin treatment with high time in therapeutic range (TTR) is as effective and safe as non-vitamin K antagonist oral anticoagulants (NOACs). It is crucial to compare warfarin with effective TTR and NOACs to predict long-term adverse events in patients with atrial fibrillation.

Aims: We aimed to compare the long-term follow-up results of patients with atrial fibrillation (AF) who use vitamin K antagonists (VKAs) with effective TTR and NOACs.

Methods: A total of 1140 patients were followed at 35 different centers for five years. During the follow-up period, the international normalized ratio (INR) values were studied at least 4 times a year, and the TTR values were calculated according to the Roosendaal method. The effective TTR level was accepted as >60% as recommended by the guidelines. There were 254 patients in the effective TTR group and 886 patients in the NOAC group. Ischemic cerebrovascular disease/transient ischemic attack (CVD/TIA), intracranial bleeding, and mortality were considered primary endpoints based on one-year and five-year follow-ups.

Results: Ischemic CVD/TIA (3.9% vs. 6.2%; $P = 0.17$) and intracranial bleeding (0.4% vs. 0.5%; $P = 0.69$), the one-year mortality rate (7.1% vs. 8.1%; $P = 0.59$), the five-year mortality rate (24% vs. 26.3%; $P = 0.46$) were not different between the effective TTR and NOACs groups during the follow-up, respectively. The CHA2DS2-VASC score was similar between the warfarin with effective TTR group and the NOAC group (3 [2–4] vs. 3 [2–4]; $P = 0.17$, respectively). Additionally, survival free-time did not differ between the warfarin with effective TTR group and each NOAC in the Kaplan-Meier analysis (dabigatran; $P = 0.59$, rivaroxaban; $P = 0.34$, apixaban; $P = 0.26$, and edoxaban; $P = 0.14$).

Conclusion: There was no significant difference in primary outcomes between the effective TTR and NOAC groups in AF patients.

Key words: anticoagulants, atrial fibrillation, international normalized ratios, warfarin

WHAT'S NEW?

Non-vitamin K antagonist oral anticoagulants (NOACs) are non-inferior compared with warfarin in preventing stroke in atrial fibrillation, with similar or decreased risk of bleeding. However, it is unclear whether warfarin treatment with high time in therapeutic range (TTR) is as effective and safe as NOACs. A few studies were performed to compare real-life clinical outcomes of oral anticoagulants. It is crucial to compare warfarin with effective TTR and NOACs to predict long-term adverse events in patients with atrial fibrillation.

INTRODUCTION

Atrial fibrillation (AF) is one of the leading causes of morbidity and mortality in patients with chronic arrhythmias. The Framingham Heart Study demonstrated that it increases the risk of stroke 5-fold and the risk of mortality 2-fold [1]. The guidelines recommend the use of non-vitamin K antagonist oral anticoagulants (NOACs) instead of vitamin K antagonists (VKAs) for stroke prevention because VKAs have a narrow therapeutic range and multiple drug and food interactions [2]. In that context, the guidelines recommend strict international normalized ratio (INR) monitoring and calculation of time in therapeutic range (TTR) to maintain the efficacy of VKA treatment [2].

There is no definite value for TTR in the literature. Real-life data, especially from developed countries, show that the TTR value is typically below 60% [3]. Previous studies have reported that TTR ranges from 55.8% up to 76%, which is higher than real-life data [4]. According to the Thrombosis Canada study, the TTR should be higher than 60% to keep the INR effective [5]. Additionally, previous studies have shown that TTR >60%–65% reduces the risk of stroke [6, 7]. A low TTR, on the other hand, raises the risk of stroke [7]. Therefore, in patients with low TTR, more frequent INR monitoring, patient education, or switching to NOACs is recommended.

The INR is not routinely monitored in patients using NOACs [8]. Furthermore, meta-analyses have demonstrated that NOACs are not inferior to VKAs in terms of efficacy and safety [9]. However, there is still no clear consensus on whether NOACs are cost-effective or not [10]. The major disadvantages of NOACs are the lack of experience and data on the use of antidotes in the case of bleeding and contradiction in acute renal failure [11]. Ineffective anticoagulant therapy may be the primary cause of ischemic stroke and mortality in AF patients [12]. As a result, the 2016 European Cardiac Society Guidelines for the Management of Atrial Fibrillation developed in collaboration with the EACTS (European Association for Cardio-Thoracic Surgery) recommend the use of NOAC rather than VKAs due to the difficulty to provide effective TTR in the follow-up [8].

The purpose of this multicenter, prospective trial was to compare the real-life long-term follow-up results of patients using VKAs with effective TTR and NOACs.

METHODS

Study design

The study is a subgroup analysis of the trial: "Oral Anticoagulant Use and Long-Term Follow-Up Results in Patients with Non-valvular Atrial Fibrillation in Turkey AFTER-2" [13]. The study population reflected twelve regions of Turkey, according to the Statistical Regional Units Classification. The study was designed as a multicenter, prospective, and observational study. All patients were briefed, and an informed consent form was obtained from each participant. The study was conducted in accordance with the 2013 Declaration of Helsinki. The study enrolled 1140 patients in total. They were divided into two groups: 254 patients in the VKA with effective TTR group and 886 patients in the NOAC group (Figure 1). The study was approved by the local ethics committee (AFTER-2 Study ClinicalTrials.gov number, NCT02354456, Dicle University Ethics Committee; date and number: 26/12/2014-47).

Patient characteristics and follow-up data

The study included all consecutive atrial fibrillation patients older than 18 years of age who were admitted to the cardiology outpatient department, except for patients with prosthetic heart valves and rheumatic mitral valve stenosis.

TTR levels of less than 60%, switching between oral anticoagulants (OACs), and the absence of follow-up data or consent forms were determined as exclusion criteria (Figure 1).

AF classifications, demographic and echocardiographic characteristics of the patients, TTR values, OAC treatment regimens, and long-term follow-up results were evaluated. Stroke risk was calculated with the CHA2DS2-VASc score and the bleeding risk with the HAS-BLED score as appropriate. Ischemic cerebrovascular disease (CVD/TIA), intracranial bleeding, and mortality were considered as primary endpoints based on one-year and five-year follow-ups. One-year follow-ups were also added to five-year follow-up clinical endpoints. Telephone interviews or clinical visits were used to collect follow-up data.

Definitions

Hypertension (HT) was defined as systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP)

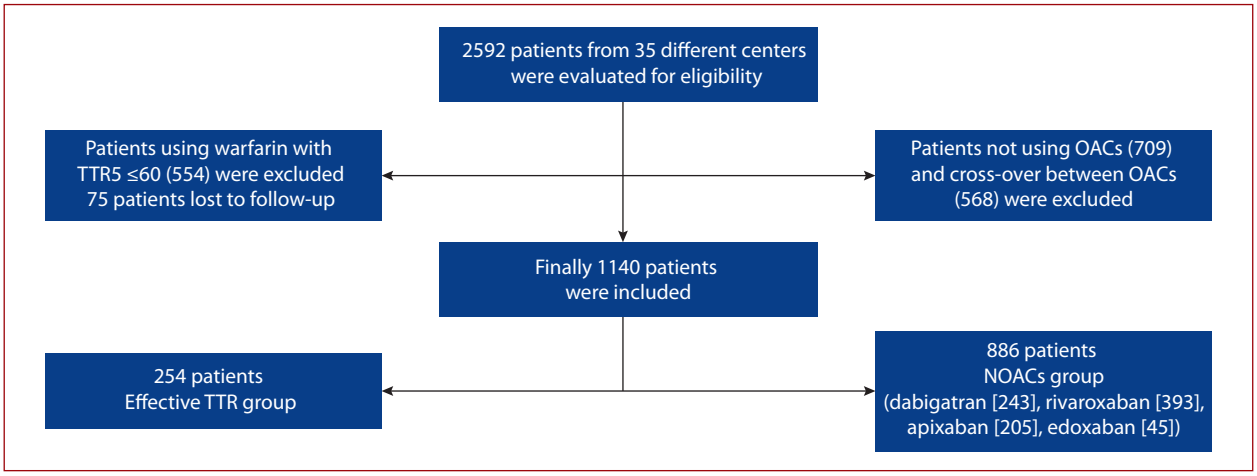

Figure 1. Flowchart of the study design

Abbreviations: NOACs, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulants; TTR, time in therapeutic range

≥90 mm Hg or using antihypertensive medication. Diabetes mellitus (DM) was defined as a fasting glucose level of 126 mg/dL or the use of antidiabetic agents or HbA1c >7%. Dyslipidemia was defined as a total cholesterol level >200 mg/dl or a low-density lipoprotein (LDL) cholesterol level >130 mg/dl. Smoking was defined as current smoking. Peripheral vascular disease (PVD) was defined as >50% stenosis in peripheral arteries. INR values were examined in the local laboratories of each center. The percentage of time in the therapeutic INR range was calculated according to the Rosendaal method, assuming that the changes (at least 4) between consecutive INR measurements were linear with time [14]. While determining the TTR values, the results with an interval of less than 100 days between the INR values during the follow-up period were evaluated. The effective TTR level was accepted as >60% as recommended by the guidelines [3]. Major bleeding was defined according to the criteria of the International Society for Thrombosis and Hemostasis [15]. The symptomatic and/or mortal bleeding in critically important areas or organs, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intraarticular, resulting in a decrease in hemoglobin of at least 2 g per deciliter or in transfusion of two or more whole blood or red blood cells or with intramuscular compartment syndrome, was accepted as major bleeding.

Statistical analysis

Data were analyzed using SPSS for Windows version 25.0 (IBM Corp., Armonk, NY, US). The distribution of continuous variables was evaluated by the Kolmogorov-Smirnov or Shapiro-Wilk tests as appropriate. Continuous variables were expressed as mean (standard deviation [SD]) or median (IQR). Continuous variables between two independent groups were analyzed by Student's t-test or the Mann-Whitney U test as appropriate. Categorical variables were presented as percentages (%) and statistical analysis was performed by the χ^2 test or Fisher's exact test. Univariable and multivariable logistic regression analysis was performed to determine independent predictors of the primary endpoints. The parameters with a *P*-value <0.05 in the univariable logistic analysis were added to the multivariable logistic analysis. A Kaplan-Meier analysis was used to determine the difference in event-free survival rates between the two groups. A *P*-value of <0.05 was considered statistically significant.

RESULTS

A total of 1140 patients with a mean age of 69.4 (10.4) years (57% female) were enrolled in the study. The patients were divided into two groups: 254 patients were in the VKA with effective TTR group and 886 patients in the NOAC group (Figure 1, Table 1). Baseline clinical characteristics, outcomes, and echocardiographic findings of the patients according to treatment strategies are shown in Table 1. HT (69.2%), chronic kidney disease (65.7%), ischemic cardiomyopathy (26.6%), and DM (23.1%) were the most common comorbid diseases in both groups. The mean ejection fraction % (EF%) was 50.9 (11). EF% was significantly higher in the VKA with effective TTR group compared to the NOAC group (52.7 [10.9] vs. 50.3 [11], respectively; $P = 0.003$, Table 1).

Persistent-permanent AF (75.4%) was the most common AF type in both groups, and it was significantly higher in the VKA with effective TTR group than in the NOAC group (82.7% vs. 73.3%, respectively; $P = 0.002$, Table 1). Most patients (82.7%) were classified as European Heart Rhythm Association (EHRA) class 1 and 2 based on admission symptoms. Moreover, rate control was the most preferred treatment management (75.4%) in all patients. The rate of patients who underwent the rhythm control strategy was significantly higher in the NOAC group (26.4%) compared to the VKA with effective TTR group (26.4% vs. 18.5%, respectively; $P = 0.01$, Table 1).

The comparison of other drugs used by the patients is summarized in Table 2.

The median follow-up period time of the patients was 2011 (960–2160) days. Ischemic CVD/TIA (3.9% vs. 6.2%;

Table 1. Demographic characteristics and echocardiographic results

Parameters	Overall (n = 1140)	Effective TTR (n = 254)	NOAC (n = 886)	*P*-value
Sex, female, n (%)	650 (57)	140 (55.1)	510 (57.6)	0.49
Age, years, mean (SD)	69.37 (10.38)	68.56 (10.43)	69.60 (10.37)	0.16
Persistent-permanent AF, n (%)	859 (75.4)	210 (82.7)	649 (73.3)	0.002
EHRA 1–2, n (%)	943 (82.7)	213 (83.9)	730 (82.4)	0.59
Treatment strategy, rhythm control, n (%)	281 (24.6)	47 (18.5)	234 (26.4)	0.01
Body mass index, kg/m^2, mean (SD)	28.46 (3.94)	28.23 (3.94)	28.52 (3.94)	0.31
Ischemic CMP, n (%)	303 (26.6)	57 (22.4)	246 (27.8)	0.09
Dilated CMP, n (%)	51 (4.5)	14 (5.5)	37 (4.2)	0.36
Chronic obstructive pulmonary disease, n (%)	191 (16.8)	47 (18.5)	144 (16.3)	0.40
Deep venous thrombus, n (%)	5 (0.4)	1 (0.4)	4 (0.5)	0.69[a]
Pulmonary embolism, n (%)	8 (0.7)	3 (1.2)	5 (0.6)	0.26[a]
Thyroid dysfunction, n (%)	37 (3.2)	5 (2)	32 (3.6)	0.19
GFR, ml/min/1.73 m^2, median (IQR)	44 (33.13–63.91)	41.79 (30.13–68.68)	44 (33.83–61.72)	0.36
Chronic renal failure, n (%)	749 (65.7)	170 (66.9)	579 (65.3)	0.64
Smoker, n (%)	63 (5.5)	24 (9.4)	39 (4.4)	0.002
Hypertension, n (%)	789 (69.2)	165 (65)	624 (70.4)	0.10
Diabetes mellitus, n (%)	263 (23.1)	45 (17.7)	218 (24.6)	0.02
Ischemic CVD/TIA, n (%)	84 (7.4)	13 (5.1)	71 (8.0)	0.12
Intracranial bleeding, n (%)	9 (0.8)	2 (0.8)	7 (0.8)	0.10
EF, %, mean (SD)	50.86 (11.02)	52.68 (10.92)	50.33 (11.0)	0.003
Left atrial diameter, mean (SD)	45.40 (6.70)	45.22 (6.42)	45.45 (6.78)	0.62
Left atrial thrombus, n (%)	5 (0.4)	1 (0.4)	4 (0.5)	0.90

[a]Fisher's exact test
Abbreviations: AF, atrial fibrillation; CMP, cardiomyopathy; CVD, cerebrovascular disease; EF, ejection fraction; EHRA, European Heart Rhythm Association; GFR, glomerular filtration rate; NOAC, non-vitamin K antagonist oral anticoagulant; TIA, transient ischemic attack; TTR, time in therapeutic range

Table 2. Comparison of other drugs used by patients

Parameters	Effective TTR (n = 254)	Dabigatran (n = 243)	Rivaroxaban (n = 393)	Apixaban (n = 205)	Edoxaban (n = 45)	*P*-value
ASA, n (%)	41 (16.1)	53 (21.8)	93 (23.7)	48 (23.4)	14 (31.1)	0.09
Clopidogrel, n (%)	8 (3.1)	13 (5.3)	28 (7.1)	14 (6.8)	6 (13.3)	0.06
Prasugrel, n (%)	1 (0.4)	0	0	1 (0.5)	0	0.36[a]
Ticagrelor, n (%)	0	0	0	1 (0.5)	0	0.22[a]
Beta-blocker, n (%)	161 (63.4)	171 (70.4)	249 (63.4)	131 (63.9)	26 (57.8)	0.30
Diltiazem, n (%)	50 (19.7)	36 (14.8)	75 (19.1)	29 (14.1)	7 (15.6)	0.35
Verapamil, n (%)	6 (2.4)	3 (1.2)	8 (2.0)	2 (1.0)	3 (6.7)	0.16[a]
Digoxin, n (%)	51 (20.1)	47 (19.3)	78 (19.8)	45 (22.0)	6 (13.3)	0.77
Amiodarone, n (%)	11 (4.3)	9 (3.7)	16 (4.1)	11 (5.4)	1 (2.2)	0.86
Propafenone, n (%)	2 (0.8)	14 (5.8)	18 (4.6)	3 (1.5)	0	0.004
Sotalol, n (%)	6 (2.4)	1 (0.4)	0	2 (1)	0	0.015[a]
ACEi, n (%)	74 (29.1)	71 (29.2)	112 (28.5)	70 (34.1)	17 (37.8)	0.47
ARB, n (%)	60 (23.6)	70 (28.8)	103 (26.2)	50 (24.4)	13 (28.9)	0.70
DHP-CCB, n (%)	32 (12.6)	18 (7.4)	27 (6.9)	15 (7.3)	2 (4.4)	0.07
Statin, n (%)	44 (17.3)	41 (16.9)	51 (13.0)	34 (16.6)	7 (15.6)	0.54
Diuretic, n (%)	99 (39.0)	90 (37.0)	146 (37.2)	84 (41.0)	20 (44.4)	0.78
Nitrate, n (%)	14 (5.5)	6 (2.5)	23 (5.9)	16 (7.8)	4 (8.9)	0.11
Alpha-blocker, n (%)	4 (1.6)	4 (1.6)	8 (2.0)	0	1 (2.2)	0.22[a]
PPI, n (%)	35 (13.8)	45 (18.5)	43 (10.9)	19 (9.3)	4 (8.9)	0.02

[a]Fisher's exact test
Abbreviations: ASA, acetylsalicylic acid; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; DHP-CCB, dihydropyridine calcium channel blocker; PPI, proton pump inhibitor

P = 0.17, respectively) and intracranial bleeding (0.4% vs. 0.5%; *P* = 0.69, respectively) were not different between the VKA with effective TTR and NOAC groups during the five-year follow-up period (Table 3). One-year mortality (7.1% vs. 8.1%; *P* = 0.59, respectively) and five-year mortality (24% vs. 26.3%; *P* = 0.46, respectively) were not significantly different between the VKA with effective TTR and NOAC groups (Table 3). The HAS-BLED score was significantly higher in the NOAC group compared to the VKA with effective TTR group (*P* = 0.004, Table 3). The CHA_2DS_2-VASC score was not statistically different between groups (*P* = 0.17, Table 3). The comparisons of primary clinical endpoints

Table 3. Comparison of the results in the effective TTR group and the patients using NOACs

Parameters	Overall (n = 1140)	Effective TTR (n = 254)	NOAC (n = 886)	*P*-value
Ischemic CVD/TIA in follow-up, n (%)	65 (5.7)	10 (3.9)	55 (6.2)	0.17
Intracranial bleeding in follow-up, n (%)	5 (0.4)	1 (0.4)	4 (0.5)	0.69[a]
Death at 1-year follow-up, n (%)	90 (7.9)	18 (7.1)	72 (8.1)	0.59
Death at 5-year follow-up, n (%)	294 (25.8)	61 (24)	233 (26.3)	0.46
Primary endpoint, n (%)	324 (28.4)	62 (24.4)	262 (29.6)	0.11
HAS-BLED score, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	0.004
CHA_2DS_2-VASC score, median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	0.17

[a]Fisher's exact test
Abbreviations: CVD; cerebrovascular disease, NOAC; non-vitamin K antagonist oral anticoagulant, TIA; transient ischemic attack; TTR; time in therapeutic range

Table 4. Comparison of the results in the effective TTR group and the patients using dabigatran, rivaroxaban, apixaban, and edoxaban

Effective TTR-dabigatran 110–150 mg relationship	Effective TTR (n = 254)	110 mg (n = 201)	*P*-value	150 mg (n = 42)	*P*-value
Ischemic CVD/TIA in follow-up, n (%)	10 (3.9)	11 (5.5)	0.44	3 (7.1)	0.41[a]
Intracranial bleeding in follow-up, n (%)	1 (0.4)	2 (1.0)	0.59	0	N/A[b]
Death at 1-year follow-up, n (%)	18 (7.1)	13 (6.5)	0.80	0	0.09[a]
Death at 5-year follow-up, n (%)	61 (24.0)	51 (25.4)	0.74	7 (16.7)	0.29
Primary endpoint, n (%)	62 (24.4)	61 (30.3)	0.16	10 (23.8)	0.93
HAS-BLED score, median (IQR)	1 (1–2)	1 (1–2)	0.05	1 (1–2)	0.63
CHA_2DS_2-VASC score, median (IQR)	3 (2–4)	3 (2–4)	0.48	3 (2–4)	0.95
Effective TTR-rivaroxaban 15–20 mg relationship	**Effective TTR (n = 254)**	**15 mg (n = 356)**	***P*-value**	**20 mg (n = 37)**	***P*-value**
Ischemic CVD/TIA in follow-up, n (%)	10 (3.9)	26 (7.3)	0.08	1 (2.7)	N/A[b]
Intracranial bleeding in follow-up, n (%)	1 (0.4)	1 (0.3)	N/A[b]	1 (2.7)	0.24[a]
Death at 1-year follow-up, n (%)	18 (7.1)	30 (8.4)	0.54	2 (5.4)	N/A[b]
Death at 5-year follow-up, n (%)	61 (24.0)	95 (26.7)	0.46	8 (21.6)	0.75
Primary endpoint, n (%)	62 (24.4)	109 (30.6)	0.09	8 (21.6)	0.71
HAS-BLED score, median (IQR)	1 (1–2)	1 (1–2)	0.03	1 (1–2)	0.92
CHA_2DS_2-VASC score, median (IQR)	3 (2–4)	3 (2–4)	0.32	3 (2–4)	0.66
Effective TTR-apixaban 2.5–5 mg relationship	**Effective TTR (n = 254)**	**2.5 mg (n = 181)**	***P*-value**	**5 mg (n = 24)**	***P*-value**
Ischemic CVD/TIA in follow-up, n (%)	10 (3.9)	9 (5)	0.60	2 (8.3)	0.28[a]
Intracranial bleeding in follow-up, n (%)	1 (0.4)	0	N/A[b]	0	N/A[b]
Death at 1-year follow-up, n (%)	18 (7.1)	21 (11.6)	0.10	2 (8.3)	0.69[a]
Death at 5-year follow-up, n (%)	61 (24.0)	52 (28.7)	0.27	5 (20.8)	0.73
Primary endpoint, n (%)	62 (24.4)	54 (29.8)	0.21	5 (20.8)	0.70
HAS-BLED score, median (IQR)	1 (1–2)	1 (1–2)	0.009	2 (1–2)	0.11
CHA_2DS_2-VASC score, median (IQR)	3 (2–4)	3 (2–4)	0.07	3 (2–4)	0.78
Effective TTR-edoxaban 30–60 mg relationship	**Effective TTR (n = 254)**	**30 mg (n = 32)**	***P*-value**	**60 mg (n = 13)**	***P*-value**
Ischemic CVD/TIA in follow-up, n (%)	10 (3.9)	3 (9.4)	0.16	0	N/A[b]
Intracranial bleeding in follow-up, n (%)	1 (0.4)	0	N/A[b]	0	N/A[b]
Death at 1-year follow-up, n (%)	18 (7.1)	2 (6.3)	N/A[b]	2 (15.4)	0.25
Death at 5-year follow-up, n (%)	61 (24.0)	11 (34.4)	0.20	4 (30.8)	0.53
Primary endpoint, n (%)	62 (24.4)	11 (34.4)	0.22	4 (30.8)	0.74
HAS-BLED score, median (IQR)	1 (1–2)	2 (1–2)	0.02	2 (1–3)	0.19
CHA_2DS_2-VASC score, median (IQR)	3 (2–4)	4 (3–4)	0.03	3 (1–4.5)	0.67

[a]Fisher's exact test; [b]Statistics not applicable due to variables being constant
Abbreviations: CVD, cerebrovascular disease; N/A, statistics not applicable due to variables being constant; TIA, transient ischemic attack; TTR, time in therapeutic range

of the patients using dabigatran, rivaroxaban, apixaban, edoxaban, and VKA with effective TTR were shown in Table 4 and Figure 2. Dabigatran, rivaroxaban, apixaban, and edoxaban were non-inferior to VKA with effective TTR in terms of primary clinical outcomes among all doses of treatment regimens (Table 4).

To identify the predictors of the primary endpoint, multivariable logistic regression analysis was performed using variables with a *P*-value <0.05 such as age, male sex, VKA with effective TTR, diabetes mellitus, hypertension, AF classification (persistent/permanent or paroxysmal/lone AF), EHRA classification (1–2 or 3–4), treatment strategy

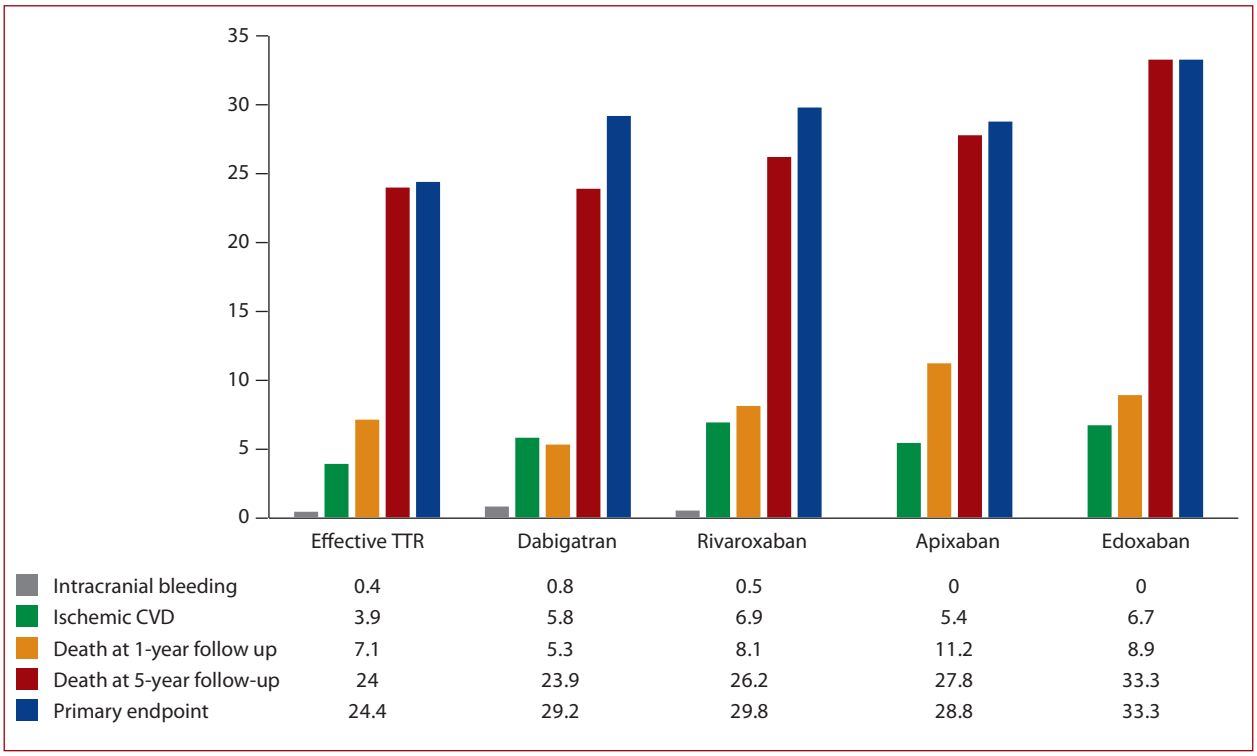

Figure 2. Bar chart of oral anticoagulants in terms of major clinical endpoints

Abbreviations: CVD, cerebrovascular disease; other — see Figure 1

Table 5. Predictors of the primary endpoint in the univariable and multivariable logistic regression analysis model

Parameters	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age, years	1.08 (1.06–1.10)	<0.001	1.08 (1.06–1.09)	<0.001
Male sex	1.31 (1.01–1.70)	0.04	1.08 (0.81–.145)	0.56
VKA with effective TTR	0.76 (0.55–1.06)	0.11		
Atrial fibrillation classification	1.82 (1.31–2.52)	<0.001	1.44 (1.00–2.08)	0.046
Treatment strategy	1.40 (1.05–1.87)	0.02	1.10 (0.75–1.62)	0.61
EHRA classification	1.57 (1.14–2.18)	0.006	1.36 (0.94–1.96)	0.09
Ejection fraction	0.95 (0.94–0.96)	<0.001	0.96 (0.94–0.97)	<0.001
Hypertension	1.30 (0.97–1.73)	0.07		
Diabetes mellitus	1.33 (0.99–1.79)	0.06		
Chronic renal failure	1.24 (0.94–1.63)	0.12		
Smoking	1.00 (0.57–1.76)	0.98		
Chronic obstructive pulmonary disease	1.86 (1.35–2.58)	<0.001	1.52 (1.06–2.18)	0.02
Pulmonary embolism	4.24 (1.00–17.87)	0.049	4.28 (0.90–20.17)	0.07

Abbreviations: 95% CI, 95% confidential interval; OR, odds ratio, primary endpoint (includes ischemic cerebrovascular disease/transient ischemic attack (CVD/TIA), intracranial bleeding, and five-year mortality)
Atrial fibrillation classification (persistent/permanent or paroxysmal/lone AF), treatment strategy (rhythm or rate control), EHRA classification (EHRA 1–2 or 3–4)

(rhythm or rate control), ejection fraction, chronic renal failure, smoking, chronic obstructive pulmonary disease, and pulmonary embolism in univariable logistic regression analysis (Table 5). Age (odds ratio [OR], 1.08; 95% confidence interval [CI], 1.06–1.10; P <0.001), ejection fraction (OR, 0.96; CI, 0.94–0.97; P <0.001), chronic obstructive pulmonary disease (OR, 1.52; CI, 1.06–2.18; P = 0.02), atrial fibrillation type (OR, 1.44; CI, 1.00–2.08; P = 0.046) were found to be associated with the primary endpoint in multivariable logistic regression analysis (Table 5). Using VKA with effective TTR was not found to be associated with the primary endpoint (OR, 0.76; 95% CI, 0.55–1.06; P = 0.11).

Kaplan-Meier analysis was conducted to examine the survival of an average of 5 years between the VKA with effective TTR and each NOAC during the five-year follow-up period; no significant difference was found between the groups (dabigatran; P = 0.59, rivaroxaban; P = 0.34, apixaban; P = 0.26 and edoxaban; P = 0.14, Figure 3).

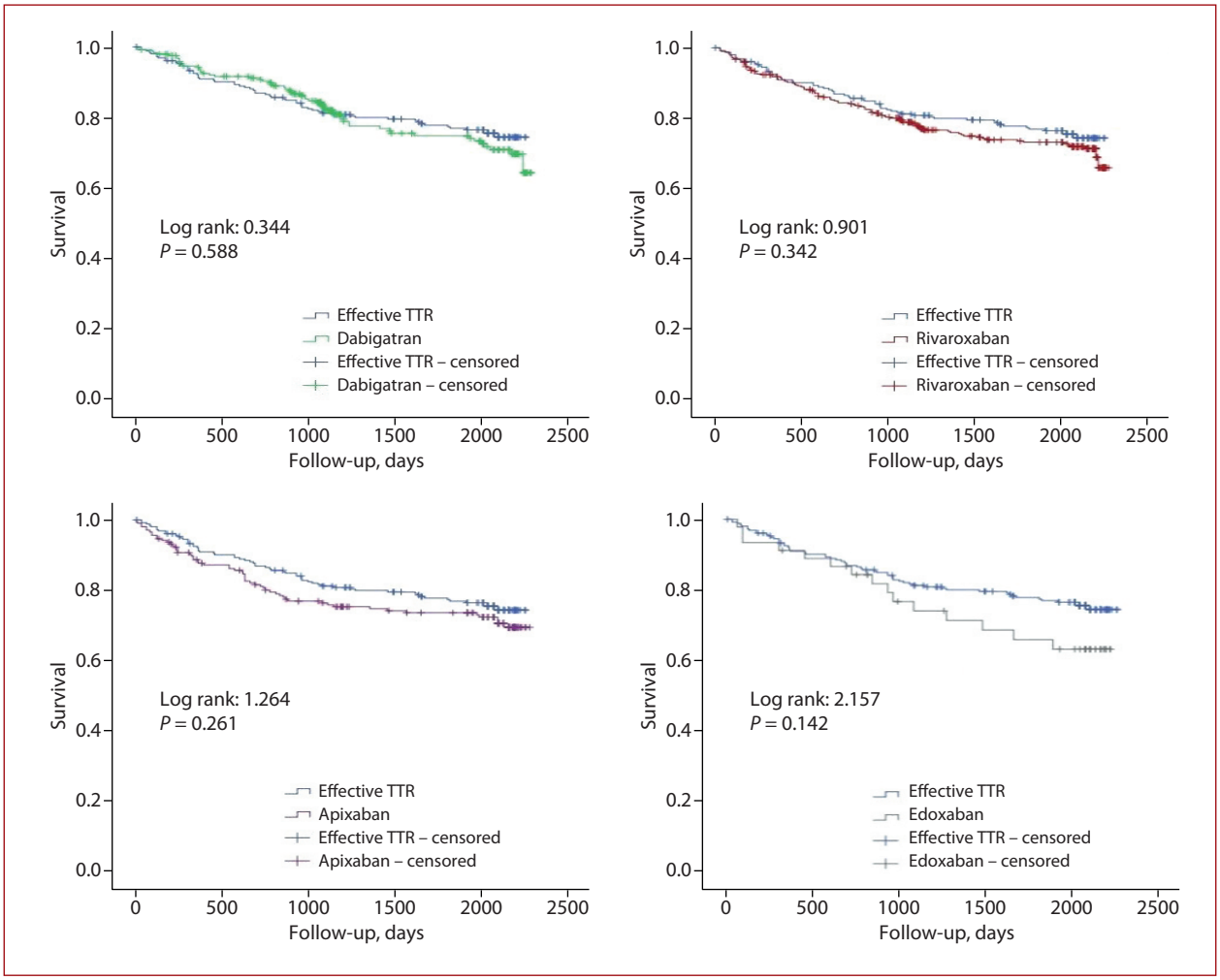

Figure 3. Comparison of survival of an average of 5 years by effective TTR with each of NOACs

Abbreviations: see Figure 1

DISCUSSION

In this multicenter, prospective, observational study, we compared the real-life long-term follow-up results of patients using VKAs with effective TTR and using NOACs. Our study showed significant real-life clinical outcomes for patients with AF in the Turkish population. One-year mortality, five-year mortality, and ischemic CVD, and intracranial bleeding were similar between the patients using VKA with effective TTR and those using NOACs, as well as with each component of NOACs.

The definitive cut-off value for TTR is a matter of debate in the literature. A study conducted in 2008 showed that VKA with dual antiplatelet therapy in AF should be more effective clinically if the TTR values are kept in the 58%–65% range [7]. Moreover, it has been shown that the clinical effectiveness of VKA decreases sharply as TTR falls below 65% compared to antiplatelets [7]. In the AFTER-2 study, the mean TTR of the patients was 40%, and only 31.4% of the patients' TTR values were in the effective range [13]. INR measurements should be done more frequently to improve VKA management, but this implies additional costs for laboratory resources [16]. Alternative treatments can be considered if VKA management cannot be optimized. TTR assessment indicates less effective management of care with warfarin therapy, thus leading to the derivation of the greatest benefit from NOACs. In addition, stronger systems for administering and monitoring VKA use in daily practice are warranted to improve the quality of care in terms of sustained oral anticoagulation. The 2014 National Institute for Health and Care Excellence guidelines for stroke prevention in people with AF recommend the use of NOACs instead of VKA if TTR is under 65% [17]. The Sportif III and V randomized trials reported that the risks of death, myocardial infarction, stroke, and systemic embolic events were lower when the TTR was kept above 60% [18]. It has been reported that TTR rates are mostly below 40% in the Asia-Pacific region [19].

In recent years, there has been widespread use of NOACs in clinical practice worldwide, as they have become a more effective and safer option for preventing the development of stroke in patients with AF [20]. Replacement of a VKA with a NOAC should be considered, particularly in patients with TTR <60%. Poor anticoagulation therapy has been associated with increased risk of stroke, bleeding,

and all-cause mortality [21]. Therefore, strict INR control is imperative. Some studies have reported that VKAs can lead to high health expenditures due to high thromboembolism and bleeding risks in patients with poor INR control [22]. NOACs may be cost-effective in such cases as previously shown [22]. In our study, NOACs were preferred in patients with high HAS-BLED scores. Furthermore, although the apixaban and edoxaban groups had higher-risk patient populations in terms of bleeding, no significant difference was observed. Thus, apixaban and edoxaban may be quite safe for patients at risk of bleeding.

In the RELY study, dabigatran 110 mg twice a day and warfarin were compared, and systemic embolism and stroke rates were found to be similar. However, lower rates of major bleeding were observed in the dabigatran arm. Comparing dabigatran 150 mg twice a day with warfarin, lower rates of stroke and systemic embolism were observed in the dabigatran arm, and major bleeding rates were observed to be similar [23]. In the ROCKET-AF study, rivaroxaban was non-inferior to warfarin in the prevention of stroke or systemic embolism [24]. Although intracranial or fatal bleeding occurred less often in the rivaroxaban group than in the VKA group, there were no significant differences in terms of major bleeding. In the ARISTOTLE study, apixaban was superior to warfarin in preventing stroke, systemic embolism, and major bleeding, as well as lowering the mortality risk [25]. In the ENGAGE-AF study, edoxaban was non-inferior to warfarin in the prevention of stroke and systemic embolism. Also, bleeding and cardiovascular death were significantly lower in the edoxaban arm [26].

Mean TTR is generally lower in Asians or East Asians compared with non-Asians or non-East Asians. In the RELY study, TTR was 56.5% in the Asian population while in the ROCKET-AF study, it was 47.1% in East Asia. In the ARISTOTLE study, the TTR was 60% while in the ENGAGE-AF study, the median TTR was 67.1% [27]. In our study, the median TTR was 78%. This high rate is because only patients with TTR >60% were included in our study. Our study demonstrates that if TTR is kept within the therapeutic ranges, warfarin should be at least as effective as NOACs. NOACs have been compared with ineffective warfarin treatments in most studies, especially in the Asian population sub-analysis of these major trials [23–26]. Thus, one of the strengths of our study is that we compared effective VKA treatment with NOACs using real-life data.

In a study conducted in Sweden involving 81 176 patients, dabigatran, rivaroxaban, and apixaban treatments were compared with warfarin with effective TTR [28]. Time in the therapeutic range was 71.4% in patients treated with warfarin [28]. The study found no difference in ischemic stroke frequency between apixaban, dabigatran, or rivaroxaban compared to high-TTR warfarin therapy [28]. However, fewer bleeding events were seen with apixaban and dabigatran than with effective TTR warfarin, whereas results were similar with rivaroxaban [28]. In our study, no difference was found between warfarin treatment with effective TTR and NOACs in terms of both ischemic stroke and intracranial bleeding outcomes. Similarly, in the EORP-AF General Long-Term registry study by Lodziński et al. [29], no association was found between VKAs and NOACs in Polish patients with AF in terms of long-term thromboembolic and hemorrhagic outcomes.

Renal insufficiency is an important barrier to the use of NOACs. Treatments that are not adjusted based on the patient's glomerular filtration rate (GFR) may result in insufficient and uncontrolled prescription of NOACs [30]. In our study, the renal insufficiency rate was 65.3% which is relatively high. This can be attributed to the elderly age of the participants, predominance of females, and the definition of chronic renal failure in the study (the patients with GFR <60 ml/min/1.73 m^2). Although the current guidelines [31] strongly recommend the use of NOACs, the prescription of NOACs is relatively low in Turkey due to cost issues. Warfarin is still preferred in many developing or less developed countries due to healthcare budget restrictions and affordability [32].

Study limitations

Limitations are also inherent in our study, like other trials. This subgroup analysis was not prespecified, and there may be a lack of statistical power to reliably detect differences in the efficacy and safety of VKAs versus NOACs. Although study participants were drawn from many geographic regions of the country, the results cannot be generalized. Although TTR is calculated with the Rosendaal method, there may be some INR fluctuations. In addition, there may have been errors because the data were obtained from the hospital systems and national data recording systems.

CONCLUSION

Our study has shown that VKAs with effective TTR are at least as effective and safe as NOACs in terms of all-cause mortality, and one- and five-year frequency of cerebrovascular events.

Article information

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