



Research Paper: The Prevalence of Prescription of New Anticoagulant Drugs and Its Determinant Factors in Patients With Ischemic Stroke and Non-valvular Atrial Fibrillation



Yaser Moaddabi¹, Amirreza Ghayeghran², Hamidreza Hatamian², Sara Alimohammadi², Maryam Shakiba³, Sama Noroozi Guilandehi⁴, Alia Saberi^{*}

1. Department of Neurology, Neuroscience Research Center, Poursina Hospital, Guilan University of Medical Sciences, Rasht, Iran

2. Department of Neurology, Poursina Hospital, Guilan University of Medical Sciences, Rasht, Iran

3. Road Trauma Research Center, School of Health, Guilan University of Medical Sciences, Rasht, Iran

4. Student of Medicine, Department of Neurology, Student Research Committee of Neuroscience Research Center, Poursina Hospital, Guilan University of Medical Sciences, Rasht, Iran



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ABSTRACT

Background: Patients with ischemic stroke and underlying Atrial Fibrillation (AF) have a high risk of recurrent embolic events. New Oral Anticoagulant (NOAC) is highly effective and reduces the risk of recurrence in AF-associated Ischemic Stroke (AFAIS).

Objectives: This study aimed to determine the prescription pattern of NOAC and its determinant factors in patients with non-valvular AFAIS.

Materials & Methods: This research was a cross-sectional descriptive study and the participants were referred to an academic hospital in the north of Iran from 2017 to 2018. The study variables included demographic variables such as the use of new anticoagulants, age, sex, place of residence, income level, education, the history of stroke and Myocardial Infarction (MI), medication, and stroke severity based on The National Institutes of Health Stroke Scale criteria. The patient's functional status based on the modified Rankin Scale (mRS) was extracted from the patients' medical records. The data analysis was conducted by SPSS V. 19, using the Chi-square test and t-test, as well as the logistic regression model.

Results: In this study, 363 patients with ischemic stroke with the origin of non-valvular AF and the mean age of 67.87 years were studied. Of them, 191 (52.6%) patients were women, and 30.6% were prescribed rivaroxaban at the time of discharge. The results showed that women were more likely to use rivaroxaban than men ($P=0.001$, $OR=0.422$). The history of stroke ($P=0.004$, $OR=2.17$) and the stroke severity ($P=0.05$, $OR=2.19$) was associated with an increase in rivaroxaban prescription.

Conclusion: The results of this study showed that the administration of NOAC in this population was low and associated with gender and the severity and the history of stroke.

Keywords: Anticoagulants; Stroke; Atrial fibrillation

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* Corresponding Author:

Alia Saberi

Address: Department of Neurology, Neuroscience Research Center, Poursina Hospital, Guilan University of Medical Sciences, Rasht, Iran

Tel: +98 (13) 33368646, **Fax:** +98 (13) 33368646

E-mail: alia.saberi.1@gmail.com

Highlights

- NOAC prescription frequency is low in Guilan Province of Iran
- NOAC prescription in stroke was more frequent among women and patients with more severe stroke

Introduction

Stroke is a leading cause of death and disability all over the world [1]. Ischemic stroke is the most common type of stroke, and hemorrhagic stroke accounts for 10% to 20% of all strokes [2]. Ischemic stroke has different subtypes based on etiology, including large arteries atherosclerotic changes, cardiac emboli, small vessel occlusion, and stroke due to other etiologies [3]. Cardioembolic strokes are presented with more acute neurologic deficits symptoms compared with other strokes and are responsible for 15% to 20% of ischemic strokes [4]. Around 50% to 65% of cardiogenic emboli are the result of Atrial Fibrillation (AF) [2].

AF risk factors include age, especially age above 50 years, male gender, hypertension, obesity, and underlying structural heart diseases such as heart failure [5]. AF predisposes patients to develop atrial thrombi [6]. AF-associated Ischemic Strokes (AFAIS) usually have a worse prognosis compared with other etiologies [5] and can cause disability and often have higher mortality [7]. Patients with acute ischemic stroke and underlying AF have a high risk of recurrent embolic events without adequate secondary prevention [8]. Warfarin, a vitamin K antagonist, has been an effective anticoagulant therapy for over 50 years [9].

New Oral Anticoagulants (NOAC) include Xa factor antagonists and direct thrombin inhibitors [7]. Oral Anticoagulants (OACs) in AFAIS are highly effective and reduce the risk of recurrence [8]. NOACs are much easier to use than warfarin. The dosing of warfarin needs to be adjusted by the International Normalized Ratio (INR), which requires routine blood drain. Besides, warfarin interacts with lots of medications and foods. In contrast, NOACs are administered once or twice daily at a fixed dosage, do not require routine INR monitoring, and have fewer interactions with other medications [10]. NOAC is often avoided and particularly susceptible to be discontinued by patients or even physicians in high-risk situations after a previous embolic stroke to prevent possible complications [8].

To the best of our knowledge, studies on AFAIS treatments are scarce, especially after new anticoagulants introduction. So, we aimed at studying the prescription patterns, the prevalence of NOAC administration, and the determinative factors of taking NOAC in a population in the north of Iran.

Materials and Methods

The present cross-sectional descriptive single-teaching center survey was conducted to investigate the NOAC prescription in patients with AFAIS who were admitted to an academic hospital in the north of Iran from 2017 to 2018.

Study population

The study population included stroke patients who were hospitalized in Poursina Hospital between April 1, 2017, and 2018 in the north of Iran. They had a documented diagnosis of non-valvular AF on electrocardiogram or during cardiac monitoring.

A total of 363 patients of non-valvular AFAIS participated in our study. Based on the Brais et al. study, 28% of AFAIS patients use NOAC, and given the 95% confidence interval, the sample size would be 303 [11]. Also, considering 5 patients for each predictor (12 predictors), the final sample size would be 363.

$$1. N = [Z1 - (\alpha \div 2)]^2 [p(1-p)] \div d^2$$

N: sample size

p: expected prevalence

d: precision

Z: confidence level at 95% (standard value of 1.96)

Inclusion and exclusion criteria

The patients would be included if they were diagnosed with ischemic stroke based on sudden onset focal neurological deficit, which is documented by imaging (CT scan or MRI) and the presence of AF rhythm on electrocardiogram or cardiac monitoring.

The patients would be excluded if they were diagnosed with non-ischemic stroke diseases after imaging or if they had rheumatic valve disease or valvular repair or replacement and death during admission.

Variants and data collection

Our primary variant is the administration of NOAC (rivaroxaban). The demographic factors include age, gender, place of residence, income level, education, underlying diseases, and the history of stroke or Myocardial Infarction (MI) drug history including Non Steroid Anti Inflammatory Drug (NSAID) and clopidogrel extracted from patient's medical records. In the case of deficient medical records, the missing data were collected and recorded by a telephone interview with the patient or during the subsequent visits. Prescribed drugs to prevent recurrent ischemic stroke were extracted from the patient's medical records.

Other variants, including ischemic stroke severity based on National Institutes Health Stroke Score (NIHSS) and functional status based on the modified Rankin Scale (mRS), were extracted from the medical records [12]. The scores of mRS disability scales range from 0 to 6, where perfect health and without symptoms is 0 and death scores 6 [13].

Data analysis was conducted in SPSS V. 19, using the Chi-squared test and t-test. The characteristics were described using Mean±SD, absolute frequency, and relative abundance. The Chi-squared test and t-test assessed the relationship between variables. We used logistic regression to estimate the matched odd ratio of each variant in NOAC prescription prediction.

Results

The present study was performed on 363 patients with non-valvular AFAIS, 191 (52.6%) of whom were female. The Mean±SD age of the patients was 67.87±12.27 years. Also, 109 patients (30%) were 61 to 70 years old. Almost half of the patients (170 patients, 46.8%) lived in the center of Guilan Province, and 129 patients (35.5%) had medium income (Table 1).

Generally, 127 patients (35%) had mild stroke based on NIHSS. The functional status of patients was assessed on admission based on mRS, and 76 patients (20.9%) scored 1, indicating no significant disability.

In this study, we divided patients into two groups: patients who used NOAC and patients who did not use it.

We compared these groups according to the variables. The results showed that females used rivaroxaban more than men ($P=0.004$). Patients with worse neurological deficits based on NIHSS used rivaroxaban more than other patients ($P=0.024$) (Table 1). Both sides of functional status (lower and higher mRS) used more rivaroxaban than other patients ($P=0.005$).

The results showed that the most common comorbidity among hospitalized patients with ischemic stroke was hypertension (235 patients, 64.73%). The history of prior MI or Cerebrovascular Accident (CVA) was taken, and 73 patients (20.1%) had prior MI. None of these parameters were different between the two study groups (Table 2).

Drug history was also extracted from the medical records and showed that 165 patients (45.45%) were taking aspirin before referring to the hospital. Almost half of the patients (178 subjects, 49.03%) were discharged with warfarin, and 111 patients (30.6%) used rivaroxaban after the discharge. The relationship between drug history and rivaroxaban usage was also assessed and showed no relationship between taking other drugs and rivaroxaban usage.

We used variants, which had less than 0.2 level of significance on bivariate analysis, including sex, functional state score, stroke severity based on NIHSS, and prior CVA to assess variables-matched odds ratio applying logistic regression (Table 3). The matched odds ratio showed that female gender ($P=0.001$, OR=0.422), stroke severity ($P=0.05$, OR=2.19), and prior CVA ($P=0.04$, OR=2.17) were significantly related to NOAC prescription. NOAC prescription probability in men was 58% that was less than women ($P<0.001$). It was 2.19 times more in patients with moderate to severe stroke compared with patients with mild stroke and it had 2.17 times more with the history of CVA compared with patients without a history of CVA ($P=0.04$). The results showed that functional status was not related to NOAC prescription.

Discussion

The current study aimed to identify NOAC prescription prevalence and its related factors, including age, gender, ischemic stroke severity, place of residence, income level, co-medications, prior MI and CVA, and functional status. Despite the strong recommendations of guidelines, the frequency of NOAC administration for ischemic stroke prevention is still low.

We studied 363 patients of non-valvular AFAIS, 191 of whom (52.6%) were female, and their mean age was

Table 1. Baseline characteristics and predictors of NOAC(Rivaroxaban) use

Variable	No. (%)		Sig.	
	Rivaroxaban User	Non-rivaroxaban User		
Sex	Female	71(37.2)	120(62.8)	0.004
	Male	40(23.2)	132(76.7)	
Place	Center of province	57(33.5)	113(66.5)	0.461
	Other cities	43(28.9)	106(71.1)	
	Village	11(25)	33(75)	
Income	Poor	29(25.4)	85(74.6)	0.259
	Medium	59(30.7)	133(69.3)	
	Good	13(39.4)	20(60.6)	
	High	10(41.7)	14(58.3)	
NIHSS score	Mild	30(23.6)	97(76.4)	0.024
	Moderate	33(27.7)	86(72.3)	
	Moderate to severe	20(40)	30(60)	
	Severe	28(41.8)	39(58.2)	
Functional status (mRS)	0	18(34)	35(66)	0.005
	1	15(19.7)	61(80.3)	
	2	10(17.9)	46(82.1)	
	3	23(31.9)	49(68.1)	
	4	22(46.8)	25(53.2)	
	5	23(39)	36(61)	
Age (y)	41-50	8(36.4)	14(63.6)	0.335
	51-60	27(32.9)	55(67.1)	
	61-70	26(23.9)	83(76.1)	
	71-80	25(31.6)	54(68.4)	
	81-90	22(39.3)	34(60.7)	
	>90	3(20)	12(80)	
Prior CVA or MI	MI	24(32.9)	49(67.1)	0.112
	CVA	20(41.7)	28(58.3)	
	Both	7(43.8)	9(56.3)	
	None	60(26.5)	166(73.5)	

Table 2. The relationship between comorbidities and rivaroxaban usage

Variable	No. (%)		Sig.
	Rivaroxaban User	Non-rivaroxaban User	
Hypertension	76 (32.3)	159 (67.7)	0.324
Diabetes mel- litus	38 (35.2)	70 (64.8)	0.215
Chronic kidney disease	5 (22.7)	17 (77.3)	0.41
Cardiac artery disease	11 (31.4)	24 (68.6)	0.909

Significance level: <0.05



67.87 years. Hill et al. conducted a study on 1135 patients with ischemic stroke, 55% of whom were men and 59% were older than 70 years old [14]. The results of Wahlgren et al. study showed that 60% of the patients were men and their mean age was 68 years [15]. In Grotta et al. study [16], the mean age of patients with ischemic stroke was 68 years, whereas it was reported 72 years in research by Saver et al. [17]. Investigating 39149 patients, Joo et al. reported that the mean age of the patients was 54.3 years and 58.4% of them were female [18]. Fang et al. showed that 56% of the patients were women and their mean age was 73 years [19].

According to Owais et al. 71% of the patients were men and their mean age was 60.7 years [20]. Also, Gioia et al. stated that among 60 patients with ischemic stroke, 67% were men and their mean age was 73.5 years [21]. These studies showed that gender dominance is variable, but the interesting point is that the frequency of both sexes is close to each other. These studies showed that the mean

age of onset is also variable, but the most common age of onset is between 70 and 80 years.

We found hypertension as the most common comorbidity (n=235, 64.7%). Other studies mentioned diabetes mellitus and hyperlipidemia in addition to hypertension as common risk factors in AFAIS patients [15, 20, 22].

Unlike a previous study in which NOAC usage was significantly related to hypertension and Ischemic Heart Disease (IHD) [10], in the present study, the data analysis showed that none of these comorbidities are significantly related to rivaroxaban usage.

In this study, we also found that stroke severity was about mild and moderate in the majority of patients (67.76%), and 35.53% of the patients had the functional status of 0 to 1 based on mRS, which is compatible with other studies results [5, 23-25]. Logistic regression showed that patients with moderate to severe

Table 3. Multivariate analysis of AFAIS patients' characteristics and Rivaroxaban prescription (Logistic regression model)

Variable	Chance Ratio	95% CI		
		Lower	Higher	
NIHSS	Minor	Reference	-	-
	Moderate	1.19	0.65	2.17
	Moderate to severe	2.19	1.001	4.77
	Severe	1.93	0.96	3.87
Gender	Male	0.422	0.26	0.69
(mRS)		1.07	0.91	1.26
Strokes	No strokes	Reference	-	-
	Myocardial infarction	1.02	0.54	1.92
	Cerebrovascular accident	2.17	0.05	4.46
	Both	1.48	0.49	4.5

NIHSS: National Institutes Health Stroke Score; mRS: modified Rankin Scale



NIHSS were more likely to use rivaroxaban compared with patients with mild to moderate NIHSS ($P=0.05$, $OR=2.19$). Regular INR monitoring in patients with severe stroke after the discharge is troublesome, while NOAC is a more convenient option. There was no significant relationship between functional status and rivaroxaban usage.

In this study, warfarin was the most commonly-prescribed drug on the discharge (49.3%), while rivaroxaban was prescribed for only 30.6% of the patients, which is a small amount of studied population.

The data analysis also showed that women used more rivaroxaban than men ($P=0.001$). The history of prior ischemic stroke and stroke severity increased NOAC usage ($P=0.004$).

In a study on patients with ischemic stroke, Baik et al. reported that 3.11% of the patients used rivaroxaban, while 82.75% used warfarin, and 14.14% used dabigatran. It showed that 17.25% used NOAC [10], which is compatible with our results and shows that NOAC prescription is still low among different societies. They also showed that NOAC usage was significantly related to age ($P<0.001$), female gender ($P=0.009$), hypertension ($P=0.02$), IHD ($P=0.016$), race ($P<0.001$), and mortality ($P<0.001$). In line with the results of this study, female patients tend to use NOAC more than men. After the variant modification, only prior CVA was significantly related to rivaroxaban usage and the other comorbidities such as Hypertension and Cardiac Artery Disease were not the predictor factors for NOAC prescription.

Schoof et al. reported that dabigatran usage in non-valvular ischemic stroke was about 39.5% [26]. Comparing with the current study, NOAC is at a higher level of prescription. In contrast to this study, dabigatran usage was more in male sex ($P=0.029$) with medical history ($P<0.001$). Despite different sex dominance in these two studies, the frequency of both genders is very close, but in our research, having the medical history of HTN, IHD, Chronic Kidney Disease, or Diabetes Mellitus did not change the NOAC prescription rate.

Desai et al. reported warfarin usage as 59.04% and NOAC usage as 40.96% [27]. They shared dabigatran 28.75%, rivaroxaban 11.91%, and apixaban 0.3%, whereas the population of the present study used warfarin almost twice more than NOAC. With the availability of NOAC since October 2010, a significant decline in the proportion of warfarin-prescribed AF patients happened in their society.

They also showed that NOAC usage was significantly related to male sex ($P<0.001$), no history of coronary artery disease ($P<0.001$), heart failure ($P<0.001$), and diabetes mellitus ($P<0.001$). In line with the results of this study, NOAC users were healthier and had a lower stroke recurrence.

Abu Dagga et al. reported dabigatran usage in patients with ischemic stroke as 14.92%, which is lower than our study results [28]. The results showed that NOAC users were younger (67 versus 73 years old) ($P<0.001$), and it was significantly related to male gender ($P<0.001$) and concurrent cardiovascular disease ($P<0.001$). They also suggested that the higher cost of NOACs is the reason why the NOAC users' rate remains low, which can describe low NOAC prescriptions in our study.

In a study on patients with cerebrovascular diseases, Huang et al. reported that 44% of the patients used rivaroxaban, and 56% used warfarin after the discharge [29]. The results showed that rivaroxaban usage increased with older age, female sex, higher risk of vascular events, hypertension, and heart failure, but these relations were not statistically significant. It means that patients in the rivaroxaban group were older, more commonly diagnosed with systemic thromboembolism and hypertension, and had higher CHA_2DS_2 -VASc scores compared with the warfarin group. Their observations are in contrast to this study, where our NOAC user patients are in a healthier status.

Considering these results, we found that NOAC prescription is low, but at an optimum level comparing with other studies. The following reasons may explain this issue:

1. NOACs are expensive, which makes the role of patient income, socio-demographics, and prior prescribed drug costs vital as they relate to the patient's willingness to pay for NOACs. Abu Dagga et al. also considered it a reason why NOAC users' rate has remained low [28].
2. Little knowledge about NOACs therapies among physicians leads to prescribing old generation drugs that will change over time as prescribers and patients gain more intimacy and experience with the newer OACs.

Conclusion

This study showed that NOAC prescription is low in Guilan Province, Iran. Besides, we found that NOAC administration increased with ischemic stroke severity and in women rather than men. We also found that war-

farin is the most prescribed drug on discharge possibly because of its lower cost and precedence.

Study limitations

We did not compare the efficacy and cost benefits of (oral anticoagulant). We suggest performing another study to compare the efficacy, complications, and cost benefits of NOAC with warfarin therapy.

Ethical Considerations

Compliance with ethical guidelines

The Ethics Committee of Guilan University of Medical Sciences approved the study protocol (No: IR.GUMS.REC.1397.276). In this study, no intervention in medical treatment was performed. All data will be classified private and will be published as the study population.

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Authors contributions

Drafting: Moaddabi Yaser, Alimohammadi Sara; Writing, review and editing: Moaddabi Yaser, Noroozi Guilandehi Sama, Saberi Alia, Hamidreza Hatamian, Amirreza Ghaywghran ; Resources: Moaddabi Yaser, Alimohammadi Sara; Supervision: Moaddabi Yaser, Saberi Alia; Data collecting: Alimohammadi Sara.

Conflict of interest

The authors declared no conflict of interest.

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