

## Oral anticoagulant use in patients with atrial fibrillation

### Atriyal fibrilasyonlu hastalarda oral antikoagülan kullanımı

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**Objectives:** Oral anticoagulant treatment has been shown to decrease the risk for vascular complications in patients with atrial fibrillation (AF). We evaluated the frequency of oral anticoagulant use in patients with AF, whether oral anticoagulant use was associated with effective INR values, and the reasons for not including an anticoagulant in the treatment.

**Study design:** The study included 426 consecutive patients (256 women, 179 men; mean age 66±11 years) who presented with a diagnosis of AF between October 2007 and November 2008. The patients were questioned about whether they were using warfarin and/or aspirin and the reasons for not taking an oral anticoagulant. The INR levels were measured in those receiving warfarin.

**Results:** Permanent AF was present in 72.8%, and paroxysmal AF was present in 27.2% of the patients. Patients ≥75 years old accounted for 32.4%. The risk for stroke was high in 69.3%, moderate in 21.8%, and low in 8.9%, hypertension being the most frequent risk factor (66.7%). Inquiry about medications showed that 107 patients (25.1%) were taking aspirin and warfarin, 21 patients (4.9%) and 237 patients (55.6%) were taking warfarin and aspirin alone, respectively, while 61 patients (14.3) used none of these drugs. The incidence of oral anticoagulant use was 30.1%, being significantly low in patients ≥75 years old (p=0.0001), patients with hypertension (p=0.023) or coronary artery disease (p=0.004). Effective INR values recommended by the guidelines were attained in 47.7% (n=61) of patients receiving warfarin. Sex, age, clinical risk factors, and socioeconomic parameters were not associated with attainment of target INR values. The most frequent reason for not starting anticoagulant treatment was the low tendency of physicians to prescribe the drug (74.3%), followed by the presence of contraindications (9.8%).

**Conclusion:** The most important factor for the inadequate oral anticoagulant use especially in patients having a high risk for stroke is the low incidence of prescription of the drug by the physicians, suggesting low influence of the guidelines on clinical practice.

**Key words:** Anticoagulants/therapeutic use; atrial fibrillation/drug therapy; stroke/prevention & control; warfarin/therapeutic use.

**Amaç:** Oral antikoagülan tedavinin atriyal fibrilasyonlu (AF) hastalarda vasküler olay riskini düşürdüğü gösterilmiştir. Bu çalışmada AF tanısı konmuş hastalarda oral antikoagülan tedavinin uygulanma sıklığı, oral antikoagülan tedavi görenlerin etkili INR değerlerine ulaşılıp ulaşmadığı ve hastaların hangi nedenle oral antikoagülan ilaç kullanmadığı araştırıldı.

**Çalışma planı:** Çalışmada Ekim 2007- Kasım 2008 tarihleri arasında polikliniğimize AF tanısıyla başvuran ardışık 426 hasta (256 kadın, 170 erkek; ort. yaş 66±11) değerlendirildi. Hastaların warfarin ve/veya aspirin kullanıp kullanmadığı, oral antikoagülan kullanmıyorsa nedeni sorgulandı. Ayrıca, oral antikoagülan kullanan hastaların INR değerleri ölçüldü.

**Bulgular:** Hastaların %72.8'inde sürekli/kalıcı AF, %27.2'sinde paroksizmal AF vardı. Hastaların %32.4'ü 75 yaş ve üstü gruptaydı. İnme gelişim riski açısından hastaların %69.3'ü yüksek, %21.8'i orta, %8.9'u düşük risk grubundaydı. İnme açısından hipertansiyon (%66.7) en sık görülen risk faktörüydü. Hastaların 107'si (%25.1) aspirin ve warfarin, 21'i (%4.9) sadece warfarin, 237'si (%55.6) sadece aspirin kullanırken, 61 hasta (%14.3) hiçbirini kullanmamaktaydı. Oral antikoagülan kullanma oranı %30.1 bulundu. Yetmiş beş yaş ve üstü hastalarda (p=0.0001), hipertansiyon (p=0.023) ve koroner arter hastalığı (p=0.004) olanlarda oral antikoagülan kullanımı anlamlı derecede azdı. Oral antikoagülan kullanan hastaların %47.7'si (n=61) kılavuzların önerdiği hedef INR değerlerine ulaşabilmişti. Cinsiyet, yaş, klinik risk faktörleri ve sosyoekonomik parametrelerin hiçbirisi hastaların hedef INR değerine ulaşmasında etkili bulunmadı. Oral antikoagülan kullanmama nedenleri arasında ilk sırada ilacın hekim tarafından reçetelendirilmemesi (%74.3), ikinci sırada tıbbi kontrendikasyonlar (%9.8) gelmekteydi.

**Sonuç:** Özellikle inme riski yüksek olan AF'li hastalarda yetersiz oral antikoagülan kullanımının en önemli nedeninin hekimlerden kaynaklandığı görülmekte; bu durum kılavuzların klinik uygulamaya yeterince yansımadığını düşündürmektedir.

**Anahtar sözcükler:** Antikoagülan/terapötik kullanım; atriyal fibrilasyon/ilac tedavisi; inme/önleme ve kontrol; warfarin/terapötik kullanım.

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Atrial fibrillation (AF) is the most common supra-ventricular tachyarrhythmia seen in routine clinical practice which increases with age. Thromboembolic events account for most cases of mortality and morbidity associated with atrial fibrillation. Ischemic stroke is the most common type of thromboembolic events.<sup>[1-4]</sup> The annual risk of ischemic stroke in this patients is 3 to 8%.<sup>[5]</sup>

Review of the findings of various studies conducted to demonstrate the most effective treatment in preventing such a vital complication due to atrial fibrillation and recommendations of the guidelines, has shown that warfarin exerts effective anticoagulation.<sup>[6]</sup> Many randomized controlled studies have demonstrated that oral anticoagulant treatment which reached target levels reduced the risk of ischemic stroke by up to 68% in patients with AF who were not randomized.<sup>[7]</sup>

In this study, we evaluated the frequency of oral anticoagulant use in patients with AF, whether oral anticoagulant use was associated with effective INR values, and the reasons for not including an anticoagulant in the treatment.

## PATIENTS and METHODS

A total of 606 consecutive patients who presented with a diagnosis of AF between October 2007 and November 2008, were evaluated for eligibility in the study. The inclusion criteria were approval of the patients to participate in the study and age >15. Patients who refused to participate and from whom information could not be obtained were excluded from the study. As a result, 180 (29.7%) of the 606 patients were excluded from the study since they refused to participate or because sufficient information could not be obtained due to their low sociocultural level. A total of 426 patients (256 women, 179 men; mean age 66±11 years) were evaluated.

All patients were given information about the study and written informed consents were collected. Approval for the study was obtained from the local ethical committee. Information was obtained from the patients or first degree relatives. The following information was to be obtained for evaluation purposes:

(i) information concerning age, sex, known arterial hypertension, diabetes mellitus, coronary artery disease, thyrotoxicosis, heart failure, rheumatic mitral valve disease, prosthetic heart valve, previous ischemic stroke or transient ischemic attack or history of systemic embolism, were requested to obtain demographic and clinical data of the patients. Patients were divided into three ischemic stroke risk groups in line with this information. (Table 1)

(ii) inquiry about antithrombotic (aspirin) and/or anticoagulant (warfarin) use by the patients and the reasons for not taking the medication was made. INR levels were also checked to determine whether patients receiving oral anticoagulant treatment used the target doses.

(iii) 12-lead surface electrocardiography recordings with 25 mm/s and 10 mm/s calibration were performed on all patients during the initial visit for the diagnosis of atrial fibrillation.

(iv) Two-dimensional and M-mode echocardiography (Vivid 3, Vingmed, General Electric) were used to detect left ventricular ejection fraction (EF) in all patients.

The SPSS 14.0 program was used for statistical analyses. The Pearson Chi-square test was used to compare categorical variables.  $p < 0.05$  value was deemed statistically significant.

## RESULTS

A total of 310 (72.8%) of the 426 patients had permanent AF, while 116 (27.2%) had paroxysmal AF.

**Table 1. Classification of the risk of stroke in patients with atrial fibrillation and recommended anticoagulant and antithrombotic treatment**

High risk factors (n=295)	Medium risk factors (n=93)	Low risk factors (n=38)**
History of previous stroke or transient ischemic attack or systemic embolism	≥75 years	Female
Rheumatic mitral valve disease	Hypertension	65 < age < 74
Prosthetic heart valve	Diabetes mellitus	Coronary artery disease
Presence of two or more medium risk factors	Heart failure	Thyrotoxicosis
Warfarin (INR 2.0-3.0, Target 2.5)*	Ejection fraction ≤35%	
	Aspirin, 81-325 mg/day or warfarin (INR 2.0-3.0, Target 2.5)	

INR: International Normalized Ratio. \*INR target should be above 2.5, when there is mechanical valve. \*\*Aspirin 81-325 mg/day when there is no risk factor.

**Table 2. Distribution of clinical risk factors in 426 patients with atrial fibrillation**

	Number	Percentage		Number	Percentage
Age range			Heart failure/left ventricular dysfunction	68	16.0
≤65	177	41.6	History of stroke/transient ischemic attack or embolism	55	12.9
66-74	111	26.1	Rheumatic mitral valve disease	48	11.3
≥75	138	32.4	History of prosthetic valve	34	8.0
Sex			Thyrototoxicosis	24	5.6
Female	256	60.1	Without cardiovascular disease	32	7.5
Male	170	39.9	Ejection fraction		
Hypertension (n=424)	284	66.7	≤35%	60	14.1
Diabetes mellitus (n=421)	57	13.4	>35%	366	85.9
Coronary artery disease	94	22.1			

The distribution of clinical risk factors is shown in Table 2. Classification of patients according to the risk of stroke demonstrated that the risk was high in 69.3% moderate in 21.8%, and low in 8.9%. A total of 138 patients (32.4%) were ≥75 years old, while 288 patients (67.6%) were <75 years old including a significant proportion (41.6%) with ≤65 years old.

Hypertension was the most common risk factor (66.7%) for stroke among AF patients. This was followed by coronary artery disease (22.1%), heart failure/left ventricular dysfunction (16%) and diabetes

mellitus (13.4%). A history of stroke/transient ischemic attack or embolism, history of rheumatic mitral valve disease and prosthetic heart valve which were among the highest risk factors for development of ischemic stroke was reported in 12.9%, 11.3% and 8% of the patients, respectively. On the other hand, 75% of the patients did not have any history of cardiovascular disease (Table 2). Evaluation of the anticoagulant/antiplatelet drug profile showed that 107 patients (25.1%) were taking aspirin and warfarin, 21 patients (4.9%) and 237 patients (55.6%) were taking warfarin

**Table 3. Comparison of clinical risk factors in patients receiving and not receiving oral anticoagulant treatment**

		Warfarin use				<i>p</i>	
		Number	Present (n=128)		Absent (n=298)		
			Number	Percentage	Number		Percentage
Sex	Male	170	47	27.7	123	72.4	0.379
	Female	256	81	31.6	175	68.4	
Age range	≤65	177	71	40.1	106	59.9	0.0001
	66-74	111	34	30.6	77	69.4	
	≥75	138	23	16.7	115	83.3	
Hypertension	Present	284	75	26.4	209	73.6	0.023
	Absent	140	52	37.1	88	62.9	
Coronary artery disease	Present	94	17	18.1	77	81.9	0.004
	Absent	332	111	33.4	221	66.6	
Heart failure	Present	68	17	25.0	51	75.0	0.322
	Absent	358	111	31.0	247	69.0	
Ejection fraction	≤35%	60	12	20.0	48	80.0	0.067
	>35%	366	116	31.7	250	68.3	
Diabetes mellitus	Present	57	13	22.8	44	77.2	0.180
	Absent	364	115	31.6	249	68.4	
History of stroke/transient ischemic attack or embolism	Present	55	20	36.4	35	63.6	0.274
	Absent	371	108	29.1	263	70.9	
Rheumatic mitral valve disease	Present	48	28	58.3	20	41.7	0.0001
	Absent	378	100	26.5	278	73.5	
History of prosthetic valve	Present	34	32	94.1	2	5.9	0.0001
	Absent	392	96	24.5	296	75.5	
Thyrototoxicosis	Present	24	8	33.3	16	66.7	0.718
	Absent	402	120	29.9	282	70.2	

**Table 4. Comparison of clinical risk factors in patients attaining effective INR values**

		Effective INR values					<i>p</i>
		Number	Present (n=61)		Absent (n=67)		
			Number	Percentage	Number	Percentage	
Sex	Male	47	24	51.1	23	48.9	0.557
	Female	81	37	45.7	44	54.3	
Age range	≤65	71	36	50.7	35	49.3	0.830
	66-74	34	15	44.1	19	55.9	
	≥75	23	11	47.8	12	52.2	
Hypertension	Absent	75	37	49.3	38	50.7	0.857
	Present	53	26	49.1	27	50.9	
Coronary artery disease	Present	17	8	47.1	9	52.9	0.958
	Absent	111	53	47.8	58	52.3	
Heart failure	Present	17	10	58.8	7	41.2	0.204
	Absent	111	51	46.0	60	54.1	
Ejection fraction	≤35%	12	7	58.3	5	41.7	0.267
	>35%	116	54	46.6	62	53.5	
Diabetes mellitus	Present	13	6	46.2	7	53.9	0.852
	Absent	115	55	47.8	60	52.2	
History of stroke/transient ischemic attack	Present	20	10	50.0	10	50.0	0.819
	Absent	108	51	47.2	57	52.8	
Rheumatic mitral valve disease	Present	28	15	53.6	13	46.4	0.478
	Absent	100	46	46.0	54	54.0	
History of prosthetic valve	Present	32	13	40.6	19	59.4	0.358
	Absent	96	48	50.0	48	50.0	
Thyrotoxicosis	Present	8	4	50.0	4	50.0	0.891
	Absent	120	57	47.5	63	52.5	

and aspirin alone, respectively, while 61 patients (14.3%) used none of these drugs. Approximately 30.1% (n=128) of the patients were receiving oral anticoagulant treatment. Comparison of clinical risk factors in patients receiving and not receiving oral anticoagulant treatment is shown in Table 3. 27.7% of male and 31.6% of female patients were using oral anticoagulants and no significant difference was found between the groups in terms of sex ( $p=0.379$ ). With respect to age groups, patient ≤65 years old were observed to use oral anticoagulants mostly and the use of these drugs was seen to markedly decrease with increasing age. The incidence of oral anticoagulant use was significantly low in patients ≥75 years old who had the highest risk of developing stroke ( $p=0.0001$ ).

In respect of risk factors, it was observed that patients with rheumatic mitral valve disease and prosthetic heart valve used more oral anticoagulants ( $p=0.0001$ ), whereas patients with hypertension ( $p=0.023$ ) and coronary artery disease ( $p=0.004$ ) used less oral anticoagulants. No significant difference was observed between patients receiving and not receiving oral anticoagulant treatment in terms of history of heart failure/left ventricular dysfunction, diabetes mellitus, stroke/transient ischemic attack or embolism and thyrotoxicosis (Table 3).

Nearly half of the patients using oral anticoagulants (n=61, 47.7%) reached the target INR values recommended by the guidelines (Table 1). There was no significant difference between groups reaching and not reaching target INR values in respect of sex, age, clinical risk factors and socioeconomic parameters. In other words, none of these factors were associated with the attainment of target INR values (Table 4).

The most frequent reason for not using anticoagulant treatment was the low tendency of physicians to prescribe the drug (74.3%), followed by the presence of medical contraindications (9.8%), decision to discontinue treatment by the patient without the physician's recommendation (6.9%), socioeconomic factors (4%), recent diagnosis of AF (2.9%), and decision to reject treatment by the patient, although he/she was informed of anticoagulant treatment (2.2%) (Table 5).

## DISCUSSION

Many large-scale studies published so far have demonstrated that oral anticoagulant treatment was effective in prevention of stroke and deaths due to thromboembolism in patients with AF.<sup>[2,8-12]</sup> Based on these studies, guidelines regarding oral anticoagulant treatment in AF patients with a risk of stroke (those in

**Table 5. The reasons for not starting anticoagulant treatment in patients with atrial fibrillation (n=276)**

	Number	Percentage
Low incidence of prescription of the drug by the physician	205	74.3
Medical contraindication	27	9.8
Decision to cease treatment by the patient without any recommendation of the physician	19	6.9
Socioeconomic factors	11	4.0
New diagnosis of atrial fibrillation	8	2.9
Decision to reject treatment by the patient	6	2.2

the medium and high risk categories) were published and has received wide acceptance.<sup>[2,5]</sup> This study, conducted in a hospital which served a broad geographical region including a heterogeneous patient population, revealed some cases where oral anticoagulants were used inadequately. This will help us to understand the obstacles encountered in the primary and secondary prevention of stroke.

The first large-scale study concerning oral anticoagulant use in patients with AF was conducted by Stafford and Singer.<sup>[13]</sup> This study, including data obtained from ambulatory medical care researches, demonstrated that the rate of oral anticoagulant use which was 7% in 1980-1981, increased up to 32% in 1992-1993. On the other hand, the rate of patients not receiving treatment decreased from 90% to 48%. According to the authors, increase in oral anticoagulant use was associated with the overlap of studies conducted between 1989-1992, such as Atrial Fibrillation Aspirin and Anticoagulants (AFASAK),<sup>[14]</sup> Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF),<sup>[16]</sup> Canadian Atrial Fibrillation Anticoagulation (CAFA)<sup>[17]</sup> and Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF).<sup>[18]</sup> Another study showed the rate of oral anticoagulant use between 32-57%, whereas it was reported that 22-59% of the patients did not use oral anticoagulant treatment.<sup>[13,19-28]</sup>

In our study it was established that only 30% of the patients with AF and anticoagulation indication used anticoagulants. Although this study was conducted in a full-equipped training and research hospital considering the circumstances of our country, these findings were below global standards. Only about half of them (47.7%) reached the target INR value recommended by guidelines. With respect to comparison of patient groups reaching and not reaching target INR values, there was no significant difference between the groups in terms of sex, age, clinical risk factors and socioeco-

nomical variables (lifestyle, place of residence, level of income, etc.) In other words, none of these factors was effective in the patients reaching the target INR values. Other social factors (frequency of INR control, level of education, etc.), concomitant medications with oral anticoagulants and foods may have an effect on attaining the target INR values. Other studies may be beneficial for further investigation. 55.6% of the patients were receiving suboptimal treatment with aspirin, while 14.3% did not receive any oral anticoagulants or antithrombotics. Although our study covers a one year-period between 2007-2008 and was performed among a varied population group, our findings concerning oral anticoagulant treatment in patients with AF were found to be consistent with results reported by Stafford and Singer<sup>[13]</sup> in the mid 1990s. This suggests that oral anticoagulant use in AF patients has formed a plateau since 1990s. Even today, oral anticoagulants are used in only a minority group of patients with the indication of AF. Interestingly, the main reason for not using anticoagulant treatment is the low incidence of prescription of the drug by physicians.

Our study revealed that oral anticoagulants were not prescribed in 74.3% of the patients despite having the indication. The identification of patients who would benefit from oral anticoagulant treatment was demonstrated in several studies and various guidelines were prepared in respect of these studies. One of the leading factors for the low incidence of prescribing anticoagulants is that these guidelines are prepared for cardiologists and the treatment of most of the patients is scheduled by the physicians other than cardiologists. Other reasons for not starting oral anticoagulant treatment are as follows: presence of medical contraindications (9.8%), decision to discontinue treatment by the patient (6.9%) without the physician's recommendation, socioeconomic factors (4%), diagnosis of AF in the clinic for the first time (2.9%), and decision to reject treatment by the patient, although he/she was informed (2.2%).

Large-scale studies showed that age was the primary determinant for AF.<sup>[13,19-28]</sup> Guidelines based mostly on such studies conducted in Western countries accept age  $\geq 75$  as a moderate risk factor and age  $< 65$  as a low risk factor for the development of ischemic stroke. The mean life expectancy is known to be shorter in our country compared to Western countries.<sup>[9]</sup> Majority of the patients with AF in our study were  $\leq 65$  years old, and their mean age was 66. Therefore, it may be more appropriate to consider age  $> 65$  instead of  $> 75$  as a moderate risk factor in patients with AF while establishing risk factors for the development of ischemic stroke in Turkish population.

Risk factors for the development of stroke in our study were found to be consistent with results obtained from the study by Waldo et al.<sup>[29]</sup> We expect the incidence of rheumatic mitral valve disease to be higher in our study, since the above mentioned study was conducted in a Western country.

**Limitations of the study.** Being a single-centered study could have been one of the limitations of our study. Furthermore, follow-up evaluation of the patients with a history of heart failure and stroke/transient ischemic attack or embolism in the internal medicine and neurology clinics apart from the cardiology clinic in our hospital could have also affected the study results. In addition, low level of education of the patients who visited our hospital and a single-visit evaluation could have resulted in obtaining insufficient information from the patients. Moreover, the absence of data analysis about whether patients were treated by a cardiologist must have been a limitation which could have affected the results of our study.

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