

## Epidemiological approach to the atrial fibrillation patients

### *Atrial fibrilasyon hastalarına epidemiyolojik yaklaşım*

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#### ABSTRACT

Atrial Fibrillation (AF) is the most common arrhythmia observed in clinical practice. While the thromboembolic events are the most feared complications, these complications alone are responsible for 15% of all strokes. Anticoagulation therapy is the most effective way to prevent this significant complication caused by AF. Due to the disadvantages related to the recently launched new oral anticoagulants, warfarin still maintains its dominance as the gold standard agent. Pharmaceutical agents as well as demographic characteristics (age, sex, the type of AF, co-morbidities etc.) of the patients are crucial to provide effective coagulation. Since most of the studies on demographic characteristics of AF patients and the profile of oral anticoagulant use originate from the West and Far East, they do not reflect the real characteristics of our country. In this study, by analyzing the epidemiological studies conducted among AF patients in our country, we aimed to bring literature in data related to our society.

**Key words:** Atrial fibrillation, anticoagulation, demographic characteristics, epidemiology, guidelines

#### INTRODUCTION

Atrial Fibrillation (AF) is the most common rhythm disorders observed in our clinical practice [1]. Its prevalence in the general population is 1-2% [2]. As an important cause of cardiovascular mortality and morbidity with progressively increasing prevalence, AF became a serious health issue at the present time. Most of the epidemiological studies suggest that AF will be more commonly observed in the future. When the increasing and ageing World population is considered, the AF frequency increase and consequently, related adverse events increase. The thromboembolic events are one of the leading adverse events.

#### ÖZET

Atrial fibrilasyon (AF) klinik pratikte en sık görülen aritmidir. En korkulan komplikasyonu tromboembolik olaylar olup tüm inmelerin % 15'inden tek başına sorumludur. AF'nin yol açtığı bu önemli komplikasyonu önlemenin en etkin yolu antikoagülasyondur. Antikoagülasyonu sağlamak için son dönemlerde ortaya çıkan yeni oral antikoagülanlarla ilgili çekincelerden dolayı altın standart ajan olarak warfarin hala üstünlüğünü sürdürmektedir. Efektif antikoagülasyon sağlamada kullanılan farmakolojik ajanların yanı sıra hastanın demografik özellikleri de (yaş, cinsiyet, AF tipi, komorbid durumlar vb.) büyük önem taşımaktadır. AF hastalarının demografik karakteristiği ve oral antikoagülan ilaç kullanım profili ile ilgili yapılan çalışmalar çoğunlukla Batı ve Uzakdoğu kökenli olduğundan ülkemizin gerçek karakteristiğini yansıtmamaktadır. Bu çalışmayla ülkemizde AF hastalarında yapılmış olan epidemiyolojik çalışmalar analiz edilerek toplumumuz ile ilgili verileri literatüre kazandırmayı amaçladık.

**Anahtar kelimeler:** Atrial fibrilasyon, antikoagülasyon, demografik özellikler, epidemiyoloji, kılavuzlar

In the studies conducted, while AF in association with valvular heart disease was demonstrated to increase the risk of stroke 17-fold when compared to the normal population, nonvalvular AF increased the risk of stroke 5-fold [3]. When the results of the studies on the effective treatment for the prevention of such an important AF-related complication and the suggestions of the published guidelines are considered, effective anticoagulation provided by oral coagulant therapy appears to be the most effective [4]. Many randomized controlled studies revealed that achieved target levels of oral anticoagulation reduced the risk of stroke 68%, in unselected patients with AF [2]. Since the epidemiological stud-

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ies evaluating the prevalence of AF, demographic characteristics of the patients, the antiplatelet/ anticoagulation medication use profile, the predictors of oral anticoagulation use have been mostly conducted in Western and Far Eastern populations, they do not reflect the real characteristics of the patients with AF in our society [5-8]. In this article, we aimed to gather together the prevalence of AF, demographic characteristics of the patients, the profile of antiplatelet/ anticoagulant medication use, the physicians' adherence to the guidelines, and the predictors of oral anticoagulant use, in the light of the previous epidemiological studies conducted in our country and to compare our results with those of the studies conducted in Western and Far Eastern countries.

### Prevalence

The prevalence studies relevant to AF are of North American and European origin. According to ATRIA (the Anticoagulation and Risk Factors in Atrial Fibrillation), Cardiovascular Health Study and Framingham records, the overall prevalence of AF in a population varies from 0.5% to 1% [1,9-11]. The prevalence of AF doubles every ten years of age and after the age of 80, its prevalence reaches 10%. In a large epidemiological study recently conducted in Japan including approximately 630 thousand persons over the age of 40, the prevalence of AF in population aged over 40 was found as 1.3% in males and 0.4% in females [12]. In the same study, the prevalence of AF in people over 80 years old was found as 4,4% in males and 2,1% in females. In another study conducted in Hong Kong, the prevalence of AF was found as 1,3% in the age range of 60-94 [13]. These values show that the prevalence of AF in the Far East populations is approximately half that of the Western populations. In our country, data regarding the prevalence of AF come from the TEKHARF (Cardiac Diseases and Risk Factors in Adults in Turkey) study. In this study including three thousand four hundred fifty persons who were followed up for ten years, while the overall prevalence of AF was reported as 1.25 %, it was reported as 0.46% in the age group of 32-59, 2.09% in the age group of 60-69 and 2.49% in the age group 70

and over [14]. Another study conducted on this subject in our country, is a study of 4721 patients, presented by Karaçağlar et al. as an experience in a tertiary health care center [1]. In this study assessing the prevalence of AF retrospectively regardless of age distribution, the prevalence of AF was found as 9.1% (Table 1). When the data of TEKHARF study are particularly considered, the prevalence and incidence of AF in our country show similarity to the profile of Far East populations rather than that of Western populations.

### Types of atrial fibrillation

Although there are different classifications of AF, the most commonly used classifications in the guidelines published by both AHA (American Heart Association) /ACC (American College of Cardiology) [16] and ESC (European Society of Cardiology) [2] are the classification as valvular and nonvalvular AF, according the presence or absence of valve involvement (mitral stenosis, prosthetic valve) and the classification as paroxysmal, persistent or permanent AF according to the duration of AF. We commonly use these two classifications in clinical practice. When evaluating in terms of valve involvement, nonvalvular AF is the most common type of AF in World populations [2]. In case of valvular AF, with a rate of 22%, our country ranks highest among the developed countries records [17,18]. For example, the rate of valvular AF was found as 14% in Japanese records and 9% in the AFNET study conducted in Germany [5,7]. The prevalence of valvular AF is definitely related to the high prevalence of rheumatic heart disease in our country. When evaluating in terms of the duration of AF, while the most common type of AF is the permanent AF in most of the studies [1,5,17,19,20], in a study conducted by Waldo et al. [6] in American population, the paroxysmal AF was reported to be the most common type of AF. When the data of our country are considered, permanent AF is found to be the most common type of AF in single-center studies as well as in the AF-TER (Atrial Fibrillation in Turkey: Epidemiologic Registry) study which reflects the whole Turkish society [17] (Table 2).

**Table 1.** Prevalence of atrial fibrillation in several studies

Furberg et al, 1994	Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study).	5201 subjects	Prevalence of atrial fibrillation $\geq$ 65 age; Female: 4.8%	Prevalence of atrial fibrillation $\geq$ 65 age; Male: 6.2%
Benjamin et al, 1994	Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study.	4731 subjects	Prevalence of atrial fibrillation between 55-94 years; Female: 12.6% (38 years follow up)	Prevalence of atrial fibrillation between 55-94 years; Male: 11.2% (38 years follow up)
Lok et al, 1996	Prevalence of palpitations, cardiac arrhythmias and their associated risk factors in ambulant elderly.	1454 subjects	Prevalence of atrial fibrillation between 60-94 years; 1.3 %	—
Go et al, 2001	Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study.	17 974 subjects	Prevalence of atrial fibrillation < 80 age: 0.95%	Prevalence of atrial fibrillation > 80 age: 9.0%
Uyarel et al, 2008	Incidence, prevalence, and mortality estimates for chronic atrial fibrillation in Turkish adults (TEKHARF study)	3450 subjects	Prevalence of atrial fibrillation general population: 1.25%	—
Inoue et al, 2009	Prevalence of atrial fibrillation in the general population of Japan: an analysis based on periodic health examination.	630 138 subjects	Prevalence of atrial fibrillation > 40 age: Female: 0.4%	Prevalence of atrial fibrillation > 40 age: Male: 1.3%
Karaçağlar et al, 2012	The frequency of embolic risk factors and adequacy of anti-embolic treatment in patients with atrial fibrillation: a single tertiary center experience, retrospectif study	4721 subjects	Prevalence of atrial fibrillation general population: 9.1%	—

## Age

The significant increase in prevalence and thromboembolic complications with increasing age is the most important common point of the epidemiological studies on AF. The increased incidence of AF in elderly may be related to several mechanisms. The age-related alterations in heart form a significant part of the relevant mechanisms [23]. Apart from the alterations due to senility, the intensified cardiovascular processes in elderly, resulting in degenerative changes in atria and in the cardiac conduction system are the other significant factors. A multicenter, randomized TAF study published in our country in the 2000s which compared the effects of anticoagulants and aspirin on the risk of thromboembolism in patients with nonvalvular AF revealed that while the mean age of the anticoagulant group was  $66.1 \pm 9.2$ , it was  $63.0 \pm 8.7$  in the AF group taking aspi-

rin [24]. In the TEKHARF study the mean age was  $52 \pm 13$  and in the study conducted by Ertaş et al, the mean age was  $66 \pm 11$  [14]. According to the records of AFTER, the first prospective, multicenter study conducted in our country, the mean age of AF patients was found as  $66.8 \pm 12.3$  [17,18]. These results are consistent with the results of two other large epidemiological studies (J-RHYTME study, conducted in Japan and the KORAF study examining the Korean population) [5,8]. The AFNET study of 9582 patients conducted in Germany, the average age was found as 68.4 [7]. This situation may be explained by the higher overall average age of the Western populations than that of our country. In conclusion, our age profile shows similarity to that of Far Eastern population. However, in comparison with Western populations, our population has AF in a younger age (Table 2).

**Table 2.** Comparison of demographic characteristics of AF patients

Studies and guidelines		Mean age (years)	Gender	AF type in terms of valvular involvement	AF type in terms of duration	Valvular AF prevalence (%)	Most common comorbidity
Guidelines of ACC (American College of Cardiology) / AHA (American Heart Association) /ESC (European Society of Cardiology)		–	Male predominance	Non-valvuler	Permanent	–	Hypertension
Waldo et al, 2005	NABOR Steering Committee. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. 945 subjects	71.5±13.5	Male predominance	Non-valvuler	Paroksismal	6	Hypertension
Uyarel et al, 2008	Incidence, prevalence, and mortality estimates for chronic atrial fibrillation in Turkish adults (TEKHARF study), 3450 subjects	52±13	Female predominance	Non-valvuler	Permanent	–	Hypertension
Nabauer et al, 2009	The Registry of the German Competence NETwork on Atrial Fibrillation: patient characteristics and initial management. Europace (AFNET Study), 9582 subjects	68.4±11.0	Male predominance	Non-valvuler	Permanent	9	Hypertension
Atarashi et al, 2011	Present status of Anticoagulation treatment in Japanese patients with atrial fibrillation: a report from the J-RHYTHM Registry, 7937 subjects	10.0±68.6	Male predominance	Non-valvuler	Permanent	14	Hypertension
Ertaş et al, 2012	AFTER (Atrial Fibrillation In Turkey: Epidemiologic Registry) Study, 2242 subjects	66.8±12.3	Female predominance	Non-valvuler	Permanent	22	Hypertension
Shin et al, 2012	KORAF Investigator. Trends in Oral Anticoagulation Therapy Among Korean Patients With Atrial Fibrillation: The KORean Atrial Fibrillation Investigation. 5616 subjects	63.6±12.2	Male predominance	Non-valvuler	Permanent	–	Hypertension

## Gender

While AF is a more common arrhythmia in the male sex, in sex analyses obtained from the population studies, study cohorts and cohort studies and surveys, higher thromboembolism rates were detected in female sex when compared to those of males.

This situation made the female sex a parameter of CHA2DS2-VASc score which is frequently used for the calculation of thromboembolism risks in patients with AF [2]. When evaluating the data of our country in terms of female sex analysis, the incidence of female patients was interestingly found 1.5

times higher than that of males [17]. This result is consistent with the results of the TEKHARF study [14]. According to Framingham records examining the American society, AF incidence in males was 1.5 to 2 times higher than females [12]. While the Japanese records had a similar incidence in males, the rates of female and male patients were found close in Korean population [5,8]. When a subgroup analysis of AFTER study was performed in order to examine the reasons of the difference between the data of our country and those of the Western and Far Eastern populations, the predominance of valvular pathologies in females (358/497; 72% ) appears to increase the rate of female patients by 60% in the overall cohort [17]. This situation demonstrates that the rheumatic heart disease is still a significant health problem particularly for the women of our country (Table 2).

### Co-morbidities

The presence of pathological conditions associated with AF is very important. These pathological conditions significantly contribute to the thromboembolic events of AF patients (a history of cerebrovascular event, hypertension, cardiac failure, diabetes mellitus etc.) The incidence of comorbidities associated with AF may differ from population to population. According to the records of AFTER study reflecting our country to a large extent, hypertension was observed as the most common comorbidity associated with AF (67%). Other associated risk factors in patients with AF are heart failure with an incidence of 29%, and vascular disease with an incidence of 25%. A story of stroke, transient ischemic attack or systemic thromboembolism was present in 15.3% of the patients [17]. While hypertension was similarly the most common comorbidity detected in many epidemiological studies conducted in Western and Far Eastern populations [5-8,25], a lower rate of coronary artery disease was observed in Japanese population when compared with our data [5]. On the other hand, a higher rate of coronary artery disease was observed in American population when compared with our data [6]. While the rate of concomitant heart failure in AFTER cohort was similar to those of the American, Spanish and German populations [6,26], it was higher than the Japanese population [5]. When the populations were compared to each other in terms of history of stroke, while the highest rate was observed in a single cen-

ter study with a rate of 20% [6], a similar rate to the results of AFTER (15%) study [17] with a rate of 13% was observed in the German population. In spite of lower rate of valvular AF, a relatively higher rate of ischemic events in these societies may be related to the higher overall mean age of the patients (Table 2).

### The assessment of the profile of oral anticoagulant/antiplatelet use in patients with AF

Although, several medications have been tested, and despite the difficulties in its use and its risk of bleeding, Warfarin, an oral vitamin K antagonist, is commonly used for the pharmacological prevention of stroke in patients with AF. Antithrombotic drugs are used for the prevention of stroke in AF patients. These drugs are absolutely recommended in patients with valvular AF and their use is recommended in nonvalvular AF in line with the scoring scheme for the risk of stroke, by AHA/ACC/ESC consensus guidelines. Among these new agents, even dabigatran etexilate, rivaroxaban and apixaban are particularly presented as alternatives to warfarine [27-29] for being the most developed agents with maximal evidence and even their properties of constant dose no requirement of monitoring and predictable efficacy are particularly emphasized, one should remember that it is not clear how to act in cases of emergency situations requiring to know their efficiency in laboratory for making an immediate decision, such as the need for emergency surgery, the relationships between the intensity of complication and the dose, in cases of intoxication and how to act in terms of patient compliance and failure of the treatment. One should take into account the cost efficiency of these drugs and the high incidence of the valvular AF in our country since they are not indicated in valvular AF. Besides, in terms of drug safety, one should know that these drugs were recently launched for clinical use and the phase 4 studies are still in progress and the long term monitoring studies are not completed yet.

When all of the disadvantages related the new drugs are considered, warfarin seems to maintain its position as the gold standard pharmacological agent for a long time in oral anticoagulation of AF patients. This kind of gold standard and the studies conducted on this subject indicate that in Western and Far Eastern societies as well as in our society no

adequate attention is paid to the subject in clinical practice.

In the Euro Heart Survey study [20] the analysis of 2706 patients with AF revealed that when the patients were assessed in terms of the profile of oral anticoagulant/ antiplatelet medication use, while 57% of all patients were on warfarin treatment alone, 7% were on warfarin+ASA treatment and 27% were on ASA treatment alone and 9% of the patients were not using any of these treatment options. In the J-RYHTM [5] study of 7937 AF patients which was conducted in Japan, while the rate of anticoagulant use was 87%, the rate of ASA use was found as 22%. In the subgroup analysis [30] of the same study, 89% of the 6324 patients with nonvalvular AF were on warfarin treatment and 23% were on ASA treatment. In these studies the effective INR level (2.0-3.0) was achieved only in 34% of the patient. According to the data of AFTER study, the distribution of the medication use of AF patients in our country was as follows: 25%

of all patients were on warfarin treatment alone, 15 % were on warfarin+ASA treatment and 42% were on ASA treatment alone and 18 % of the patients were not receiving any of these treatment options. Effective INR levels were detected in 41.3% of the patients on oral anticoagulation therapy. When the patients were classified according to the risk of stroke by using CHA2DS2-VASc scoring, while 23% of the low risk patients were unnecessarily on warfarin therapy, 58% of the high risk patients were not receiving anticoagulation therapy [17]. When our results were compared with those of the studies of Western and Far Eastern origins, while the rates of warfarin use were dramatically lower, the effective INR levels were surprisingly similar to those of the aforementioned studies. [5-8] (Table 3). These dramatic results obtained from the studies indicate that the problem became a global one and they also lead in questioning why warfarin is not started when indicated.

**Table 3.** Evaluation of drug profile used in patients with atrial fibrillation

Studies	Warfarin (%)	ASA (%)	Warfarin+ASA (%)	None	INR within Therapeutic range (%)
Nieuwlaat et al, 2005 European Heart Survey Investigators. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation, 2706 Subjects (European population)	57	27	7	9	34
Waldo et al, 2005 NABOR Steering Committee. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. 945 subjects (American population)	33	25	20	22	—
Atarashi et al, 2011 Present status of anticoagulation treatment in Japanese patients with atrial fibrillation: a report from the J-RHYTHM Registry, 7937 subjects (Far eastern population)	87	22	18*	—	34
Ertas et al, 2012 AFTER (Atrial Fibrillation in Turkey: Epidemiologic Registry) Study, 2242 Subjects (Turkish population)	25	42	15	18	41

\*Warfarin plus antiplatelet, ASA- acetylsalicylic acid, INR- international normalized ratio

Although there are a few specific studies of Western and Far Eastern origin on this subject, Bazec et al. asserted the following reasons in a meta-analysis [31] Advanced age, sex, rural settlement, language differences, socioeconomic status, falls

risk, fear of bleeding and disabilities. Based on AFTER records, the most common and principal reason in our country was the physician neglect with a rate of 69%. The rate of discontinuation of therapy by the patients without consulting their physicians

was 4%, the rate of the refusal of the treatment was 4% and the rate of not receiving medication due to socioeconomic reasons such as not being able to have INR monitored, living alone or living in regions where transportation presented difficulties, was found as 16%. The reasons related to the patient was 24% in total. Only 7% of the patients were not receiving anticoagulant therapy due to a contraindication [17].

## CONCLUSION

It was determined that the prevalence of AF in the overall population in our country was 1.25%, the majority of the patients with AF were included in nonvalvular and permanent group, the overall average age of the patients in our country was 65, the female sex was dominant over the male population hypertension was the most common concomitant risk factor, the stroke incidence was 15%, the rate of anticoagulant use was 49%, the rate of achieving an effective INR level in patients on anticoagulant medication was 41.3%, the principal reason of not receiving anticoagulant medication was the physician neglect. On the other hand, it was also demonstrated that the studies of Western and Far Eastern origin did not completely reflect the characteristics of our country and warfarin would maintain its position as gold standard agent as long as the disadvantages of the newly launched antithrombotic drugs continued to exist and the physicians should be more careful in their clinical practice particularly in the treatment field.

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