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Turkish Real Life Atrial Fibrillation in Clinical Practice: TRAFFIC Study

ABSTRACT

Background: Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia worldwide and is associated with an increased risk of thromboembolism, ischemic stroke, impaired quality of life, and mortality. The latest research that shows the prevalence and incidence of AF patients in Türkiye was the Turkish Adults' Heart Disease and Risk Factors study, which included 3,450 patients and collected data until 2006/07.The Turkish Real Life Atrial Fibrillation in Clinical Practice (TRAFFIC) study is planned to present current prevalence data, reveal the reflection of new treatment and risk approaches in our country, and develop new prediction models in terms of outcomes.

Methods: The TRAFFIC study is a national, prospective, multicenter, observational registry. The study aims to collect data from at least 1900 patients diagnosed with atrial fibrillation, with the participation of 40 centers from Türkiye. The following data will be collected from patients: baseline demographic characteristics, medical history, vital signs, symptoms of AF, ECG and echocardiographic findings, CHADS2-VASC2 and HAS-BLED (1-year risk of major bleeding) risk scores, interventional treatments, antithrombotic and antiarrhythmic medications, or other medications used by the patients. For patients who use warfarin, international normalized ratio levels will be monitored. Follow-up data will be collected at 6, 12, 18, and 24 months. Primary endpoints are defined as systemic embolism or major safety endpoints (major bleeding, clinically relevant nonmajor bleeding, and minor bleeding as defined by the International Society on Thrombosis and Hemostasis). The main secondary endpoints include major adverse cardiovascular events (systemic embolism, myocardial infarction, and cardiovascular death), all-cause mortality, and hospitalizations due to all causes or specific reasons.

Results: The results of the 12-month follow-up of the study are planned to be shared by the end of 2023.

Conclusion: The TRAFFIC study will reveal the prevalence and incidence, demographic characteristics, and risk profiles of AF patients in Türkiye. Additionally, it will provide insights into how current treatments are reflected in this population. Furthermore, risk prediction modeling and risk scoring can be conducted for patients with AF.

Keywords: Arrhythmias, atrial fibrillation/flutter, atrial fibrillation, bleeding, catheter ablation

INTRODUCTION

In the general adult population, atrial fibrillation (AF), which affects 2% of people, is the most prevalent sustained cardiac arrhythmia.[1] A systematic review that included 184 population-based studies from around the world estimated that 33.5 million people had AF in 2010. However, the global prevalence of AF is thought to be much higher due to the scarcity of data from regions outside of Europe and North America and undiagnosed subclinical cases of AF.[2]

More than 6 million people have been diagnosed with AF in Europe alone, and the prevalence of the condition is expected to at least double over the next 50 years as the population ages. To determine the prevalence, progression, and mortality of chronic AF in the Turkish population, the Turkish Adults' Heart Disease and Risk Factors (TEKHARF) study was carried out. The study estimated an annual incidence of 35 000 (22 000 in females) and a prevalence of 310 000 (200 000 in

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females) for chronic AF after following 3450 participants (1707 males, 1743 females; mean age 5213) until the 2006-2007 screening.[3]

Atrial fibrillation can be defined as a global health problem due to its higher risk of stroke and thromboembolism, impaired quality of life, and its significant contribution to morbidity and mortality.[4,5] Management strategies for AF, including thromboprophylaxis, rate or rhythm control, and management of associated comorbidities, have rapidly evolved in the past 15 years.[6-12] Additionally, in recent years, major evidence is supporting the importance of active screening for asymptomatic AF and initiating appropriate treatment, including OAC therapy for thromboprophylaxis.[13] The impacts of ethnic differences on the risk of developing AF, thromboembolic risk, efficacy and safety of anticoagulant medications, and accessibility of these treatments have been well characterized. It has been demonstrated that Caucasians have a higher prevalence of AF compared to other ethnic populations.[14-16] Similarly, it suggests that individuals of Caucasian ethnicity with AF may be at higher risk for AF-related cardiovascular morbidity and mortality compared to non-white ethnic groups.[17] Considering this evidence, the Turkish Real Life Atrial Fibrillation in Clinical Practice (TRAFFIC) study aims to investigate the frequency characteristics of AF, including its incidence and prevalence, as well as the variability of morbidity and mortality indicators that may be caused by racial differences in the Turkish population compared to other populations. The study also aims to evaluate the adoption and implementation of novel treatment and risk approaches in current clinical practice. Ultimately, the study aims to develop new risk prediction models for risk stratification in patients with AF.

METHODS

The TRAFFIC study is a national, prospective, multicenter, observational registry. The study has been reviewed and approved by the Ethics Committee. Signed informed consent forms will be obtained from all patients before their enrollment in the study.

Study Population

The study population will consist of consecutive patients presenting with AF in the cardiology departments of the participating hospitals, whether they are hospitalized or receiving outpatient treatment. Additionally, patients in emergency or non-cardiology departments, but under the supervision of a cardiologist, will also be included. The inclusion criteria are as follows: (1) being 18 years of age or older; (2) having an estimated life expectancy of more than 6 months; an (3) having a diagnosis of non-valvular AF (paroxysmal, persistent, or permanent). Patients with atrial flutter, those participating in other clinical studies, patients with valvular AF, and those with AF due to temporary causes will be excluded from the study.

Atrial fibrillation will be diagnosed if it is detected through an electrocardiogram (ECG) or a 24-hour Holter recording conducted during or within the 6 months before enrollment in the study. Additionally, patients with a confirmed diagnosis of AF in their medical history or those currently receiving treatment for AF will also be considered as having AF. The presence of AF on the ECG will be defined as the absence of discernible P waves and the presence of irregular RR intervals, without atrioventricular conduction abnormalities.[18] During the 2 years following the commencement of data collection, all eligible patients meeting the criteria will be enrolled in the study without any maximum limit on the number of participants.

Study Centers

Subdivisions are selected according to geographical codes known as NUTS, which is known as the regional unit nomenclature for statistical purposes by the Statistical Office of the European Union (EUROSTAT).[19]The NUTS classification consists of 3 separate categories based on the country's previous regional classification (NUTS-1), grouping regions with similar characteristics (NUTS-2), and population size (NUTS-3). The NUTS-2 regions are classified based on "shared socioeconomic and cultural characteristics, common social issues and problems, and similar geographic conditions." Furthermore, EUROSTAT is considering conducting regional studies based on NUTS-2 regions. For these reasons, the selection of centers in the study was based on the NUTS-2 regions, aiming to include

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40 centers with cardiology specialists and to reflect as much as possible the 26 NUTS-2 regions of Türkiye (Figure 1).

DEFINITIONS AND ENDPOINTS

Diabetes mellitus is defined as having a fasting blood glucose level ≥126 mg/dL and/or a previous diagnosis of diabetes mellitus receiving medication treatment for diabetes or having a hemoglobin A1c level ≥6.5%. Hypertension is defined as having a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg in at least 2 separate resting measurements or having a previous diagnosis of hypertension. Hypercholesterolemia is defined as having a fasting total cholesterol level >200 mg/dL or a low-density lipoprotein (LDL) cholesterol level >130 mg/dL without the presence of conditions such as hypothyroidism or pregnancy. Additionally, individuals receiving treatment for hypercholesterolemia are also included in this definition. Dyslipidemia is defined as having a total cholesterol level ≥200 mg/dL (or an LDL cholesterol level ≥130 mg/dL) and/or a triglyceride level ≥150 mg/dL and/or a HDL cholesterol level <40 mg/dL in men or <50 mg/dL in women without the presence of conditions such as hypothyroidism or pregnancy. Additionally, individuals who have been previously diagnosed with dyslipidemia or are receiving treatment for dyslipidemia are also included in this definition. Chronic kidney disease is defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2.

The CHA2DS2-VASc Thromboembolic Risk Assessment System calculates the total score by entering parameters such as age, gender, heart failure, hypertension, history of ischemic stroke/transient ischemic attack/thromboembolism, history of vascular disease, and diabetes in an online calculator.[9] The HAS-BLED bleeding risk score is calculated based on parameters including hypertension, renal dysfunction, liver dysfunction, history of stroke, prior bleeding or predisposition to bleeding, labile INR, age, drug usage contributing to bleeding risk, and alcohol usage.[20]

Primary endpoints have been defined as systemic thromboembolism (stroke, transient stroke, and peripheral embolism) and major safety endpoints (major bleeding, CRNM bleeding, or minor bleeding defined by ISTH). Secondary endpoints of the study included MACE (systemic embolism, myocardial infarction, and cardiovascular death), all-cause mortality, death related to heart failure, intracranial hemorrhage, sudden cardiac death, quality of life associated with AF, hospitalizations for all causes and reasons, outcomes related to anticoagulation use (type of anticoagulant therapy used, patient satisfaction level, time in therapeutic range for anticoagulation, reasons for discontinuation, interruption, or modification of anticoagulation), AF-related interventions

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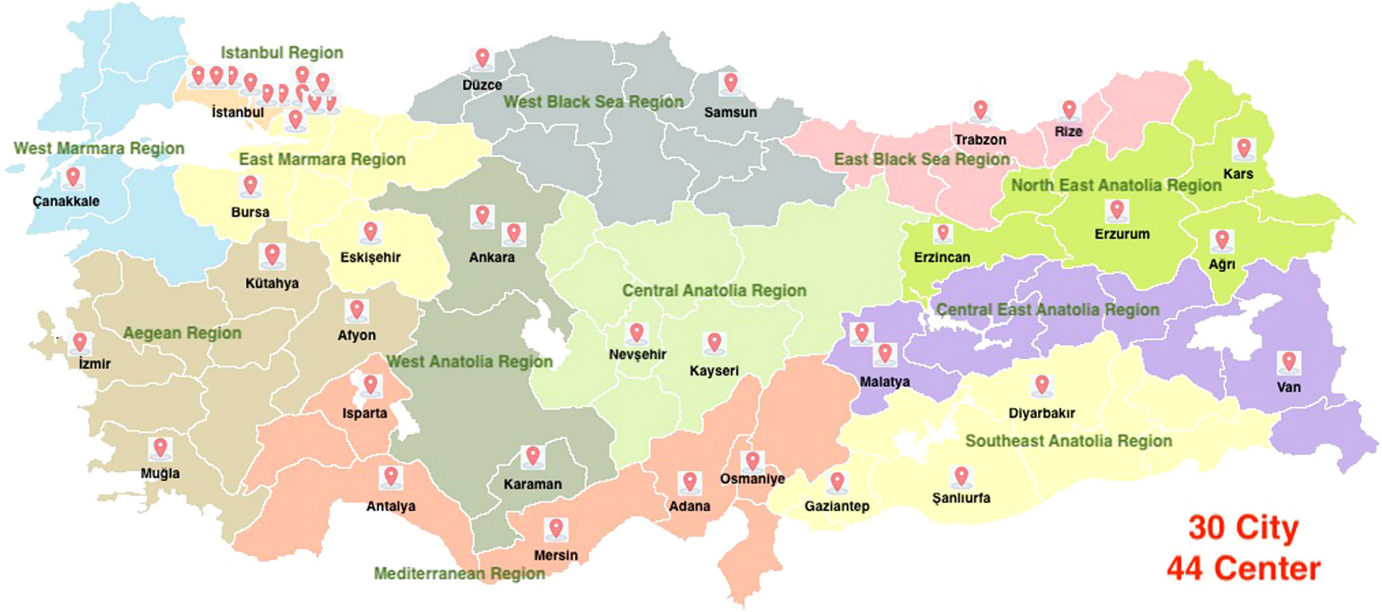

Figure 1. Study centers and cities divided by Nomenclature of Territorial Units for Statistics 2 classification.

(transesophageal echocardiography, cardioversion, atrioventricular node ablation, left atrial appendage closure, pacemaker implantation, cryoablation, or radiofrequency ablation), international normalized ratio (INR) values of patients using warfarin and fluctuations in INR values, mini-mental test, and adherence and continuity of treatment used to treat stroke.

Baseline and Follow-Up Data

The baseline and follow-up data of patients will be obtained and documented through various methods, including clinical visits, telephone interviews, archival records, and the Turkish Republic Health Ministry's e-Pulse (e-Nabız) System. Researchers will have data and record it into internet-based electronic case reports. Data will be recorded in this report on a biannual basis, with follow-up assessments conducted 1 year after enrollment for each participant. The data to be collected from patients during the baseline and each follow-up period are specified in Table 1. Baseline data will include demographic characteristics, medical history, vital signs, AF symptoms, ECG and echocardiographic findings, CHADS2-VASC2 and HAS-BLED risk assessment results, interventional treatments, antithrombotic and antiarrhythmic drugs or other medications taken. For patients using warfarin, the INR level will be monitored. Follow-up data will be scanned and recorded at the 6th, 12th, 18th, and 24th months for each patient.

Data Management

All patient records uploaded to the system on electronic open reading frame will be automatically converted to Excel format and scanned for missing and incompatible data. In the presence of any inconsistency in the data, the coordinators will try to solve the problem by contacting the participants directly. After all, data are collected, they will be analyzed and evaluated by the study protocol and design.

Table 1. Data to Be Collected From Patients at the First Assessment and at Each Follow-Up

	Base	6 months	12 months	18 months	24 months
Include or not	x				
Demographics	x				
Medical history	x				
Vital signs	x	x	x	x	x
AF symptoms	x	x	x	x	x
ECG–ECHO laboratory	x		x		x
Risk assessment	x		x		x
Interventional treatments	x	x	x	x	x
Antiplatelet	x	x	x	x	x
Antiarrhythmics	x	x	x	x	x
Other treatments	x	x	x	x	x
INR	x	x	x	x	x
Endpoints		x	x	x	x
Approval	x				

ECG, electrocardiogram; ECHO, echocardiography; INR, international normalized ratio.

Statistical Analysis and Sample Size Calculation

All statistical analyses will be performed with the R statistical package (R statistical software, Institute for Statistics and Mathematics, Vienna, Austria). The median and interquartile range will be used to present numerical variables, and percentages and numbers will be used to present categorical data. Clinical prediction models for primary and secondary outcomes will be developed (both descriptive and predictive modeling). When developing clinical prediction models, the candidate predictors to be included in the model must be clinically and biologically relevant and be associated with primary/secondary outcomes in previous studies, and the variables to be included in the model will be determined according to these principles. To develop a clinical model, the sample should be sufficiently large and the number of predictors sufficiently conservative. Specifically, there should be at least 10 patients ensuring endpoint (endpoint/df >10) relative to the degrees of freedom of the candidate predictors included in the model.

However, in cases where endpoint/df <10, the penalized regression method will be used along with conventional regression methods to reduce the risk of over-fitting. In addition, the numerical variables to be included in the model will be included as nonlinear parameters using restricted cubic splines. The relationship between primary/secondary outcomes and candidate predictors will be investigated using Cox proportional or logistic regression analysis, and the relationship between outcome and predictors will be shown by hazard or odds ratio. Calibration will be evaluated by plotting the observed result on the y-axis and the predicted result on the x-axis for internal model validation and performance. Deviations from the 45-degree line will indicate bias for the predicted outcome. To evaluate the relationship between observed outcomes and predicted outcomes, the Loess algorithm will be used. The model's discrimination will be assessed by calculating the c-index. For sample size calculation, it is known from the previously published RELY[21], ROCKET-AF[12], ARISTOTLE[10] and ENGAGE[11] studies that the estimated probability of realization of the primary outcome in AF patients is around 2%-3%/year. It is anticipated that patients will be included in the study for 2 years and the estimated mean follow-up period will be 1.2 years. When a conservative Cox–Snell adjusted R^2 value of 0.05 is selected, and considering the inclusion of approximately 10 predictors in the statistical model with a shrinkage factor of 0.9, the estimated sample size is approximately 1750 patients.[22] Considering the patients lost to follow-up and losses, the minimum required sample volume of 1900 patients is necessary. However, to utilize both time and cost more efficiently, 2 interim analyses are planned (after 500 and 1000 patients). In the interim analyses, if the expected primary event rates are significantly less or more than 3%, the number of patients to be included and/or the follow-up period can be redetermined, and the sample size will be calculated again.

DISCUSSION

The TRAFFIC study is designed to be the largest study ever conducted in Türkiye, showing the prevalence and risk profile, as well as their treatment management and outcomes. Additionally, through predictive modeling, effective risk assessment models can be developed for primary and secondary endpoints in this patient population.

The first cohort study conducted in Türkiye on this subject was the TEKHARF study, which was conducted with a total of 3450 participants until 2006-2007.[3] According to the data of the TEKHARF study, the mean survival was 5-9 years, and the mortality rate was 6.8 per 100 person-years. It has been reported that a quarter of the total deaths are caused by ischemic stroke in the Turkish population, where AF is more common without statistical significance in women, unlike in Western societies.

The impacts of ethnic differences on the risk of AF, patients' thromboembolic risk profile, the safety of vitamin K antagonists (VKA), and access to various AF treatments have been well characterized. Numerous population-based and other studies have shown a higher prevalence of AF in Caucasians compared to other ethnic groups.[14-16] The available data suggest that Caucasians with AF may be more vulnerable to AF-related cardiovascular morbidity and mortality compared to non-white ethnic groups.[17] However, AF-related outcome rates in the ORBIT-AF registry were similar among white, black, and Hispanic AF patients, suggesting that AF treatment may reduce ethnicity-related differences in outcomes.[23] Recent data suggest a higher annual risk of ischemic stroke in Asian patients with AF compared to non-Asian individuals, both in non-anticoagulated [24,25] and in anticoagulated[10-12,26] patients. Standard doses of NOACs have been found to be more effective and safer in Asians than in non-Asians, while low-dose NOACs show similar effects in both populations.[27] African Americans have a lower likelihood of receiving VKA, require higher warfarin doses to maintain therapeutic anticoagulation,[28] and have a greater risk of intracranial hemorrhage compared to Caucasians. African-American and Hispanic patients are treated with rate control more frequently and are less likely to undergo AF catheter ablation compared to Caucasians.[29] In a subgroup analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management study, Hispanics and whites had a higher 5-year survival in the rate control arm, whereas blacks had similar survival in both the rate and rhythm control arm.[30] Data on ethnic differences in AF-related quality of life and cognitive impairment are lacking. Guideline-based AF treatment has been shown to improve outcomes,[31,32] but the management of patients with AF in clinical practice may sometimes differ from evidence-based recommendations. The idea of systematically collecting current data on the management and treatment of AF in different regions of Türkiye with the aim of evaluating AF management in clinical practice has been considered for many years but has not been fully realized. The first Turkish study of AF management was obtained from the cohort of the TEKHARF study, which was followed up until 2006-2007. Since then, both the introduction of new treatments and methods in AF patient management and the need for treatment according to new risk scores (CHA2DS2-VASc and HAS-BLED scores) have necessitated a more comprehensive patient registry study. The precise data regarding health-care costs associated with AF in our country are not known. To uncover these data, there is a need for such a registry study.

As of today, multiple risk prediction models and scoring systems have been developed for assessing outcomes in patients with AF. There are numerous studies in the literature that compare these scoring systems, and they have shown varying results in terms of superiority. One of these is the CHA2DS2-VASc scoring system, which allows for the calculation of ischemic stroke risk and enables the selection of appropriate treatment management. The ATRIA Stroke risk scoring, which was developed later, has been reported to have a higher discriminative ability than CHA2DS2-VASc in determining ischemic stroke[33] (*c*-index = 0.712 vs. 0.697). The HAS-BLED score has been shown to be a good predictor not only of bleeding risk but also of cardiovascular events and mortality in patients with AF.[34] A study has also reported that the HATCH scoring system, which consists of hypertension, age, transient ischemic attack or stroke, chronic obstructive pulmonary disease, and heart failure, compared to CHA2DS2-VASc, has a higher capacity to predict mortality in patients with AF.[35] According to a network meta-analysis of studies comparing ATRIA, CHADS2, CHA2DS2-VASc, HAS-BLED, HATCH and ORBIT risk scores in terms of predicting mortality outcome in patients with AF, CHA2DS2-VASc was found to have the highest negative predictive value and the highest predictive value.[36] As previously mentioned, it is known that demographic characteristics have a significant impact on the treatment response and outcomes in AF. Therefore, we believe that developing a prediction risk-scoring system on a large-scale population in our country, accompanied by current data, would be beneficial for the management of patients.

Study Limitations

The major limitation of the study is that not all centers with cardiology clinics could participate in the study. However, the selection of centers was done in accordance with the recommended regional distribution based on NUTS-2 regions, so it is not expected to have a significant impact on the results. Another limitation is that the participants who collected data for the study did not have similar levels of facilities and experience. It should be kept in mind that there may be unaccounted factors in the modeling process.

CONCLUSION

The AF registry study, covering a period of 2 years, provides us a timely assessment of the adoption and implementation of new therapeutic and risk approaches in clinical practice with valuable insights into the contemporary management of AF in accordance with the guidelines. Assessment of adherence to guidelines will allow targeted educational programs to improve practice. Furthermore, using prediction modeling,

risk-scoring systems for primary and secondary endpoints could be developed with proven efficacy in AF patients.

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by Republic of Türkiye Ministry of Health and the Ethics Committee of Haydarpaşa Numune Training and Research Hospital (March 29, 2021, HNEAH-KAEK 2019/KK/150).

Informed Consent: All subjects gave their informed consent for inclusion before they participated in the study.

Peer-review: Externally peer-reviewed.

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