

Protocol

# Design and Rationale of the National Tunisian Registry of Atrial Fibrillation: Protocol for a Prospective, Multicenter Trial

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## Abstract

**Background:** Atrial fibrillation (AF) is an important health problem in Tunisia. A significant change in the epidemiological pattern of heart disease has been seen in the last 3 decades; however, no large prospective multicenter trial reflecting national data has been published so far. Robust data on the contemporary epidemiological profile and management of AF patients in Tunisia are limited.

**Objective:** The aim of this study is to analyze, follow, and evaluate patients with AF in a large multicenter nationwide trial.

**Methods:** A total of 1800 consecutive patients with AF by electrocardiogram, reflecting all populations of all geographical regions of Tunisia, will be included in the study, with the objective of describing the epidemiological pattern of AF. Patients will be officially enrolled in the National Tunisian Registry of Atrial Fibrillation (NATURE-AF) only if an electrocardiogram diagnosis (12-lead, 24-hour Holter, or other electrocardiographic documentation) confirming AF is made. The qualifying episode of AF should have occurred within the last year, and patients do not need to be in AF at the time of enrollment. Patients will be followed for 1 year. Incidence of stroke or transient ischemic attack, thromboembolic events, and cardiovascular death will be recorded as the primary end point, and hemorrhagic accidents, measurement of international normalized ratio, and time in therapeutic range will be recorded as secondary end points.

**Results:** Results will be available at the end of the study; the demographic profile and general risk profile of Tunisian AF patients, frequency of anticoagulation, frequency of effective treatment, and risks of thromboembolism and bleeding will be evaluated according to the current guidelines. Major adverse events will be determined. NATURE-AF will be the largest registry for North African AF patients.

**Conclusions:** This study would add data and provide a valuable opportunity for real-world clinical epidemiology in North African AF patients with insights into the uptake of contemporary AF management in this developing region.

**Trial Registration:** ClinicalTrials.gov NCT03085576; <https://clinicaltrials.gov/ct2/show/NCT03085576> (Archived by WebCite at <http://www.webcitation.org/6zN2DN2QX>)

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## KEYWORDS

atrial fibrillation; registry; North African; NATURE-AF

## Introduction

### Background

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, and recent projections in Europe estimate that from 2010 to 2060, the number of adults aged 55 years and older with AF in the European Union will more than double [1]. With the aging population and associated prevalence of other cardiovascular diseases, the burden of AF is projected to increase. It is estimated that by 2050, the prevalence of AF in Africa will be greater than in any other region of the world [2]. Given the increasing prevalence and AF's association with significant morbidities and mortality, this increase would have major public health implications.

In the last decades, a significant change in the epidemiologic and etiologic patterns of cardiovascular diseases has been seen in North Africa with a decrease in rheumatic heart disease and increase in hypertensive and ischemic heart disease [2,3]. The World Health Organization reported trends in the incidence and prevalence of acute rheumatic fever and rheumatic heart disease for each continent based on literature from 100 countries around the world between 1970 and 2009 [4,5]. However, data from

Africa are scarce and do not capture the entire time frame. As for all heart diseases, there are insufficient contemporary population-based data describing the epidemiologic pattern of AF in North Africa and especially in Tunisia. In 2003, valvular AF secondary to rheumatic heart disease was the most common etiologic form of AF [6].

Numerous registries and surveys have been described in different European, Asian, and American countries—Euro Observational Research Programme—Atrial Fibrillation pilot general registry [7], Japanese Rhythm Registry [8], Global Anticoagulant Registry in the Field [9], Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation [10], the nationwide US Practice Innovation and Clinical Excellence Registry [11], Outcomes Registry for Better Informed Treatment of Atrial Fibrillation [12], and Chinese Atrial Fibrillation Registry study [13]. However, few data on the demographic characteristics, outcome of AF patients, and quality of anticoagulation control achieved in AF patients receiving routine medical care are available in North Africa and especially in Tunisia.

Demographic and prognostic AF data from other ethnic groups would not be generalizable to our population. Thus, a register

or a survey dealing with the demographic and prognostic characteristics of AF in Tunisia is essential, making it possible to identify its specific characteristics inherent in part to ethnic particularities but especially to particularities of the local health system.

### Registry Objectives

The National Tunisian Registry of Atrial Fibrillation (NATURE-AF) is a prospective observational accumulation of data used in the investigation of the optimal intensity of anticoagulation in Tunisian AF patients and present status of anticoagulation treatment in Tunisia.

The primary end point of NATURE-AF is to describe the incidence of stroke or transient ischemic attack (TIA), thromboembolic event, and cardiovascular death every 3 months up to 1 year.

The secondary end points are as follows:

- Hemorrhagic accidents, every 3 months up to 1 year
- International normalized ratio (INR) every month for 1 year
- Mean time in therapeutic range (TTR) obtained in patients who receive anticoagulant therapy

## Methods

### Study Design and Patient Enrollment

NATURE-AF is a prospective, observational registry with a 1-year follow-up period. The enrollment occurred all over Tunisia between March 1, 2017, and May 31, 2017. The registry population comprised consecutive in- and outpatients with AF presenting to cardiologists. Consecutive patients were screened for eligibility at the time of their presentation to a cardiologist (hospital or medical center). All patients provided written informed consent. Patients were officially enrolled in NATURE-AF only if they were aged 20 years and older and had had at least 1 episode of AF recorded on a standard 12-lead electrocardiogram or on 24-hour Holter monitor. The qualifying episode of AF should have occurred within the last year and could be valvular or nonvalvular AF. Valvular AF is AF in patients with mitral stenosis or prosthetic heart valves. Patients did not need to be in AF at the time of enrollment. All patients admitted for catheter ablation, initiation of drug therapy, or cardioversion (electrical or pharmacological) were eligible to be included.

Exclusion criteria were AF due to reversible causes (eg, thyroid disease and pulmonary embolism) including postoperative AF ( $\leq 3$  months), life expectancy less than 12 months, acute coronary syndrome, isolated atrial flutter, mental disorders, and ongoing anticoagulation for reasons other than AF.

### Sample Size and Data Collection

A minimum of 10 consecutive patients per cardiologist were enrolled with a target of 1800 patients for NATURE-AF. A total of 186 cardiologists agreed to participate.

While it was anticipated that most investigators would be hospital-based cardiologists, recruitment by office-based cardiologists was allowed if follow-up of patients was deemed feasible.

The plan was to have 1 baseline visit and 1 visit every 3 months over a 1-year period. Enrollment into the registry started March 1, 2017, with an inclusion period estimated up to 3 months. All patients were followed for 12 months. During this period, all participants revisited their cardiologists at the usual intervals (3 months), and patients taking oral anticoagulant therapy consult (or visited) at least once every month for INR to be measured.

The data collected were managed by the Clinical Suite platform (Dacima Software), which complies with international standards including US Food and Drug Administration 21 Code of Federal Regulations Part 11, US Health Insurance Portability and Accountability Act, International Conference on Harmonisation, and Medical Dictionary for Regulatory Activities. The Clinical Suite platform allowed us to track the data entered, check for inconsistencies and missing data, and schedule monitoring visits. A steering committee was set up to monitor patient inclusions, verify data sources, perform the audit trail, and prepare the statistical analysis plan for the study. Data were collected every 3 months regardless of patient clinic follow-up. All incident events and therapeutic changes were entered at each collection interval.

Baseline data included patient demographics, medical history, cardiovascular history, details of AF history and therapies, vital signs, laboratory measurements, electrocardiographic data, cardiac imaging parameters, details of medical management, and any contraindications to anticoagulation. At follow-up, major incident events and procedures, subsequent vital signs, laboratory studies, imaging parameters, and medication changes were recorded, and the daily acenocoumarol (Sintrom) dose and INR value were noted for all patients taking acenocoumarol. In-depth data regarding antithrombotic therapies, dosing, discontinuations, and reasons for discontinuations were included in follow-up medication data.

### Timeline

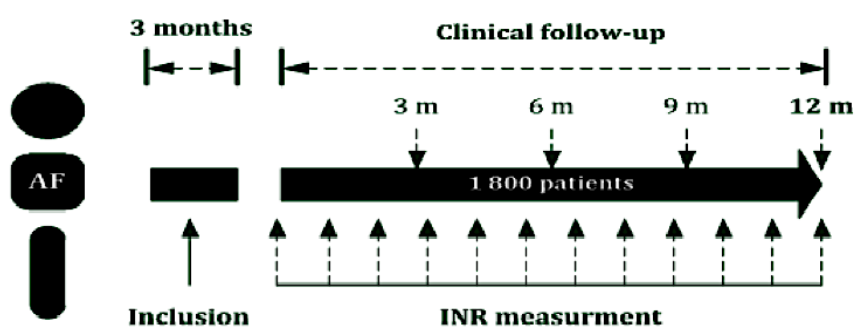
Patient enrollment and data collection began in March 2017 and continued until the end of May 2017. Follow-up continued until all patients had 1-year data. [Figure 1](#) describes the study protocol.

### Outcomes

During follow-up, the end points of this observational study were symptomatic stroke including TIA, systemic thromboembolism, myocardial infarction, incident heart failure, cause-specific hospitalization, major bleeding, and all causes of death.

Major bleeding is defined by the International Society of Thrombosis and Hemostasis criteria; this includes bleeding events meeting at least one of the following criteria [14]:

- Decrease in hemoglobin  $\geq 2$  g/dL
- Transfusion of  $\geq 2$  units of packed red blood cells or whole blood
- Any bleeding in a critical site (intracranial, intraspinal, intraocular, intra-articular, pericardial, retroperitoneal, or intramuscular with compartment syndrome)
- Any fatal bleeding

**Figure 1.** Study protocol AF: atrial fibrillation; INR: international normalized ratio.

Additional unique, detailed data on management of bleeding events were collected and included the use of any blood products or transfusions, potential reversal agents, and necessity for invasive management of bleeding events. Any patient in whom a primary end point was encountered was evaluated by computed tomography or magnetic resonance imaging for precise diagnosis and required an INR value on the closest possible day to their revisit day to their cardiologist.

INR will be recorded monthly and TTR will be calculated according to Rosendaal's algorithm with linear interpolation [15].

### Ethical Considerations

Ethics approval was obtained from the Human Research Ethics Committees at Abderrahmen Mami Hospital in Tunis. Ethics review boards in each participating hospital approved their participation. Informed consent from individual patients was obtained before participation in long-term follow-up. The study was performed according to the ethical principles for medical research involving human subjects specified in the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practices.

### Statistical Analysis

Continuous variables will be described by mean and standard deviation or as median and interquartile range. Categorical variables will be described by the size and frequency of every modality. Means comparison will be performed by analysis of variance or by nonparametric tests if the hypothesis of normality is rejected. The normality of continuous variables will be verified with the Shapiro-Wilk test. The statistical tests are bilateral with a 95% confidence interval.

A chi-square test will be performed for categorical variables. Yates correction or the Fisher exact test will be used if the conditions of validity for the chi-square test are not met.

A multivariate analysis will be performed with anticoagulant treatment (over or undertreated) as dependant factor. The independent variables will be age, gender, body mass index, type of AF, combined therapy. Univariate logistic regression will be carried out with a 10% output threshold. The final model will be performed with the parameters selected by the backward stepwise method of Wald. The selected variables in the final model will be tested at the 5% threshold. The interaction between selected parameters is tested at the 10% threshold.

The TTR will be calculated by the method first described by Rosendaal et al [8], which uses linear interpolation of INR values in each patient under oral anticoagulant treatment to calculate the percentage of days when the INR is in the therapeutic range (2.0-3.0) for nonvalvular AF.

### Expected Implications

The NATURE-AF is the first large-scale investigation to clarify the contemporary demographic data, management and outcomes of AF patients, and frequency and quality of oral anticoagulation in Tunisian AF patients.

### Oversight and Leadership

The protocol of NATURE-AF was approved by the Tunisian Society of Cardiology and Cardiovascular Surgery. The NATURE-AF study was submitted to ClinicalTrials.gov [NCT03085576].

### Study Sponsorship

NATURE-AF is sponsored by the Tunisian Society of Cardiology and Cardiovascular Surgery.

## Results

About 95 cardiologists included 918 patients in the registry with a 1-year follow-up period. All patients provided written informed consent. Patients were officially enrolled in NATURE-AF only if they were aged 20 years and older and had had at least 1 episode of AF recorded on a standard 12-lead electrocardiogram or on 24-hour Holter monitor.

## Discussion

### Summary

Numerous registries and surveys have been described in different European, Asian, and American countries [7-13,16-19], but few contemporary data on the demographic characteristics, outcome of AF patients, and quality of anticoagulation control achieved in AF patients receiving routine medical care are available in North Africa and especially in Tunisia.

Only 2 published studies have described the epidemiological data on Tunisia [5,15,16]. In 2003, Drissae et al [6] described a multicentric study with 1134 patients presenting with a first episode of AF between January 1985 and December 2000. The average age was 58.6 (SD 15-60) years; 57.8% (656/1134) were



male and 42.2% (478/1134) were female. The most common etiology of AF identified was rheumatic carditis (36.1%). AF was idiopathic in 27.7% of cases. Higher morbidity and mortality were demonstrated in AF patients with a 5-year survival of 85%.

Recently, geographic differences have been highlighted by Gamra et al [16,17]. The RealiseAF international cross-sectional survey enrolled 10,523 patients (with at least 1 documented AF episode in the preceding 12 months) from 831 sites; 26 countries from 4 continents participated in the study with Middle East and North Africa participation from Algeria (n=310), Egypt (n=458), Lebanon (n=191), Morocco (n=250), and Tunisia (n=471). AF patients from the Middle East and Africa were significantly younger and more frequently female compared with those originating from the rest of the world. A CHADS<sub>2</sub> (congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke) score  $\geq 2$  was observed in 64.2% of the patients originating from Europe versus 58.3%, 57.8%, and 43.6% from Latin America, Asia, and the Middle East and Africa, respectively. Among those patients with a CHADS<sub>2</sub> score  $\geq 2$ , there were also important geographical differences with respect to the use of antithrombotics: the proportion of patients not receiving any antithrombotic therapy ranged from 11.4% in the Middle East and Africa to 27.6% in Latin America. Conversely, the use of oral anticoagulants was highest in the Middle East and Africa (66.7%) and lowest in Asia (31.7%) [16,17].

Despite the many complexities associated with the use of vitamin K antagonists (VKA), it remains a mainstay of anticoagulation therapy. Acenocoumarol, a derivative of

coumarin, is the most popular VKA used in Tunisia and numerous countries around the world. Maintaining therapeutic range in patients treated with VKAs has always been challenging, and the potential consequences of deviating from the therapeutic range are deleterious.

Although not easily achieved, high anticoagulation control, expressed as TTR, has a paramount effect on patient outcomes, reducing stroke events and mortality rates.

This large, contemporary longitudinal study of Tunisian AF patients will provide a unique opportunity to answer many clinical questions. The NATURE-AF study is important in several respects. First, systematic observational and outcomes data can be generated from this registry study, which is especially valuable given that evidence for Tunisian AF patients is limited. Second, treatment of AF is changing dramatically, and AF management needs to be evaluated in real-world studies. Third, the NATURE-AF study provides a good opportunity to compare treatment and response variation among AF populations in Africa for comparison with different countries and evaluate adherence to recent guidelines.

## Conclusions

NATURE-AF will fill a significant gap in the dynamic landscape of AF care and research. It will provide unique and necessary data on the management and outcomes of AF patients treated. This study will yield the largest contemporary longitudinal cohort of patients with AF in Tunisia and would provide a valuable opportunity for real-world clinical epidemiology with insights into the uptake and outcomes of contemporary AF management.

## Conflicts of Interest

None declared.

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## Abbreviations

**AF:** atrial fibrillation

**CHADS<sub>2</sub>:** congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke

**INR:** international normalized ratio

**NATURE-AF:** National Tunisian Registry of Atrial Fibrillation

**TIA:** transient ischemic attack

**TTR:** time in therapeutic range

**VKA:** vitamin K antagonist

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