ORIGINAL ARTICLE

Rationale, design and methodology of the RAMSES Study: ReAl-life Multicenter Survey Evaluating Stroke Prevention Strategies

Türkiye'de nonvalvuler atriyum fibrilasyonlu hastalarda inme önleme stratejilerinin değerlendirilmesi RAMSES (ReAl-life Multicenter Survey Evaluating Stroke Prevention Strategies) çalışması

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ABSTRACT

Objective: Atrial fibrillation is the most common arrhythmia and is associated with a five- fold increased risk of thromboembolic events. Vitamin K antagonists (VKAs) have been the mainstay of oral anticoagulant prophylaxis and the data on stroke prevention strategies are limited to VKA era. The purpose of this study is to evaluate the use of VKA, non-Vitamin K antagonist oral anticoagulants (NOAC), and antiplatelet agents in patients with non-valvular atrial fibrillation (NVAF).

Methods: The ReAl-life Multicenter Survey Evaluating Stroke prevention strategies in Turkey (RAMSES) is an observational, multicenter, prospective study of patients with NVAF. The study targeted enrollment of 7835 patients from 68 sites in Turkey. All the data will be collected at one point in time and current clinical practice will be evaluated. (ClinicalTrials.gov number NCT02344901).

Results: Baseline characteristics of patients, antithrombotic therapies, transition to NOACs and rate/rhythm control strategies will be evaluated.

Conclusion: The RAMSES registry will be the largest study in Turkish NVAF patients. The study will provide insights into real-world problems and anticoagulant treatment in patients with NVAF.

ÖZET

Amaç: Atriyum fibrilasyonu (AF) en sık saptanan aritmi olup tromboembolik olay oranında 5 kat artışla ilişkilidir. Nonvalvüler atriyum fibrilasyonunda (NVAF) inme önleme stratejileri ile ilgili olan bilgilerimiz daha çok vitamin K antagonisti (VKA) olan ilaçlar hakkındadır. Bu çalışma NVAF olan hastalarda VKA, non-vitamin K antagonisti oral antikoagülan (NOAK) ve antiagregan tedavilerin kullanımını değerlendirmek için tasarlanmıştır.

Yöntemler: RAMSES (ReAl-life Multicenter Survey Evaluating Stroke prevention strategies in Turkey) çalışması NVAF'li hastalarda gözlemsel, çok merkezli ve ileriye dönük bir çalışma olarak tasarlandı. Çalışmaya Türkiye'de 68 merkezden 7835 hasta alınması planlandı. Hastalarla ilgili tüm verilerin tek bir ziyarette alınması ve klinik yaklaşımların değerlendirilmesi planlandı. (ClinicalTrials.gov numarası NCT02344901).

Bulgular: Hastaların bazal demografik verileri, kullanmakta oldukları antitrombotik tedavileri, NOAK'lara geçiş ve hız/ritm kontrol stratejilerinin değerlendirilmesi planlandı.

Sonuç: RAMSES kayıt çalışması NVAF'li hastalar hakkında Türkiye'de yapılmış en büyük çalışma olacaktır. Bu çalışmanın NVAF'li hastalarda antikoagülan tedavileri ve sorunlarla ilgili gerçek hayattan veriler sağlaması beklenmektedir.

Atrial fibrillation (AF), classified as nonvalvular (NVAF) in the absence of rheumatic mitral stenosis or valvular prosthesis, is the most common arrhythmia, with an estimated prevalence of 1.5–2%.[1] AF is associated with a 5-fold higher risk of arterial thromboembolic events.[2] The risk of death is also doubled, and AF-related stroke is more severe and causes greater disability than stroke in patients with-

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out AF.[3] To prevent stroke in patients with NVAF, antithrombotic treatments are employed with oral anticoagulants (OAC) such as vitamin K antagonists (VKA) and, in a number of circumstances, with antiplatelet agents. Oral anticoagulation with dose-adjusted VKA has resulted in a 64% risk reduction of stroke rates 4. However, reduction in the relative risk of stroke in patients with AF treated with antiplatelets compared with placebo or no treatment is only 19%.[4] Current guidelines for the management of AF recommend OAC therapy for patients who are at moderate to high risk for thromboembolic events, and no antithrombotic or antiplatelet therapy is recommended for patients who are at low risk.[5,6] Although VKAs (mainly warfarin) are highly effective in reducing the risk of stroke, and have been the sole choice for stroke prevention during the last 50 years, their use is limited for a number of reasons: narrow therapeutic range, drug and food interactions, need for monitoring, and risk of bleeding. Recently, non-vitamin K antagonist oral anticoagulants (NOACs) have been marketed for this indication. These relatively new agents have been evaluated in large randomized multicenter clinical trials and shown to be at least as effective as warfarin with a better safety profile.[7–9] However, these trials may not reflect real-world settings, due to inclusion of selected populations without severe comorbidities.

Abbreviations:

AF	*Atrial fibrillation*
EORP-AF	*EURObservational Research Programme Atrial Fibrillation*
INR	*International normalized ratio*
NOACs	*Non-vitamin K antagonist oral anticoagulants*
NVAF	*Nonvalvular atrial fibrillation*
OAC	*Oral anticoagulants*
TTR	*Time in therapeutic range*
VKA	*Vitamin K antagonists*

Although large observational cohort studies have been performed to overcome this limitation, these studies mainly focused on VKA therapy.[10,11] The introduction of NOACs to clinical practice might have led to a change in physicians' approach to NVAF patients.

The aims of this study are: (1) to demonstrate the current status of the clinical background of patients with NVAF, (2) to determine standard clinical practice on stroke prevention, and (3) to analyze the appropriateness of anticoagulant therapies in patients with NVAF in a large multicenter nationwide trial.

METHODS

Study design

The RAMSES study (ClinicalTrials.gov identifier NCT02344901) is planned as a national multicenter cross-sectional registry. Sample selection and loss to follow-up are common concerns in longitudinal studies. To overcome this bias, this study has been designed as a cross-sectional study to allow inclusion of all consecutive patients with NVAF.

Setting

The study will be conducted in outpatient cardiology clinics, and all data collected in a single visit. We planned to enroll a total number of 7835 patients after contacting 68 sites, which are all expected to participate. To ensure inclusion of adequate geographic diversity, it is planned to enroll a proportional number of patients to the population of every region. State, university, education and research, and private hospitals are included to represent all patients treated within the different health care settings. The study was initiated in February 2015 and the last patient was enrolled in May 2015.

Study population

All consecutive patients admitted to the outpatient cardiology clinics with electrocardiographically confirmed NVAF of age ≥18 years will be enrolled. Although the definition of NVAF is controversial, valvular AF is defined as AF related to rheumatic valvular disease (predominantly mitral stenosis), or prosthetic heart valves in the RAMSES study. The RAMSES trial excluded patients with mitral stenosis, or a mechanical prosthetic heart valve.

Outcomes

Patient characteristics and demographics, including geographical diversity, of the patient characteristics and OAC use will be described. Guideline-based use of anticoagulation in eligible patients and reasons for not being on OAC therapy will be analyzed. The primary outcome of the RAMSES study is the appropriateness of stroke prevention strategies in patients with NVAF. Secondary outcome measures include time in therapeutic range (TTR) for patients on warfarin, CHA_2DS_2VASc (congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 years, diabetes, thromboembolism or stroke history, vascular

disease, age 65–74 years, and sex) and HAS-BLED (hypertension, renal or liver failure, stroke history, bleeding history, labile international normalized ratio, age >65 years, drugs, or alcohol) scores and their relation with OAC use. The impact of coronary artery disease, congestive heart failure and renal failure on OAC therapy will be evaluated. Particular interest will be devoted to the lower dosages of NOACs and their consistent use with recommendations.

Data collection

Patient characteristics will be questioned by survey. Demographic data including age, sex, body weight, smoking status, pulmonary disease, level of education, place of residence (rural or urban), and type of AF will be noted. Stroke-associated risk factors such as coronary artery disease, hypertension, diabetes mellitus, previous stroke, congestive heart failure, and vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque) will also be questioned. Subsequently patients' ongoing pharmacologic treatment for stroke prevention (antiplatelet, anticoagulant, or none) and antiarrhythmic drug therapy will be questioned. Hemorrhagic events related to the current therapy, international normalized ratio (INR), and creatinine levels will be noted. For patients on VKA therapy, time in therapeutic range (TTR) will be calculated by two methods (1) cross-sectional: The ratio of in-range (2-3) INRs to all INRs at a specific time and (2) traditional: The ratio of in-range (2-3) INRs to all INRs of a patient. Renal functions will be estimated using creatinine clearance calculated by the Cockroft-Gault formula. Inappropriate use of OACs will be assessed according to current guidelines. Major bleeding is defined according to International Society on Thrombosis and Haemostasis criteria[12] and minor bleeding is defined as a non-major bleeding. Lastly, any type of valvular pathology and the reason for not being on OAC therapy will be evaluated.

The study was approved by local ethics committee (Mugla Sitki Kocman University). The enrollment of patients was started in February 2014. All the participating institutions will enroll all consecutive patients with NVAF under regular outpatient care. Written informed consent will be obtained from patients.

Sample size

The goal of enrolling 7835 patients was determined after contacting 68 invited sites. This will allow for capture of a large, representative number of patients with AF in Turkey. In addition, it was planned to enroll proportional numbers of patients according to the seven regions of Turkey.

Statistical analyses

Continuous variables will be summarized by median and interquartile range or mean±standard deviation (SD). Categorical variables will be expressed as frequencies and percentages. Univariate analysis will be performed for continuous variables and chi-square or Fisher exact test will be applied for categorical variables. Correlation between variables will be assessed by Pearson or Spearman test. A p value of <0.05 will be considered significant.

DISCUSSION

The RAMSES study will be the largest study among Turkish patients with NVAF, and one of the largest in the world. The findings of this study will provide important real world evidence, as well as potentially providing a better understanding of the burden of NVAF and the variability in disease management in individual units. The design of the study will allow an evaluation of both newly-diagnosed and prevalent patients with NVAF in a non-randomized, non-selected population. Patients who are at risk for thromboembolic events will be identified. Underuse of oral anticoagulation in patients at elevated risk, barriers to prescribing antithrombotic therapy, and overuse in those at low risk will be researched. The study will also provide information regarding NOAC use in a real-life, large cohort of patients in Turkey for the first time. A snapshot of the characteristics and antithrombotic therapies of NVAF patients will guide physicians in future treatment decisions.

Contemporary ongoing large-scale registries provide data on management and prevention of thromboembolism in patients with AF.[13–16] The design of these and previous studies is shown in Table 1. The registry data regarding stroke prevention strategies in NVAF patients is limited to VKAs and antiplatelet agents. The preliminary results of "The Global Anticoagulant Registry in the FIELD (GARFIELD)", "A Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF), and "EURObservational Research Programme Atrial Fibrillation (EORP-AF)" have shown

Table 1. Comparison of study designs of observational studies

	GLORIA-AF	GARFIELD	ORBIT-AF II	EORP-AF	AFTER	RAMSES
Population	Inpatient and outpatient, newly diagnosed, at risk for stroke	Inpatient and outpatient, newly diagnosed, at risk for stroke	Outpatient, newly diagnosed	Inpatient and outpatient	Outpatient	Outpatient
Enrollment	56.000	55.000	15.000	3119	2242	7835 (intended)
Follow-up	3 years	2 years	2 years	3 years	Cross-sectional	Cross-sectional
Study period	2011-ongoing	2009- ongoing	2013-ongoing	2012-ongoing	2012	2015
No of countries	50 (5 regions)	50	1 (USA)	9 (Europe)	1 (Turkey)	1 (Turkey)
No of sites	2200	1000	300	N/A	17	68 (intended)
OAC studied	W, D, R, A	W, D, R, A	W, D, R, A	W, D, R, A	W	W, D, R, A

GLORIA-AF: Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation; GARFIELD: Global Anticoagulant Registry in the FIELD; ORBIT-AF II: Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II; EORP-AF: EURObservational Research Programme Atrial Fibrillation; AFTER: The atrial fibrillation in Turkey: Epidemiologic Registry, W: Warfarin; D: Dabigatran; R: Rivaroxaban; A: Apixaban.

NOAC use in a minority of patients. These large scale registries were undertaken at the beginning of the NOAC era, and follow-up data will provide information regarding transition from VKAs to NOACs. However, our study will provide current data showing recent problems in the management of AF.

The utilization of OAC therapy among patients with AF has gradually increased. The overall use of OAC therapy was 70% in the EuroHeart survey and AFNET registries, and rose to 80% in the EORP-AF registry.[10,16,17] However, a large multicenter study from our country found that only 40% of patients with NVAF were anticoagulated (VKA) and TTR was 39% for these patients. In addition, antiplatelet therapy was widely used (about two-third of patients were receiving at least one antiplatelet drug), while 17% of patients were not receiving any antithrombotic therapy.[18] VKA-associated problems and low TTR might be reasons for undercoagulation in our country, as the main reason of not being anticoagulated was physician neglect.[19] This study will shed light on whether these reservations are ongoing and if they lead to a transition from VKA to NOAC.

Our study will provide data how emerging therapies in the OAC era are applied in daily practice, and reveal adherence among physicians to current practice guidelines.

Limitations

The RAMSES study is a limited cross-sectional survey that will provide a snapshot of the disease. Therefore, it will not be able to observe the course of the disease and information regarding stroke and mortality data will be limited. Another limitation is dependence on the quality of medical records. Lastly, the coverage of the study is limited to outpatient cardiology clinics.

Conclusion

Awareness of AF and AF-related stroke has increased and the drug of choice is OAC. This study is designed to evaluate current clinical practice regarding stroke prevention strategies in patients with NVAF. The results will help to generate hypotheses for the improvement of prevention strategies and for better understanding the course of the disease.

Collaborators

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Keywords: Atrial fibrillation; oral anticoagulant; risk scores; stroke; Turkey.

Anahtar sözcükler: Atriyal fibrilasyon; oral antikoagülan; risk skorları; inme; Turkey.