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Evaluation of Treatment Safety in Patients with Atrial Fibrillation on Edoxaban Therapy in Real-Life in Turkey Study: Design and Rationale

Türkiye'de Gerçek Yaşam Şartlarında Edoksaban Tedavisi Altındaki Atriyal Fibrilasyon Hastalarında Tedavi Güvenliğinin Değerlendirilmesi: Tasarım ve Amaç

ORIGINAL ARTICLE
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ABSTRACT

Objective: Safety and effectiveness of edoxaban was demonstrated in phase III, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE-AF-TIMI 48) trial and is being confirmed in the post-authorization Edoxaban Treatment in routiNe clinical prActice for patients with Atrial Fibrillation in Europe (ETNA-AF-Europe) study in patients with atrial fibrillation. However, any post-authorization safety study focusing on the safety of edoxaban treatment in Turkey with a prospective design has not been performed yet. The Evaluation of Treatment Safety in Patients with Atrial Fibrillation on Edoxaban Therapy in Real-Life in Turkey (ETAF-TR) study is designed to evaluate the safety and effectiveness of edoxaban treatment in atrial fibrillation in routine practice. The present article describes the design and rationale for the ETAF-TR Study.

Methods: The ETAF-TR (NCT04594915) is a national, multicenter, prospective, observational study that enrolled 858 patients from 32 centers. The primary outcome of the ETAF-TR study is any overt bleeding (consisting of major bleeding or clinically relevant nonmajor bleeding or any bleeding that does not meet this definition but is considered as overt bleeding by the participating physician). Effectiveness, treatment persistence, and posology will also be evaluated in an explorative manner. The overall duration of follow-up will be 1 year; the first patient was enrolled in August 2020.

Conclusions: Results of ETAF-TR will add data from clinical practice to those from ENGAGE-AF trial and also ETNA-AF study. Comparing their results will enable to test the external validity of ENGAGE-AF trial in the country conditions.

Keywords: Arrhythmias, atrial fibrillation/flutter, edoxaban, real life, safety

ÖZET

Amaç: Atriyal Fibrilasyonlu olgularda edoksaban tedavisinin etkinlik ve güvenliği, faz III, ENGAGE-AF (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) Çalışması ile gösterilmiş, otorite onayı sonrası bir gerçek yaşam çalışması olan ETNA-AF-Europe (Edoxaban Treatment in routiNe clinical prActice for patients with Atrial Fibrillation in Europe) Çalışması ile doğrulanmıştır. Bununla birlikte, Türkiye'de edoksaban tedavisinin güvenliğine odaklanan herhangi bir otorite onayı sonrası prospektif çalışma bu tarihe kadar gerçekleştirilmemiştir. ETAF-TR Çalışması, rutin pratikte edoksaban tedavisinin güvenlik ve etkinliğini değerlendirmek için tasarlanmıştır. Bu makalede ETAF-TR Çalışması'nın tasarım ve amacı sunulmaktadır.

Yöntemler: ETAF-TR Çalışması (NCT04594915), 32 merkezden 858 olgunun dâhil edileceği, ulusal, çok merkezli, prospektif gözlemsel çalışmadır. Primer sonlanım, herhangi bir aşikâr kanama (major kanama, klinik olarak anlamlı non-major kanama, bu ölçütleri karşılamayan ancak klinisyen tarafından aşikâr kanama olarak tanımlanan kanama) bileşik sonlanımıdır. Etkinlik, tedaviye devamlılık ve pozoloji konuları da tanımlayıcı biçimde değerlendirilecektir. İzlem süresi 1 yıl olup ilk hasta Ağustos 2020'de çalışmaya dâhil edilmiştir.

Sonuç: ETAF-TR Çalışması'nın sonuçları, ENGAGE AF ve ETNA-AF Çalışmaları'nın sonuçlarını, klinik pratik açıdan tamamlayıcı nitelikte olacaktır. Söz konusu çalışmaların sonuçlarının karşılaştırılması yolu ile ENGAGE-AF Çalışması'nın dış geçerliliğinin ülke koşullarında test edilmesi mümkün olacaktır.

Anahtar Kelimeler: Aritmi, atriyal fibrilasyon/flutter, edoksaban, gerçek yaşam, güvenlik

Atrial fibrillation (AF) is the common sustained cardiac arrhythmia whose prevalence is increasing with the aging of population; better methods have been used for its detection, and improvements in diagnostic methods such as smartphone applications and augmenting social consciousness help in increasing the public and health provider awareness about the disease. Its estimated prevalence in the general population is between 2% and 4%.[1,2] Stroke is the major cause of mortality in patients with AF, who have a 5-fold higher risk of ischemic stroke than patients without AF.[1-3] Long-term oral anticoagulant (OAC) therapy is a cornerstone of stroke and systemic embolism prevention in these patients. Warfarin and other vitamin K antagonists (VKAs) have been used for the prevention of stroke and systemic embolism in patients with AF (SSPAF) for over 50 years.[4-7] However, VKAs have important limitations such as narrow therapeutic window, frequent international normalized ratio (INR) monitoring requirement, and multiple drug–drug/food–drug interactions.[4] More importantly, the efficacy and safety of VKAs mainly depend on time in therapeutic range (TTR) value indicating quality measure for pharmacodynamics effects.[1] Although current guidelines recommend TTR value >70% for patients receiving VKAs, observational studies showed inadequate TTR values in routine clinical practice in many countries and also in Turkey.[8-10] Non-vitamin K antagonist oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban were developed with the aim of overcoming the limitations of VKAs. All 4 NOACs are approved for SSPAF and one or more risk factors for stroke by regulatory authorities based on their pivotal phase III non-inferiority trials.[1] Edoxaban is the most recent reversible and direct factor Xa inhibitor approved by regulatory authorities for SSPAF in 2015. The approval of edoxaban was based on a randomized, double-blind, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE-AF-TIMI 48) non-inferiority trial.[11] The recently published guideline on diagnosis and management of AF developed by the European Society of Cardiology recommends edoxaban and other NOACs instead of VKAs for SSPAF except patients with mechanical heart valves or moderate-to-severe mitral stenosis.[1] Edoxaban has been available in Turkey in both regimens (60 mg o.d. or 30 mg o.d.), and once-daily edoxaban therapy for SSPAF indication was reimbursed by Social Security Institution of Turkey (major payer around the country) since November 2016.

Phase III pivotal NOAC trials are registration trials that support marketing approval by the regulatory authorities. Although these trials had higher internal validity, they also had strict well-defined inclusion and exclusion criteria that limit their external validity. Although effectiveness and safety of edoxaban for SSPAF has been shown in ENGAGE AF-TIMI 48 trial as well, the trial may not always reflect routine clinical practice due to strict design and longer list of inclusion and exclusion criteria. So, demographic and clinical characteristics of the trial population may not reflect the characteristics of patients seen in routine clinical practice. Thus, post-marketing observational studies are needed to evaluate the effectiveness and safety of a product in real-world clinical settings. In this perspective, regulatory authorities such as European Medicines Agency (EMA) requested to conduct post-authorization safety studies as part of the post-approval plan of respective NOACs. Edoxaban Treatment in routiNe clinical prActice for patients with Atrial Fibrillation in Europe (ETNA-AF-Europe) is a multinational, post-authorization safety study of edoxaban treatment in routine clinical practice. The study was conducted in 10 European countries and enrolled unselected AF patients treated with edoxaban. The primary objective of the study was to evaluate the safety of edoxaban treatment by bleeding events.[12,13] Recently published 1-year follow-up results of 13 092 enrolled patients showed low rates of bleeding and ischemic events that consummate results of phase III pivotal trial.[14] Although ETNA-AF-Europe is the largest prospective, post-authorization safety study of edoxaban and 10 European countries were included in the study, Turkey was not included in ETNA-AF-Europe.[13] In addition, possible peculiar clinical, demographic, and pharmacogenetic characteristics of Turkish patients, different health provider infrastructure, and reimbursement requirements may limit the adaptation of the results of the ETNA-AF-Europe to routine clinical practice in Turkey. Post-marketing observational study focusing on the safety of edoxaban treatment with a prospective design has not been done yet in Turkey. Evaluation of Treatment Safety in Patients with Atrial Fibrillation on Edoxaban Therapy in Real-Life in Turkey (ETAF-TR) study is designed to evaluate the safety and effectiveness of edoxaban treatment in patients with AF in real-life practice. The present article describes the design and rationale for the ETAF-TR study.

ABBREVIATIONS

ADRs	Adverse drug reactions
AEs	Adverse events
AF	Atrial fibrillation
CRNM	Clinically relevant nonmajor bleeding
CT	Computed tomography
ECG	Electrocardiograph
eCRFs	Electronic case report forms
ENGAGE-AF-TIMI 48	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48
ETAF-TR	Evaluation of Treatment Safety in Patients with Atrial Fibrillation on Edoxaban Therapy in Real-Life in Turkey
ETNA-AF-Europe	Edoxaban Treatment in routiNe clinical prActice for patients with Atrial Fibrillation in Europe
ICF	Informed consent form
INR	International normalized ratio
LBBB	Left bundle branch block
MI	Myocardial infarction
NOACs anticoagulants	Non-vitamin K antagonist oral
OAC	Oral anticoagulant
RCTs	Randomized controlled trials
SSPAF fibrillation	Systemic embolism in patients with Atrial
TTR	Time in therapeutic range
VKAs	Vitamin K antagonists

Methods

Design

The ETAF-TR is a national, multicenter, single-arm, prospective, observational, post-marketing safety study. The study will evaluate the treatment safety in patients diagnosed with AF who are currently taking edoxaban treatment for stroke prevention in routine clinical practice in Turkey. Enrollment of 858 AF patients

Table 1. Detailed Flow Chart and Visit Calendar of the ETAF-TR Study

Data	Screening/Baseline Visit	Visit 1 (3 Months ± 15 Days)	Visit 2 (6 Months ± 1 Month)	Visit 3 (12 Months ± 2 Months)
ICF	X			
Inclusion/exclusion	X			
Demographics	X			
Lifestyle data	X			
Characteristics of AF	X	X	X	X
Medical history	X			
Concomitant diseases	X	X	X	X
Antithrombotic treatment	X[1]	X[2]	X[2]	X[2]
Concomitant medication	X	X	X	X
Clinical endpoints[3]	X[4]	X	X	X
Serious adverse event	X[4]	X	X	X
Adverse drug reaction	X[4]	X	X	X
Vital signs	X			

AF, atrial fibrillation; ICF, informed consent form; ADR, adverse drug reaction; SAE, serious adverse event;
[1] Posology of edoxaban received by the patient for prevention of stroke.
[2] Compliance of the patient with the edoxaban therapy, possible dose modifications, presence of a clinical condition leading to planned or unplanned interruptions of the therapy/temporary or permanent modification of the anticoagulant treatment regimen.
[3] The clinical endpoints are defined in the relevant section.
[4] Data between the initiation of the edoxaban therapy and the screening visit will be considered as retrospective data records.

from 32 different centers that have different provider characteristics around the country is planned. With the aim to reflect the real-life provider characteristics, study sites were selected according to the health provider subgroup projection based on the Health Statistics Yearbook 2016.[15] In this regard, of 32 study sites in total, 26 of them are university/state hospitals and 6 of them are private hospitals. Diagnosis of the disease, initiation of edoxaban treatment and maintenance, management of the disease, or treatment-related adverse events and complications are beyond the scope of research and are the responsibility of the clinician. However, if they find it necessary, the participating physicians accept the responsibility of sharing illness and/or relating elements of medical treatment to the responsible clinician.

Study Population

Since the research aims to reflect the real-life data as much as possible, factors that could lead to bias in the research plan and threat for external validity were avoided. Accordingly, for the purpose of avoiding selection bias, all consecutive patients who do not meet the exclusion criteria will be subjected to overall screening. All patients who meet the inclusion criteria and have signed an informed consent form (ICF) will be included in the study. Patients aged 18 years or older will be eligible for ETAF-TR study if they are treated with edoxaban for AF and if they provide written ICF to participate. Patients treated with edoxaban for deep vein thrombosis and/or pulmonary embolism, patients who are simultaneously participating in any other clinical trial, and patients who are not providing ICF will not be included in the ETAF-TR study. Diagnosis of AF and decision to prescribing pattern comprising the duration and regimen of edoxaban treatment is outside the scope of the present project and is the responsibility of the attending physician.

Enrollment and Follow-Up

The screening and enrollment period is planned for 6 months, followed by a 12-month follow-up period for each patient. Intermediate follow-up visits will be conducted at 3 months ± 15 days after enrollment (visit 1), 6 ± 1 months after enrollment (visit 2), and 12 ± 2 months after enrollment (visit 3). A detailed flow chart and visit calendar are shown in Table 1. No additional visits or examinations, laboratory tests, or procedures are mandated as part of ETAF-TR study. Patients who discontinue edoxaban treatment during the observation period will also be followed up until the end of the study.

Regulatory Requirements and Ethics

The ETAF-TR study protocol, ICF, and other related documents were developed according to the Guidelines of Observational Studies of Turkish Ministry of Health in compliance with the Declaration of Helsinki and Guidelines for Good Pharmacoepidemiological Practice. Study documents were approved by local ethics committee (513-SBKAEK, 2020/04-01) and Pharmaceuticals and Medical Devices Administration of Turkey (TITCK) on March 2020. The ETAF-TR study is registered with www.clinicaltrials.gov (NCT04594915).

Data Collection

Baseline demographic and clinical characteristics will be obtained at the enrollment. The baseline data will include age, sex, body mass index, pattern and characteristics of AF, previous interventions to treat AF comprising pharmacological and/or electrical cardioversion and ablation, medications comprising previous anticoagulant and antiplatelet therapies and all types of other current medications, vital signs and laboratory tests, medical history, co-morbidities, stroke, and bleeding risk profiles assessed by CHA_2DS_2-VASc (congestive heart failure,

hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age ≥65 years, sex category) score and HAS-BLED (hypertension, abnormal liver/renal function, stroke history, bleeding predisposition, labile INR, elderly, drug/alcohol usage) score, respectively.[16,17] In the course of follow-up visits, adherence to the edoxaban treatment during study period, possible changes in posology of edoxaban treatment and reasons, discontinuation of edoxaban treatment and reasons, changing anticoagulant treatment and reasons, serious adverse events/adverse drug reactions and clinical outcomes will be documented (Table 1). Data will be collected in standardized Turkish electronic case report forms (eCRFs). An English version of the eCRFs is provided as supplementary material (Supplementary Appendix 1). It will be the responsibility of the investigating clinicians to record all relevant patient data required for ETAF-TR study in the eCRFs. A data management plan will be created in the study start phase by sponsor (Daiichi Sankyo Turkey) and a contracted research organization (Ethic CRO). Quality control mechanisms, including data credibility checks and monitoring of data, will be performed accordingly. Onsite monitoring is being performed in all study sites. The monitoring process will include checks of ICF and source data verification during study process. Data quality checks will be performed on an ongoing basis on all sites. All of the data will be locked in the database of the CRO.

Outcome Measures

The aim of ETAF-TR study is to evaluate the real-world safety of edoxaban by evaluating bleeding events. The primary outcome of the ETAF-TR study is any overt bleeding [consisting of major bleeding or clinically relevant nonmajor bleeding (CRNM) or any bleeding that does not meet this definition but is considered as overt bleeding by the participating physician)].

Secondary outcomes are as follows:

- clinically relevant nonmajor bleeding;
- major bleeding;
- net clinical benefit (consisting of stroke, systemic embolism, major bleeding or death from any cause);
- stroke, transient ischemic attack, and systemic embolism;
- major cardiovascular event (myocardial infarction (MI), stroke, pulmonary embolism, systemic embolic event, or death from cardiovascular causes); and
- drug-related liver disease

Tertiary (exploratory) outcomes are as follows:

- ratio of persistence to the therapy after 1-year follow-up;
- Prevalence of primary and secondary endpoints in subgroups categorized according to continuous variables such as age or creatinine clearance; and
- ratio of patients in whom dynamic dose adjustment is made.

The results will be compared with existing datasets, namely the ETNA-AF Europe and the ENGAGE AF-TIMI 48 trial datasets.

Definitions of Outcomes

All variables in the ETAF-TR study are defined as similar to those in the ETNA-AF Europe study and as closely as possible to ENGAGE-AF-TIMI 48 trial to allow comparison of outcomes. The definitions of the outcomes are as follows:

Major bleeding: It is the clinically overt bleeding (bleeding determined by examination or radiological imaging) that meets one or more of the following criteria (fatal bleeding, symptomatic bleeding in a critical site or organ [retroperitoneal, intracranial, intraocular, intraspinal, intra-articular, and pericardial], intramuscular bleeding severe enough to cause compartment syndrome, overt bleeding leading to a decrease in hemoglobin level to at least 2.0 g/L or the need for transfusion of at least 2 units of erythrocyte suspension). In case of surgery-related bleeding, major bleeding defined as more than expected surgery/procedure-related bleeding.

Clinically relevant nonmajor bleeding: It is the clinically overt bleeding that requires medical attention.

Overt bleeding: A type of bleeding that is not classified as major bleeding or CRNM bleeding but considered as overt bleeding by the participating physician.

Minor bleeding: Other overt bleeding events that do not meet the criteria for major bleeding or CRNM bleeding (e.g., epistaxis not requiring medical attention) will be classified as minor bleeding.

Stroke: Focal neurological deficit with sudden onset, which matches with the distribution of a single cerebral artery and does not depend on an identifiable nonvascular cause (brain tumor or trauma), lasting at least 24 hours or resulting in death. Transient ischemic attack, transient neurological dysfunction without acute infarction, resulting from focal brain, spinal cord, or retinal ischemia.

Systemic embolism: Arterial embolism resulting in clinical ischemia outside of central nervous system, coronary, or pulmonary circulation is systemic embolism.

Pulmonary embolism: It is the clinical condition that meets the following criteria: in addition to the presence of symptoms and signs supporting pulmonary embolism, the presence of at least one of the following conditions can also be considered: demonstration of intravascular filling defect by pulmonary computed tomography (CT), angiography, ventilation/perfusion scintigraphy compatible with high-probability pulmonary embolism.

Myocardial infarction: The presence of at least one of the following along with the detection of an increase and/or decrease of at least 1 value exceeding the 99th percentile of the upper reference limit in cardiac biomarkers (preferably troponin) [ischemia symptoms, new or presumably new significant ST-T changes or new left bundle branch block (LBBB), development of pathological Q waves in electrocardiograph (ECG), imaging evidence of newly formed viable myocardial tissue loss or new wall motion abnormality, detection of intracoronary thrombus by angiography or autopsy, symptoms suggestive of myocardial ischemia occurring before blood is drawn for cardiac biomarkers or before cardiac biomarkers are elevated and ECG changes considered to be new or cardiac death with newly developing LBBB], MI-associated stent thrombosis revealed by coronary angiography or autopsy in the event of an increase and/or decrease in cardiac biomarkers with myocardial ischemia, with at least

1 value exceeding the 99th percentile of the upper reference limit.

Drug-related liver disease: Elevations of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3× upper limit of normal (ULN), accompanied by increases of serum bilirubin levels >2× ULN that occur concomitantly or ensue within a 1-month period.

Death: Deaths will be classified based on cardiovascular, nonvascular, or death of unknown causes.

Reporting of Adverse Events

Adverse events (AEs), serious AEs, adverse drug reactions (ADRs), and serious ADRs will be recorded on the AE report form that is appended to the eCRF. The AE report form will document the seriousness, duration, actions taken, outcomes, and causality association to edoxaban therapy.

Statistical Analysis

Overview

The objective of ETAF-TR study is to evaluate the treatment-related adverse events in routine clinical practice. Adverse events that occur from the first dose of edoxaban or up to 2 days after the last dose following discontinuation of the drug will be considered as treatment related. The demographic data will be summarized using descriptive statistics (n, mean, standard deviation (SD), minimum, maximum, median, and interquartile range (IQR)) and proportional distributions (n and %) according to the data type. Categorical variables will be presented by the number and percentage (%) of patients in each category. Continuous variables will be presented using number of missing data, mean, standard deviation, median, IQR, and minimum/maximum values. Statisctical analysis were performed with the SAS version 9.3 (SAS Institute, Cary, North Carolina, USA). All analyses will be defined prospectively and the following analyses are intended:

- final analysis of ETAF-TR study;
- indirect comparison of ETAF-TR with the results of the ETNA-AF Europe study; and
- indirect comparison of ETAF-TR with the results of the ENGAGE AF-TIMI 48 trial.

Presentation of Events

Rates of events will be presented as raw incidence rate (number of patients with events/number of patients treated) and as incidence rates per patient-year (e.g., number of patients with events per 100 patient-years). Each such estimate will be presented with 95% CIs. Additionally, a Kaplan–Meier curve will be generated to show the time course to the first event.

Calculation of the Sample Size

The rates of the primary endpoint (i.e., "any overt bleeding") of ETAF-TR study were 10.68% per year in the low-dose edoxaban arm and 14.15% per year in the high-dose edoxaban arm of ENGAGE-TIMI 48 Study. Based on the arithmetic mean of these rates, the minimum sample size was calculated as 708 patients with 95% CI by taking a 2-way precision value of 0.05 for the primary endpoint rate of 12.415% per year. When a rate of 14% was considered for the same primary endpoint, the minimum sample size was calculated as at least 780 patients with 95% CI by taking a 2-way precision value of 0.05. Based on this, the minimum number of patients to be enrolled was calculated as 858 with the assumption of a "drop out" of 10% during the 1-year follow-up.

Current Status of ETAF-TR Study

Although the study was approved by local ethic committee and regulatory authority on March 2020, first patient was enrolled in August 2020 due to coronavirus 2019 disease pandemic. The pandemic has severely affected the patients' outpatient visits and provider infrastructure of the health providers in Turkey as in the rest of the world. So, the enrollment period of the study extended from 6 months to 18 months. As of February 2021, 464 patients were enrolled in the ETAF-TR study.

Discussion

The ETAF-TR study will be the first nationwide, multicenter, prospective, noninterventional, post-marketing safety study comprising AF patients already using edoxaban. The primary goal of the present study is to assess the safety of edoxaban treatment in patients with AF in real-world clinical practice in Turkey. The ETAF-TR study will provide a detailed data about the clinical utility and safety of edoxaban treatment for SSPAF in patients with AF in routine practice. Although the main aim of the study is evaluation of the treatment safety, data on important details such as off-label usage rates, adherence/persistence rates, and switching rates will be obtained. The study results also give a chance to evaluate the external validity of ENGAGE-AF TIMI 48 trial in Turkey. Comparison of the study results with ETNA-AF Europe will also offer valuable perspective on possible differences in treatment safety, effectiveness, posology, rates of off-label usage, and other management issues between real-life conditions of Turkey and participating countries of ETNA-AF Europe.

Evidence to guide clinical decision-making has come from traditional randomized controlled trials (RCTs). Four RCTs compared NOACs to warfarin and served as the basis for regulatory approval of NOACs.[1] Although RCTs have a number of advantages such as high internal validity, near-complete data collection, and standardized outcome adjudication, their generalizability and external validity have been questioned.[18] Patient selection bias due to longer list of exclusion/inclusion criteria and limited patient participation (i.e., exclusion of patients who had comorbidities), selection of specific trial sites (i.e., selection of academic/tertiary provider centers as study sites rather than primary providers at rural areas) may limit the generalizability of trial results to overall population. Also, at classical RCT environment, close follow-up visits provide optimal adherence to the study drug, in contrast, drug adherence may not be optimal in real-life conditions.

However, from the perspective of patients and practicing clinicians, whether the patient included in respective RCT representative of patients with the disease in real life is essential. Observational post-authorization safety studies, which enroll AF patients already taking a certain NOAC, are designed and conducted to better obtain the safety and effectiveness outside of the controlled environment of RCTs. These studies provide comprehensive data in observing and confirming the effectiveness and safety of NOAC use in routine clinical practice.[9,10,12,19] They usually have only a few exclusion criteria and screen consecutive

patients to enroll a representative sample of patients. So, these studies can enroll patients who may not have been eligible for traditional RCTs. These studies also provide important data about the serious AEs and/or ADRs including the time and site of bleeding events and its management, reasons for changes in regimen of NOAC treatment, adherence to the treatment and reasons for interruptions of treatment, reasons for switching a treatment to another treatment. Furthermore, close follow-up visits provide optimal adherence to the study drug at a classical NOAC RCT environment. In contrast, OAC adherence may not be optimal due to lack of close follow-up or patient/physician motivation in real-life conditions. So, in NOAC studies' perspective, a close follow-up process may explain the differences in success levels of warfarin therapy management (i.e., TTR values) between phase III trials and real-life conditions.

In this context, ENGAGE-AF trial has some limitations in terms of generalizability of trial results to real-life conditions of Turkey.[11] First of all, the trial has strict inclusion criteria and patients who had particular comorbidities were excluded or not represented adequately in the trial. ENGAGE-AF trial has a double-blind, double-dummy design with sham INR measurement which means that the patient receives a study drug containing active treatment as well as a placebo.[11] Therefore, using such a design requires a number of tablets to be taken by the patient. Although they can be eligible according to the trial protocol, some subgroup of patients such as older, fragile patients, and/or patients who had low educational level or were less compliant to study drug may not be qualified as eligible by investigator due to environment of complex study design.

Furthermore, the quality of warfarin therapy in the trial and real-life conditions of Turkey was not similar. In the ENGAGE AF-TIMI 48 trial, mean and median TTR values in warfarin arm were 64.9% and 68.4%, respectively.[11] High TTR values in warfarin arm in the ENGAGE AF-TIMI 48 trial indicate effective and successful warfarin therapy possibly due to close visits and follow-up process during the trial conduction. These values of TTR are much higher than the real-life percentages in Turkey.[8,11] WATER Registry which prospectively evaluated the management of warfarin therapy showed poor anticoagulation control with warfarin therapy in real-life conditions in Turkey.[8] Alongside, although Turkey was one of the participating countries to ENGAGE-AF TIMI 48 Trial, only academic/tertiary centers were selected as trial sites and selective participation of these sites may cause underrepresentation of specific subgroups such as patients who had low socioeconomic and educational levels, and so on.[11] It is also known that advanced age is associated with poor drug compliance. In the ENGAGE AF-TIMI 48 trial, the median age of study participants was 72 years and the proportion of patients aged over 80 years was low. However, in routine clinical practice, a significant number of patients with AF were 80 and above, and this picture shows the need for assessment of drug safety and effectiveness in these octogenarians. Comparing the results of the ETAF-TR study and ENGAGE AF-TIMI 48 trial will provide possible discrepancies in demographics, clinical factors, safety and efficacy outcomes, and other management issues between the studies and will enable to test external validity of ENGAGE AF-TIMI 48 trial in our country conditions.

Although as a part of Global ETNA-AF Program, ETNA-AF-Europe study was designed to obtain data on effectiveness and safety of edoxaban treatment in routine clinical care in European population, only 10 European countries were included in the study.[12] Turkey was not included in ETNA-AF-Europe program. Some unique characteristics of Turkey such as demographic and clinical characteristics of AF patients, provider characteristics and infrastructure, and issues may limit the adaptation of the ETNA-AF Europe results to Turkey conditions. Essentially, ethnic and pharmacogenetics issues have a major role on drug metabolism and pharmacodynamics effects of the respective drug. So, possible pharmacogenetics differences reveal the necessity of edoxaban to be evaluated in different ethnic groups in terms of safety and effectiveness.

Conclusion

The ETAF-TR study will provide comprehensive data on the management of AF patients in real-life conditions and the safety and effectiveness of edoxaban treatment in Turkey.

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