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Baseline Clinical Characteristics of Patients from the Evaluation of Treatment Safety in Patients with Atrial Fibrillation on Edoxaban Therapy in Real-Life in TüRkiye Study

Türkiye'de Gerçek Yaşam Şartlarında Edoksaban Tedavisinin Atriyal Fibrilasyon Hastalarında Güvenliliğinin Değerlendirilmesi Çalışması Hastalarının Temel Klinik Özellikleri

ABSTRACT

Objective: A post-authorization safety study with a prospective design focusing on the safety of edoxaban treatment in Türkiye has not yet been conducted. The Evaluation of Treatment Safety in Patients with Atrial Fibrillation on Edoxaban Therapy in Real-Life in TüRkiye (ETAF-TR) study was designed to evaluate the safety and effectiveness of edoxaban treatment in atrial fibrillation (AF). The baseline results of the ETAF-TR study describe the demographic, clinical, and laboratory characteristics of the study population.

Method: The ETAF-TR study (NCT04594915) is a prospective, national, multicenter, observational, post-authorization safety study conducted in 50 outpatient cardiology clinics.

Results: Overall, 1,053 patients with AF treated with edoxaban for stroke prevention were enrolled in the study between August 2020 and May 2022. The mean age of the study population was 70.1 ± 11.3 years, and 59.0% of the patients were female. Mean CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, Stroke/TIA/thromboembolism, Vascular disease, Age 65–74 years, Sex category) and HAS-BLED scores (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history/predisposition, Labile INR, Elderly, Drugs/alcohol) were 3.5 and 1.6, respectively. Of the 1,053 patients, 843 (80.1%) received standard-dose edoxaban and 210 (19.9%) received reduced-dose edoxaban. Of the 1,053 patients, 38 (3.6%) had off-label use of edoxaban therapy. Among the remaining 1,015 patients, 834 (82.2%) received an appropriate dose of edoxaban and 181 (17.8%) received an inappropriate dose of edoxaban according to the Summary of Product Characteristics (SmPC) criteria.

Conclusion: Edoxaban has been used in a wide spectrum of patients with AF in daily routine practice, with good overall adherence to the SmPC. As the largest national pharmacovigilance study to date, the ETAF-TR study will provide detailed insight into the safety of edoxaban treatment.

Keywords: Atrial fibrillation, edoxaban, stroke, systemic embolism, bleeding, real-world data

ÖZET

Amaç: Türkiye'de edoksaban tedavisinin güvenliliğini araştıran ileri dönük bir ruhsatlandırma sonrası güvenlik çalışması henüz gerçekleştirilmemiştir. Türkiye'de gerçek yaşam şartlarında edoksaban tedavisinin atriyal fibrilasyon hastalarında güvenliliğinin değerlendirilmesi (ETAF-TR) çalışması, edoksaban tedavisinin atriyal fibrilasyon hastalarında güvenliliğini ve etkinliğini değerlendirmek üzere tasarlanmıştır. ETAF-TR çalışmasının bu sonuçları, çalışma popülasyonunun demografik, klinik ve laboratuvar özelliklerini açıklamaktadır.

Yöntem: ETAF-TR çalışması (NCT04594915), 50 kardiyoloji kliniğinde yürütülen prospektif, ulusal, çok merkezli, gözlemsel, ruhsatlandırma sonrası güvenlik çalışmasıdır.

Bulgular: Çalışmaya, Ağustos 2020 ile Mayıs 2022 tarihleri arasında inme profilaksisi amacıyla edoksaban tedavisi alan 1,053 atriyal fibrilasyon hastası dahil edildi. Çalışma grubunun yaş ortalaması 70.1±11.3 olup hastaların %59.0'ı kadındı. Ortalama CHA_2DS_2-VASc ve HAS-BLED skorları sırasıyla 3.5 ve 1.6 idi. Çalışmadaki 1,053 hastanın 843'ü (%80,1) standart doz edoksaban tedavisi alırken, 210'u (%19,9) azaltılmış doz edoksaban tedavisi aldı. Çalışma popülasyonunun %3,6'sında endikasyon dışı edoksaban kullanımı vardı. Geriye kalan 1015 hastadan 834'ü (%82,2) kısa ürün bilgisine göre uygun doz edoksaban tedavisi alırken, 181'i (%17,8) uygun olmayan dozda edoksaban tedavisi alıyordu.

ORIGINAL ARTICLE
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Sonuç: Edoksaban tedavisi, günlük rutin uygulamada atriyal fibrilasyon hastalarının büyük bir bölümünde uygun doz tercihi ile kullanılmaktadır. Bugüne kadarki en büyük ulusal farmakovijilans çalışması olan ETAF-TR çalışması, edoksaban tedavisinin güvenliliğine dair ayrıntılı bilgi sağlayacaktır.

Anahtar Kelimeler: Atriyal fibrilasyon, kanama, edoksaban, gerçek yaşam verisi, inme, sistemik embolizm

Atrial fibrillation (AF) is a significant public health problem, with a global prevalence of 60 million patients in 2019.[1] Prevalence and incidence are expected to increase due to population aging, comorbidity burden, technological evolution in detecting AF, and growing public awareness. The European Society of Cardiology guideline proposes the AF-CARE (Atrial Fibrillation, C: Comorbidity and risk factor management, A: Anticoagulation/Avoid stroke, R: Rate control, E: Early rhythm control) framework to achieve optimal care for these patients.[2] The AF-CARE framework encompasses several key elements, including management of comorbidities, prevention of stroke and systemic embolism, control of heart rate and rhythm, reduction of symptoms, and dynamic reassessment of patients. Oral anticoagulant therapy, comprising direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs), is the cornerstone of stroke and systemic embolism prevention in atrial fibrillation (SSPAF).[2] Randomized controlled trials and post-marketing data have demonstrated that DOACs are at least as effective as VKAs for SSPAF and have a more favorable safety profile for major bleeding.[2] Therefore, current European and American guidelines recommend the prescription of DOACs in preference to VKAs in patients with AF.[2,3]

Edoxaban, a direct and reversible inhibitor of Factor Xa, was approved by regulatory authorities for stroke and systemic embolism prevention in Europe in 2015. Since November 2016, edoxaban has been eligible for reimbursement by the Social Security Institution of Türkiye, the primary payer institution in the country. Although randomized controlled trials of DOACs have higher internal validity, they also employ strict, well-defined inclusion and exclusion criteria that limit the generalizability of their results to the overall patient population. Post-authorization safety studies are needed to evaluate the effectiveness and safety of a treatment in real-world clinical settings.

Edoxaban Treatment in Routine Clinical Practice for Patients with Atrial Fibrillation in Europe (ETNA-AF-Europe) is an observational safety study of edoxaban treatment in clinical practice.[4] The study was designed to evaluate the safety and effectiveness of edoxaban in real-world settings. ETNA-AF-Europe was conducted in 10 European countries, and

ABBREVIATIONS

AF	Atrial fibrillation
AF-CARE	Atrial Fibrillation, C: Comorbidity and risk factor management, A: Anticoagulation/Avoid stroke, R: Rate control, E: Early rhythm control
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, Stroke/TIA/thromboembolism, Vascular disease, Age 65–74 years, Sex category
COVID-19	Coronavirus disease 2019
CrCl	Creatinine clearance
CRNM	Clinically relevant nonmajor bleeding
DOAC	Direct oral anticoagulant
EHRA	European Heart Rhythm Association
ETAF-TR	Evaluation of Treatment Safety in Patients with Atrial Fibrillation on Edoxaban Therapy in Real-Life in Türkiye
ETNA-AF-Europe	Edoxaban Treatment in Routine Clinical Practice for Patients with Atrial Fibrillation in Europe
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history/predisposition, Labile INR, Elderly, Drugs/alcohol
SmPC	Summary of Product Characteristics
SSPAF	Stroke and systemic embolism prevention in atrial fibrillation
VKA	Vitamin K antagonist

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unselected patients with AF treated with edoxaban were enrolled. The four-year follow-up results of the ETNA-AF-Europe study corroborate the long-term efficacy and safety of edoxaban, aligning with findings from the respective randomized controlled trial.[5] Although ETNA-AF-Europe is a large-scale, prospective, post-authorization safety study, it was not conducted in Türkiye. Furthermore, the potential for distinctive clinical, demographic, and pharmacogenetic attributes among Turkish patients, the differing healthcare infrastructure, and varying reimbursement requirements may limit the applicability of ETNA-AF-Europe findings to routine clinical practice in Türkiye. Notably, edoxaban has been available for marketing since 2016, yet there is a lack of post-marketing data on its safety and efficacy in the Turkish population.

The Evaluation of Treatment Safety in Patients with Atrial Fibrillation on Edoxaban Therapy in Real-Life in TüRkiye (ETAF-TR) study is designed to evaluate the safety and effectiveness of edoxaban treatment in patients with AF in real-life practice. The baseline analysis of the ETAF-TR study aims to describe the demographic and clinical characteristics of Turkish patients with AF receiving edoxaban treatment, to define adherence to dosing patterns for edoxaban according to the summary of product characteristics (SmPC), and to compare these characteristics with those of patients enrolled in the Edoxaban versus Warfarin in Patients with Atrial Fibrillation (ENGAGE AF-TIMI 48) trial[6] and the ETNA-AF-Europe study.[4]

Materials and Methods

Design

The design of ETAF-TR has been previously published.[7] The ETAF-TR study is a prospective, national, multicenter, observational, post-authorization safety study conducted in 50 outpatient cardiology clinics with varying health provider characteristics. Study sites were selected according to the health provider subgroup projection based on the Health Statistics Yearbook 2016 to improve external validity.[8] The ETAF-TR study protocol and other study-related documents were developed in accordance with the Declaration of Helsinki and Guidelines for Good Pharmacoepidemiology Practice. Study documents were approved by Dokuz Eylül University Clinical Research Ethics Committee (Approval Number: 2020/04-01, Protocol Number: 513-SBKAEK, Date: 12.03.2020), and the Pharmaceuticals and Medical Devices Administration of Türkiye (TITCK) in March 2020. The ETAF-TR study is registered at www.clinicaltrials.gov (NCT04594915).

Study Population

All patients with AF treated with edoxaban, except those with mechanical heart valves and/or moderate-to-severe mitral stenosis, and patients aged < 18 years, were eligible to participate in the study if they provided written informed consent. Patients treated with edoxaban for deep vein thrombosis and/or pulmonary embolism and patients simultaneously participating in any other clinical trial were not included in the ETAF-TR study. The diagnosis of AF and decisions regarding the dosing pattern of edoxaban treatment were not within the remit of the present project and were under the responsibility of the attending physician.

Enrolment and Follow-up: The screening and enrolment period was planned for six months, and the first patient was enrolled in August 2020. As with other clinical studies, the study experienced challenges due to the coronavirus disease 2019 (COVID-19) pandemic, and the enrolment process was therefore completed in May 2022. The study population was followed for a 12-month period with interim visits [at 3 months ± 15 days after enrolment (visit 1), 6 ± 1 months after enrolment (visit 2), and 12 ± 2 months after enrolment (visit 3)].

Data Collection: Patients' baseline demographic and clinical characteristics were obtained at enrolment. The baseline data comprised demographics, comorbidities, AF-related information, stroke risk profile assessed by the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age ≥ 65 years, sex category) score, bleeding risk profile assessed by HAS-BLED (hypertension, abnormal liver/renal function, stroke history, bleeding predisposition, labile INR, elderly, drug/alcohol usage) score, and basic laboratory tests. Data were documented in standardized electronic case report forms. The sponsor (Daiichi Sankyo Türkiye) and a contracted research organization (Ethic CRO) devised a data management and study quality control plan. The quality control mechanisms comprised data credibility checks and data monitoring, and onsite monitoring was performed at all study sites.

Dosing Patterns of Edoxaban: Study participants were classified as receiving a standard dose of edoxaban (60 mg once daily) or a reduced dose of edoxaban (30 mg once daily). The criteria proposed by the SmPC for edoxaban were used to determine the appropriate dose selection. According to the SmPC, patients with moderate or severe renal impairment (creatinine clearance 15–50 mL/min), low body weight (< 60 kg), or concomitant use of P-glycoprotein inhibitors such as cyclosporine, dronedarone, erythromycin, or ketoconazole are recommended to receive edoxaban 30 mg once daily. After adjustment of dosing patterns, the study participants were classified as follows: (I) appropriate dose of edoxaban (using an appropriate standard dose of edoxaban or an appropriately reduced dose in compliance with the dose reduction criteria of the SmPC); (II) inappropriate low dose of edoxaban (undertreatment = using a reduced dose of edoxaban without meeting the dose reduction criteria of the SmPC); and (III) inappropriate high dose of edoxaban (overtreatment = using a standard dose of edoxaban despite meeting the dose reduction criteria of the SmPC). Off-label usage was defined as edoxaban use in patients with any of the following: lower stroke risk (i.e., CHA_2DS_2–VASc score of 0 for male and 1 for female patients), creatinine clearance (CrCl) < 15 mL/min, or mitral valve area < 1.5 cm^2 or a mechanical prosthetic valve. Following the exclusion of patients who had received the medication for an off-label purpose, dosage appropriateness ratios were calculated.

Comparison with the ENGAGE-AF-TIMI 48 and ETNA-AF-Europe Studies: The baseline demographic and clinical characteristics of patients enrolled in the ENGAGE-AF-TIMI 48 and ETNA-AF-Europe studies were used as external comparators to the baseline data collected in ETAF-TR. This was done to gain a deeper understanding of how the use of edoxaban in routine clinical practice reflects the trial setting (external validation) in which edoxaban was tested.

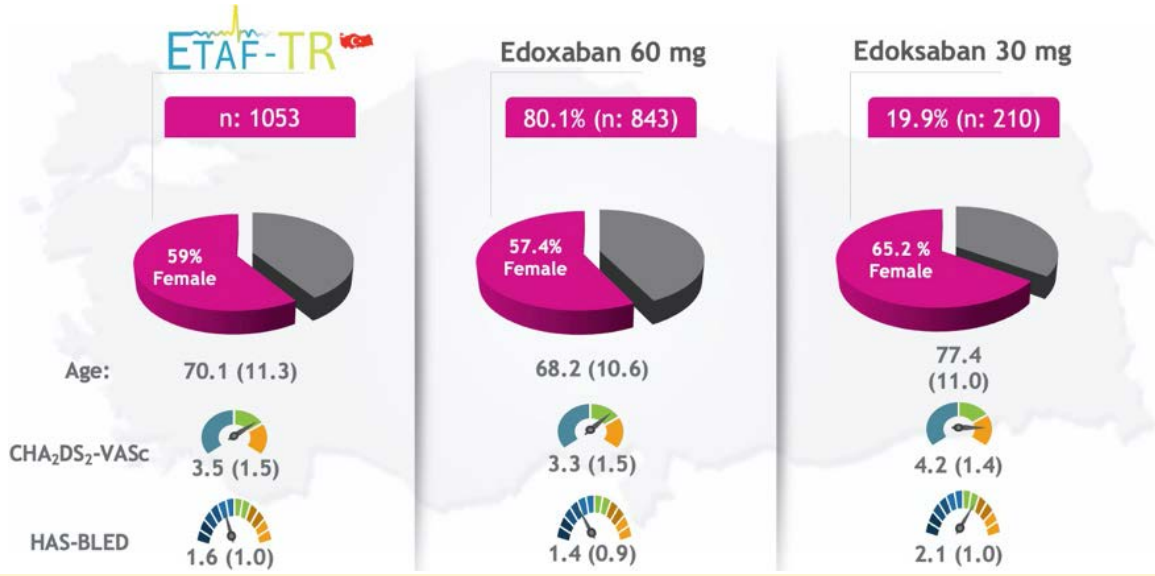

Figure 1. Baseline demographic and clinical characteristics of the ETAF-TR study population according to the edoxaban 60 mg once daily (o.d.) and 30 mg o.d. groups.

Statistical Analysis: Demographic data were 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 were presented as the number and percentage (%) of patients in each category. Continuous variables were presented using the number of missing data, mean, SD, median, IQR, minimum, and maximum values. Statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, North Carolina, USA). Various statistical tests were employed to evaluate screening visit characteristics, including the t-test, Wilcoxon rank-sum test, Analysis of Variance (ANOVA), and Kruskal–Wallis test, to analyze scores on the continuous scale across multiple groups. A chi-square or Fisher exact test was used for categorical variables. The primary outcome of the ETAF-TR study is any overt bleeding [consisting of significant bleeding or clinically relevant nonmajor bleeding (CRNM), or any bleeding that does not meet this definition but is considered overt bleeding by the participating physician)]. The rates of any overt bleeding were 10.68% per year in the low-dose edoxaban arm of the ENGAGE-TIMI 48 trial and 14.15% per year in the high-dose edoxaban arm of the ENGAGE-TIMI 48 trial. Based on these results, the minimum sample size was calculated as 708 patients with a 95% confidence interval (CI), using a two-sided precision value of 0.05 for the primary endpoint rate of 12.41% 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, again using a two-sided precision value of 0.05. Although the initial sample size was calculated as 858, assuming a 10% dropout rate during the one-year follow-up, the dropout rate was updated to 35% with a protocol amendment due to disruptions in patient follow-up during the COVID-19 pandemic. Accordingly, 1,053 patients were enrolled to ensure the reliability of the estimation of the primary outcome.

Results

Overall, 1,053 patients with AF treated with edoxaban for stroke prevention were enrolled in the study between August 2020 and May 2022. Demographic and clinical characteristics of the study population according to the edoxaban 60 mg once daily (o.d.) and 30 mg o.d. groups are summarized in Table 1 and Figure 1. The mean age of the study population was 70.1 ± 11.3 years (37% were ≥ 75 years) and 621 (59.0%) of the patients were female. The mean body mass index was 29.1 ± 5.4 kg/m^2, and 105 (10.0%) of the study participants had low body weight (< 60 kg).

Regarding the AF pattern, most patients (57.1%) had permanent AF, 29.5% had paroxysmal AF, and 13.4% had persistent or long-standing persistent AF. The mean CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke/TIA/thromboembolism, Vascular disease, Age 65–74 years, Sex category) and HAS-BLED scores (Hypertension, Abnormal renal/liver function, Stroke, Bleeding predisposition, Labile INR, Elderly, Drugs/alcohol) were 3.5 ± 1.5 and 1.6 ± 1.0, respectively, as reported by the study investigators. Among the study population, 12 (1.1%) patients had a CHA_2DS_2–VASc score of 0, and 81 (7.7%) had a CHA_2DS_2–VASc score of 1. Overall, 36 (3.4%) patients had lower stroke risk (i.e., CHA_2DS_2–VASc score of 0 for male and 1 for female patients). In total, 7.0% of the study population had a history of cardioversion, and only 2.0% had undergone an AF ablation procedure. Hypertension was the most common cardiovascular comorbidity (76.9%), followed by heart failure (29.0%) and diabetes (26.8%). The rates of patients with a previous ischemic stroke, transient ischemic attack, systemic embolism, and myocardial infarction were 10.6%, 2.8%, 0.5%, and 12.8%, respectively. A history of major bleeding was present in 1.7% of patients, and 1.3% had a history of gastrointestinal bleeding. Forty patients (3.8%) had history of cancer, and 118 patients (11.8%) were taking concomitant antiplatelet therapy. The mean creatinine clearance was 80 ± 31 mL/min, calculated using the Cockroft-Gault equation, and 16.5% of patients had a creatinine clearance between 15–50 mL/min.

Table 1. Baseline characteristics of the ETAF–TR study population

Variables	Total (n = 1053)	Edoxaban 30 mg (n = 210, 19.9%)	Edoxaban 60 mg (n = 843, 19.9%)
Demographics			
Age, mean ± SD, years	70.1 ± 11.3	77.4 ± 11.0	68.2 ± 10.6
Age group, n (%)			
< 65 years	265 (25.2)	13 (6.2)	252 (29.9)
65–74 years	397 (37.7)	46 (21.9)	351 (41.6)
≥ 75 years	391 (37.1)	151 (71.9)	240 (28.5)
Female sex, n (%)	621 (59.0)	137 (65.2)	484 (57.4)
BMI, mean ± SD, kg/m^2	29.1 ± 5.4	27.8 (5.4)	29.4 (5.3)
Low body weight (< 60 kg), n (%)	105 (10.0)	55 (26.2)	50 (5.9)
AF-related information			
AF pattern, n (%)			
Paroxysmal	311 (29.5)	49 (23.3)	262 (31.1)
Persistent	141 (13.4)	22 (10.5)	119 (14.1)
Permanent	601 (57.1)	139 (66.2)	462 (54.8)
CHA_2DS_2-VASc score, mean ± SD	3.5 ± 1.5	4.2 ± 1.4	3.3 ± 1.5
CHA_2DS_2-VASc = 0, n (%)	12 (1.1)	0 (0.0)	12 (1.4)
CHA_2DS_2-VASc = 1, n (%)	81 (7.7)	7 (3.3)	74 (8.8)
HAS-BLED score, mean ± SD	1.6 ± 1.0	2.0 ± 1.0	1.4 ± 0.9
History of cardioversion, n (%)	74 (7.0)	14 (6.7)	68 (8.1)
History of AF ablation, n (%)	21 (2.0)	3 (1.4)	18 (2.1)
Medical history and co-morbidities			
Hypertension, n (%)	805 (76.4)	166 (79.0)	639 (75.8)
Diabetes, n (%)	282 (26.8)	56 (26.7)	226 (26.8)
Heart failure, n (%)	305 (29.0)	72 (34.3)	233 (27.6)
Myocardial infarction, n (%)	135 (12.8)	29 (13.8)	106 (12.6)
Peripheral artery disease, n (%)	33 (3.1)	8 (3.8)	23 (3.0)
History of thromboembolic events, n (%)			
Ischemic stroke	112 (10.6)	19 (9.0)	93 (11.0)
Transient ischemic attack	24 (2.8)	6 (2.9)	18 (2.1)
Systemic embolism	5 (0.5)	5 (2.4)	0 (0.0)
Pulmonary embolism	4 (0.4)	0 (0.0)	4 (0.5)
Deep vein thrombosis	8 (0.8)	1 (0.5)	7 (0.8)
History of bleeding, n (%)			
Major bleeding	18 (1.7)	6 (2.9)	12 (1.4)
CRNM bleeding	19 (1.8)	7 (3.3)	12 (1.4)
Overt bleeding	9 (0.9)	5 (2.4)	4 (0.5)
Minor bleeding	44 (4.2)	12 (5.7)	32 (3.8)
Location of previous major bleeding, n (%)			
ICH	4 (0.4)	3 (1.4)	1 (0.1)
GIS	13 (1.3)	3 (1.4)	10 (1.2)
Other	1 (0.1)	0 (0.0)	1 (0.1)
History of cancer, n (%)	40 (3.8)	8 (3.8)	32 (3.8)
Smoking (current), n (%)	71 (6.7)	6 (2.9)	65 (7.7)
Antiplatelet treatment	118 (11.8)	29 (13.8)	89 (10.6)
Laboratory data			
Serum creatinine, mean ± SD, mg/dL	0.9 ± 0.3	1.1 ± 0.4	0.9 ± 0.2
CrCl, mean ± SD, mL/min	80 ± 31	55 ± 23	86 ± 30
CrCl 15–50 mL/min, n (%)	174 (16.5)	106 (50.5)	68 (8.1)
Hemoglobin, mean ± SD, g/dL	12.9 ± 1.9	12.1 ± 1.9	13.1 ± 1.8
Platelet × 10^3, mean ± SD, per mcL	241 ± 73	234 ± 82	243 ± 70
Appropriateness of edoxaban dose			
Appropriate dose, n (%)	834 (82.2)	129 (61.4)	743 (88.1)
Inappropriate low dose, n (%)	81 (8.0)	81 (38.6)	0 (0.0)
Inappropriate high dose, n (%)	100 (9.8)	0 (0.0)	100 (11.9)
Off-label usage	38 (3.6)	3 (1.4)	35 (4.2)

AF, Atrial fibrillation; BMI, Body mass index; CHA_2DS_2-VASc, Congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes, stroke (2 points), vascular disease, age 65–74 years, sex category (female); CrCl, Creatinine clearance; CRNM, Clinically relevant non-major bleeding; GIS, Gastrointestinal system; HAS-BLED, Uncontrolled hypertension, abnormal renal and liver function (1 point each), stroke, bleeding, labile International Normalized Ratio, elderly (age > 65 years), drugs or alcohol (1 point each) [concomitant antiplatelet agents or non-steroidal anti-inflammatory drugs, alcohol abuse]; ICH, Intracranial hemorrhage; LAA, Left atrial appendage; SD, Standard deviation.

Table 2. Comparison of the ETAF-TR study with the ETNA-AF Europe study and the ENGAGE AF-TIMI 48 trial

Variables	ETAF-TR (n = 1,053)	ETNA-AF Europe (n = 13,092)	ENGAGE AF-TIMI 48* (n = 2,123)	P-value (ETAF-TR vs. ETNA-AF Europe)	P-value (ETAF-TR vs. ENGAGE AF-TIMI 48*)
Age, mean ± SD, years	70.1 ± 11.3	73.6 ± 9.5	72.7 ± 8.1	<0.001	<0.001
Male sex, (%)	41.0	56.6	62.4	<0.001	<0.001
CHA_2DS_2–VASc score, mean ± SD	3.5 ± 1.5	3.1 ± 1.4	4.2 ± 1.3	<0.001	<0.001
HAS–BLED score, mean ± SD	1.6 ± 1.0	2.6 ± 1.1	1.6 ± 0.9	<0.001	1.00
Hypertension, (%)	76.4	76.9	92.4	0.71	<0.001
Diabetes, (%)	26.8	21.9	39.1	0.002	<0.001
Heart failure, (%)	29.0	5.8	48.2	<0.001	<0.001
Myocardial infarction, (%)	12.8	4.3	2.9	<0.001	<0.001
Ischemic stroke, (%)	10.6	5.9	15.5	<0.001	0.08
Creatinine clearance, mean ± SD, mL/min	80 ± 31	69 ± 24	75 ± 28	<0.001	<0.001
Atrial fibrillation pattern (%)					
Paroxysmal	29.5	53.6	26.6	<0.001	0.085
Persistent	13.4	24.4	24.1	<0.001	<0.001
Permanent	57.2	19.6	49.4	<0.001	<0.001
Dosing pattern of edoxaban (%)					
Standard dose	80.1	76.3	N/A	0.006	N/A
Reduced dose	19.9	23.7	N/A	<0.001	
Appropriateness of edoxaban dose (%)					
Appropriate dose	82.2	83.2	N/A	0.188	N/A
Inappropriate high dose (overtreatment)	9.8	8.6	N/A	0.191	N/A
Inappropriate low dose (undertreatment)	8.0	7.6	N/A	0.657	N/A

*Patients enrolled in the ENGAGE AF-TIMI 48 trial from the ETNA-AF Europe study countries. CHA_2DS_2-VASc, Congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes, stroke (2 points), vascular disease, age 65–74 years, sex category (female); 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 TüRkiye; ETNA-AF Europe, Edoxaban Treatment in routiNe clinical prActice for patients with Atrial Fibrillation in Europe; HAS-BLED, Uncontrolled hypertension, abnormal renal and liver function (1 point each), stroke, bleeding, labile International Normalized Ratio, elderly (age > 65 years), drugs or alcohol (1 point each) [concomitant antiplatelet agents or non-steroidal anti-inflammatory drugs, alcohol abuse]; SD, Standard deviation.

Of the 1,053 patients, 843 (80.1%) received standard-dose edoxaban and 210 (19.9%) received reduced-dose edoxaban. As expected, there were notable differences in the clinical characteristics of patients receiving the edoxaban 60 mg and 30 mg doses. Compared with patients receiving standard-dose edoxaban, those receiving edoxaban 30 mg were older, more likely to have low body weight, had higher CHA_2DS_2–VASc and HAS-BLED scores, were more likely to have a history of bleeding, and were more likely to receive concomitant antiplatelet therapy. The mean baseline CrCl values were 86 mL/min and 55 mL/min for the edoxaban 60 mg and 30 mg dose groups, respectively. A total of 106 (50.5%) patients in the edoxaban 30 mg group, compared to only 68 patients (8.1%) in the edoxaban 60 mg group, had a baseline CrCl of 15–50 ml/min (Table 1). Of the 1,053 patients, 38 (3.6%) had off-label edoxaban use (36 patients had lower stroke risk, i.e., CHA_2DS_2–VASc score of 0 for men and 1 for women; and two patients had significant mitral stenosis, i.e., mitral valve area < 1.5 cm^2). Among the remaining 1,015 patients, 834 (82.2%) received the appropriate dose of edoxaban, and 181 (17.8%) received an inappropriate dose of edoxaban according to the SmPC criteria. Among the 181 patients who received an inappropriate dose, 81 (8.0%) received an inappropriate low dose (undertreatment), whereas 100 (9.8%) received an inappropriate high dose (overtreatment). The prescription rate of the appropriate edoxaban dose was higher in patients receiving the 60 mg dose compared to those receiving the 30 mg dose (88.1% versus 61.4%, respectively).

The comparative analysis of the ETAF-TR study with the ETNA-AF Europe study[4] and the ENGAGE AF-TIMI 48 trial.[6] demonstrated significant differences in the clinical characteristics of enrolled patients (Table 2). The mean age of the study population was lower in the ETAF-TR study compared with the ETNA-AF Europe study and the European cohort of the ENGAGE AF-TIMI 48 trial (70.1 years versus 73.6 and 72.7 years, respectively, P-value < 0.001 for both). Although the majority of participants were male in the ETNA-AF Europe study and the European cohort of the ENGAGE AF-TIMI 48 trial (56.6% and 62.4%, respectively), the proportion of male patients was 41.0% in the ETAF-TR study (P-value < 0.001 for both).

Stroke risks profiles also differed between both studies and the phase 3 trial. The mean CHA_2DS_2–VASc score was higher in the ETAF-TR study than in the ETNA-AF Europe study, whereas it was lower than that of the European patients included in the ENGAGE AF-TIMI 48 trial (3.5 versus 3.1 and 4.2, P-value < 0.001 for both). In contrast, the HAS-BLED score was similar between the ETAF-TR study population and the European patients included in the ENGAGE AF-TIMI 48 trial (1.6 versus 1.6, P-value = 1.00); however, it was significantly lower than in the patients included in the ETNA-AF Europe study (1.6 versus 2.6, P-value < 0.001) (Table 2).

There were significant differences in the prevalence of major comorbidities between the ETAF-TR study, the ETNA-AF-Europe study, and the European cohort of the ENGAGE AF-TIMI 48 trial. Hypertension was the most common comorbidity in all cohorts. Although the prevalence of hypertension was similar between the ETAF-TR and ETNA-AF-Europe studies (76.4% versus 76.9%, respectively; P-value = 0.71), it was significantly lower than in the European cohort of the ENGAGE AF-TIMI 48 trial (76.4% and 76.9% versus 92.4%, respectively; P-value < 0.001 for both). The prevalence of diabetes, heart failure, and myocardial infarction also differed between cohorts. The proportion of patients with a history of ischemic stroke, heart failure, and diabetes was higher in the ETAF-TR study population than in the ETNA-AF-Europe cohort (10.6%, 29.0%, and 26.8% versus 5.9%, 5.8%, and 21.9%, respectively; P-value < 0.001 for both ischemic stroke and heart failure, and P-value = 0.002 for diabetes). In contrast, the prevalence of these comorbidities was lower than in the European cohort of the ENGAGE AF-TIMI 48 trial (15.5%, 48.2%, and 39.1%, respectively; P-value = 0.08 for ischemic stroke and P-value < 0.001 for both heart failure and diabetes). The prevalence of myocardial infarction in the ETAF-TR group was significantly higher than in both the ETNA-AF-Europe study and the ENGAGE AF-TIMI 48 European cohort (12.8% versus 4.3% and 2.9%, respectively; P-value < 0.001 for both) (Table 2).

The mean baseline creatinine clearance in the ETAF-TR study was significantly higher than in the ETNA-AF study and the European cohort of the ENGAGE AF-TIMI 48 trial (80 mL/m^2 versus 69 mL/m^2 and 75 mL/m^2, respectively; P-value < 0.001 for both) (Table 2).

In terms of AF pattern, there were significant differences between the cohorts. Although permanent AF was the most common pattern in both the ETAF-TR study and the European cohort of the ENGAGE AF-TIMI 48 trial, the prevalence of permanent AF was significantly higher in the ETAF-TR study (57.2% versus 49.4%, respectively, P-value < 0.001). In contrast, paroxysmal AF was the most common pattern in the ETNA-AF-Europe study (53.6%), while only a minority of patients had permanent AF (19.6%) (Table 2).

The proportions of patients receiving standard and reduced doses of edoxaban were significantly different between the ETAF-TR and ETNA-AF-Europe studies (80.1% versus 76.3% for standard dose, and 19.9% versus 23.7% for reduced dose, respectively, P = 0.008 and P < 0.005, respectively). Adherence to appropriate prescribing of edoxaban according to SmPC criteria was similar in both studies (82.2% versus 83.8%, respectively; P = 0.188) (Table 2).

Discussion

The baseline results of the ETAF-TR study provide detailed real-world data on the demographic and clinical characteristics and dosing patterns in patients with AF who are already receiving edoxaban treatment. The principal findings of this study are as follows: (I) although the majority of individuals are male in the pivotal trials of DOACs and real-world studies from Europe, 59.0% of the participants were female in the ETAF-TR study; (II) hypertension was the most common comorbidity, and permanent AF was the most common AF pattern; (III) nearly 90% of the study population had a higher stroke risk; (IV) four out of five patients were receiving a standard dose of edoxaban; (V) more than 80% of patients were receiving an appropriate dose of edoxaban according to SmPC criteria; (VI) the ETAF-TR study population was significantly younger than the European cohort of the ENGAGE AF-TIMI 48 trial and the ETNA-AF-Europe study population; (VII) the prevalence of comorbidities including diabetes, heart failure, myocardial infarction, and ischemic stroke, was significantly higher in the ETAF-TR study than in the ETNA-AF study; (VIII) the mean CHA_2DS_2–VASc score was higher than in the ETNA-AF Europe registry; and (IX) the prevalence of appropriate and inappropriate dosing patterns was broadly similar to that observed in the ETNA-AF Study.

The results of registry-based Western population studies indicate that the mean age of patients with AF is greater than 70 years.[9-11] Conversely, observational studies conducted in Türkiye have shown that the mean age of patients with AF falls between 64 and 70 years.[12,13] As observed in previous reports, the ETAF-TR study cohort exhibited a markedly younger age profile than the European cohorts enrolled in the ETNA-AF study and the ENGAGE AF-TIMI 48 trial.[4,6] Considerable differences in population age between the ETAF-TR study and the European registries may be due to differences in comorbidity burden predisposing to AF. For example, the Middle East region has the highest rates of age-adjusted ischemic heart disease incidence and prevalence among the Global Burden of Disease study regions.[14]

On the other hand, a meta-analysis focusing on the burden of cardiovascular disease risk factors in the Middle East reported a higher prevalence of hypertension, diabetes, dyslipidemia, and smoking.[15] A higher prevalence of age-adjusted ischemic heart disease and other comorbidities may be a critical factor in the development of AF in younger individuals in the ETAF-TR study. Indeed, the nearly four-fold higher prevalence of myocardial infarction in the ETAF-TR study compared with ETNA-AF Europe may reflect the ischemic heart disease burden and higher predisposition to AF development in younger patients.

A further noteworthy demographic distinction identified in the ETAF-TR study is the preponderance of female patients. While randomized controlled trials of DOACs and prior reports from Europe have indicated that more than 55% of individuals are male, this study observed that 59.0% of the study population was female.[4,6,16-18] The results of our study are consistent with those reported in previous research conducted in Türkiye. The ROTA study (Real-World Evaluation of Anticoagulant

Treatment Patterns in Patients with Atrial Fibrillation: Data from Multicenter ROTA Study) indicated that 57.4% of participants were women, which aligns with the findings of the ETAF-TR study.[19] This observed difference may be attributable to the comparatively high prevalence of metabolic syndrome, obesity, a sedentary lifestyle, and cardiovascular risk factors and diseases among Turkish women relative to the European population.[20]

The inappropriate dosing of DOACs has been linked to an increased risk of major adverse cardiovascular events. The prescription of inappropriately low doses of DOACs may increase the risk of stroke, systemic embolism, and cardiovascular hospitalization. Conversely, prescribing inappropriately high doses of DOACs may increase the risk of bleeding and all-cause mortality.[21-23] Thus, selecting an appropriate dose represents a pivotal aspect of DOAC treatments. In the ETAF-TR study, a high level of adherence to the dose selection criteria set out in the SmPC was observed, with 82.2% of participants receiving the recommended dosage. These findings are consistent with those of the ETNA-AF Europe study, in which 83.8% of patients received an appropriate dose of edoxaban.[4] Although a high proportion of participants in the ETAF-TR study received an appropriate dose, approximately one-fifth received inappropriate low or high doses of edoxaban treatment, which may increase the risk of adverse clinical events. Notably, the proportion of patients receiving an appropriate dose of edoxaban was higher among those treated with 60 mg than among those treated with 30 mg. Fear of bleeding events in elderly or frail patients without SmPC dose-reduction criteria, but with a high comorbidity burden, concomitant antiplatelet therapy, or a history of bleeding, may have been a contributing factor to the prescription of an inappropriately reduced dose of edoxaban. The European Heart Rhythm Association (EHRA) Practical Guide provides a systematic approach for reducing anticoagulant doses for each DOAC, rather than relying solely on SmPC criteria, by taking into consideration multiple patient-specific risk factors, including age, renal impairment, low body weight, hemorrhagic risk, and the concurrent use of antiplatelet agents, verapamil, diltiazem, amiodarone, or potent P-glycoprotein inhibitors.[24]

In contrast to previous observational studies, the ANATOLIA-AF study (Prevalence and Associated Factors of Inappropriate Dosing of Direct Oral Anticoagulants in Patients With Atrial Fibrillation: the ANATOLIA-AF Study) applied the criteria proposed by the EHRA for using DOACs in patients with AF in real-life settings.[25] This study reported that the proportion of patients receiving an appropriate dose of edoxaban was 72%, which is lower than in both the ETNA-AF Europe[4] and ETAF-TR studies. It should be noted that important risk factors, including age, concomitant antiplatelet use, and previous bleeding events, are not included in the SmPC of direct oral anticoagulants, which is a significant omission that warrants further investigation.

Another critical finding in the ETAF-TR study is the higher prevalence of comorbidities, including diabetes, heart failure, myocardial infarction, and ischemic stroke, compared with ETNA-AF Europe.[4] Obesity is linked with hypertension and diabetes, which together increase the risk of myocardial infarction, heart failure, and ischemic stroke. In 2019, more than 20% of people in Türkiye were obese, and the country ranks third among European countries in terms of obesity prevalence in women.[20] As indicated in the 2021 report published by the International Diabetes Federation, Türkiye has the highest prevalence of diabetes in Europe. The age-adjusted prevalence of diabetes in Europe is 7.0%. However, it is significantly higher in Türkiye, where the prevalence is 14.5% in the adult population.[26] On the other hand, the use of tobacco products represents a significant risk factor for the development of cardiovascular diseases, including myocardial infarction and ischemic stroke. Although it is well known that smoking is the single most significant avoidable health risk, the prevalence of smoking in men in Türkiye, with a rate of 42.1%, is one of the 10 highest among European countries.[20] In light of the aforementioned cardiovascular risk factors, it is unsurprising that the prevalence of myocardial infarction, ischemic stroke, and heart failure is higher in Türkiye than in European counterparts.[27] Consequently, the CHA_2DS_2-VASc score, which incorporates factors such as diabetes, heart failure, coronary artery disease, and ischemic stroke, is significantly higher in the ETAF-TR study than in the ETNA-AF Europe study, despite the younger patient population.[4] The findings of the ETAF-TR study indicate the necessity for prompt and systematic interventions targeting obesity, smoking, hypertension, and diabetes by the Ministry of Health, healthcare professionals, and non-governmental organizations in both patients with AF and the general population of Türkiye.

This study has some limitations. The ETAF-TR study is a national study and may reflect specific characteristics of the Turkish population. Therefore, extending the results to other populations may not be feasible. As noted earlier, the Social Security Institution of Türkiye is the primary payer institution within the country, and it stipulates the use of warfarin treatment before reimbursement of DOACs. Therefore, the ETAF-TR study population comprised patients with a history of warfarin use. These patients may be more aware of the significance of anticoagulant therapy and its potential adverse effects than those who have not previously undergone such treatment. Additionally, the ETAF-TR study population was limited to outpatient cardiology clinics and may not reflect all healthcare settings, such as inpatient wards or intensive care units. Although the study used limited exclusion criteria to overcome factors that limit external validation, ETAF-TR is still susceptible to several biases, such as selection bias and recall bias. However, similar population demographics such as age and sex between ETAF-TR and other recent real-life studies may reflect the all-comer nature of the study.

Conclusion

ETAF-TR is a large, national, prospective study evaluating the use of edoxaban for SSPAF. The baseline data indicate that edoxaban has been administered to a diverse patient population with appropriate dosing. The one-year results of the ETAF-TR study will provide important insights into the safety and effectiveness of edoxaban treatment in real-life settings.

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Informed Consent: Written informed consent was obtained from the participants.

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