

Edoxaban Anticoagulation in Atrial Fibrillation: Real-World Data and Evidence

Atriyal Fibrilasyonda Edoxaban Antikoagülasyon: Gerçek Dünya Verileri ve Kanıtları

ABSTRACT

Atrial fibrillation (AF) and stroke are two prevalent health conditions with many shared risk factors. Over the past two decades, non-vitamin K antagonist oral anticoagulants (NOACs) have emerged as important alternatives to vitamin K antagonists, owing to their efficacy, safety profile, and the absence of a need for frequent international normalized ratio monitoring. Introduced as the most recent NOAC, edoxaban has been approved for stroke prevention in non-valvular AF in numerous countries since 2014. The pivotal phase III Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial demonstrated that edoxaban is as efficacious as warfarin in preventing strokes and systemic embolic events. Furthermore, it is linked to reduced rates of major, life-threatening, intracranial, major, or clinically relevant non-major bleeding events and decreased cardiovascular mortality in AF when compared to warfarin. Growing data highlights the utilization of edoxaban in treating AF patients in clinical settings. This article provides an overview of real-world evidence regarding edoxaban's use in preventing stroke and systemic embolic events in AF patients, emphasizing the concerns that physicians factor into their clinical decision-making.

Keywords: Atrial fibrillation, bleeding, edoxaban, non-vitamin K antagonist oral anticoagulant, real-world, stroke, warfarin

ÖZET

Atriyal fibrilasyon (AF) ve inme, birçok ortak risk faktörü olan iki yaygın sağlık durumudur. Son yirmi yılda, K vitamini antagonisti olmayan oral antikoagülanlar (NOAK'lar), etkinlik ve güvenlik profilleri ve sık sık uluslararası normalleştirilmiş oran takibi gerektirmemeleri nedeniyle K vitamini antagonistlerine önemli bir alternatif haline geldi. Edoxaban şu anda mevcut olan en son geliştirilen NOAK'tır ve 2014'ten bu yana dünyanın birçok ülkesinde valvüler olmayan AF'de inmeyi önleme için onaylanmıştır. Önemli faz III ENGAGE AF-TIMI 48 çalışması, edoxabanın varfarin kadar etkili olduğunu göstermiştir. İnmeleri ve sistemik embolik olayları önlemektedir ve varfarine kıyasla AF'de daha düşük majör, hayatı tehdit edici, intrakraniyal, majör veya klinik olarak anlamlı majör olmayan kanama oranları ve azalmış kardiyovasküler mortalite ile ilişkilidir. Klinik pratikte AF'li hastalarda edoxaban kullanımına ilişkin veriler birikmektedir. Bu makale, hekimlerin klinik karar verme sürecinde dikkate aldığı konulara odaklanarak, AF'li hastalarda inme/sistemik embolik olayların önlenmesi için edoxaban kullanımına ilişkin gerçek dünya verilerine/kanıtlarına genel bir bakış sunmaktadır.


Anahtar Kelimeler: Atriyal fibrilasyon, kanama, edoxaban, K vitamini antagonisti olmayan oral antikoagülan, gerçek dünya, inme, varfarin

Atrial fibrillation (AF) and stroke are two prevalent health conditions with many common risk factors, including obesity, hypertension, and diabetes.^{1,2} According to the 2019 Global Burden of Disease statistics, the estimated prevalence of AF/atrial flutter³ and stroke⁴ stood at approximately 60 million and 101 million, respectively. Furthermore, stroke ranked among the leading causes of disability and mortality.⁵

Ischemic strokes (ISs) account for 62% of new stroke cases,⁴ and 17–38% of these are associated with AF.^{6–8} Critically, AF-related cerebral embolism has a high recurrence rate and is linked with more severe outcomes,^{6,9} emphasizing the essential nature of stroke prophylaxis in AF management. It is significant to note that a stroke can sometimes be the first indicator of subclinical AF.¹⁰ In a real-world study, De Angelis et al.¹¹ discovered

REVIEW DERLEME

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Received: April 16, 2023

Accepted: July 10, 2023

Cite this article as: Çay S, Kasap M. Edoxaban anticoagulation in atrial fibrillation: real-world data and evidence. *Türk Kardiyol Dern Ars.* 2023;51(8):565–573.

DOI:10.5543/tkda.2023.73869



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that AF was identified using an insertable cardiac monitor in 41% of patients with cryptogenic stroke over a 3-year follow-up period.

Vitamin K antagonists (VKAs) have long served as the standard anticoagulant treatment for preventing stroke and systemic embolic events (S/SEEs) in patients with AF.¹² However, the narrow therapeutic index, the frequent need for international normalized ratio (INR) monitoring due to poor time in therapeutic range (TTR), and interactions with food and drugs stand out as the primary drawbacks of VKAs.^{12,13} These challenges can compromise the efficacy and safety of VKAs, increasing the risk of thromboembolism and/or bleeding, and potentially reducing patient compliance. While an optimal VKA treatment suggests a TTR of $\geq 70\%$,¹³ this benchmark is often not met in everyday clinical practice.¹⁴

The emergence of non-vitamin K antagonist oral anticoagulants (NOACs) in the early 2010s marked a significant advancement in anticoagulant therapy.¹⁵ Often referred to as direct oral anticoagulants (DOACs) due to their mechanism of action, which involved direct inhibition of factor IIa (thrombin) or Xa,¹⁶ these drugs, including the factor IIa inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, have proven either comparable to or more effective than warfarin in reducing strokes and bleeding events among AF patients.¹⁷⁻²⁰ Moreover, they offer a streamlined approach to anticoagulant therapy, eliminating the need for INR monitoring and frequent dose adjustments.^{12,13} Recognizing their benefits, internationally acclaimed AF management guidelines now advocate for NOACs as the primary anticoagulant therapy for AF patients.^{13,21}

In medicine, real-world data (RWD) and real-world evidence (RWE) offer findings from routine clinical practice, capturing a diverse population not restricted by the strict eligibility criteria of randomized controlled trials (RCTs). These insights illuminate clinicians' treatment decisions, presenting information on the effectiveness and safety of drugs in broad patient groups with varied clinical and demographic characteristics (Figure 1).²²

Edoxaban is the most recent NOAC approved and reimbursed in various countries, including Turkey, for preventing S/SSEs in patients with AF, and for the prevention and treatment of venous thromboembolism.²³⁻²⁶ Since its initial approval for these indications in Japan in 2014,²⁶ a growing body of RWD/RWE has emerged, showcasing the experiences of thousands of patients using this medication across different parts of the world.

Real-World Studies are Complementary to Randomized Controlled Studies

Randomized Controlled Studies



- Homogeneous population
- Controlled environment
- Directly observed

Real-World Evidence



- Heterogeneous population
- Observational environment
- Often observed indirectly

Figure 1. Major differences between real-world and randomized controlled studies.

In this article, we examine the RWD/RWE related to edoxaban, focusing on its effectiveness (in reducing S/SEE) and safety (regarding bleeding events) in patients with AF. Our intent is to highlight considerations physicians deem vital in the treatment process within their clinical practice.

Methods

To ensure comprehensive data retrieval, literature searches were conducted in both English and Turkish using MEDLINE, EMBASE, Cochrane, and PubMed databases. Additionally, records from national and international scientific meetings between September 2014 (the date of edoxaban's first approval for stroke prevention in AF) and August 2022 were reviewed. The primary literature and data searches employed terms such as edoxaban (fixed term), AF, NOAC, DOAC, clinical studies/trials, meta-analysis, RWD/RWE, stroke, systemic embolism, SSE, death, mortality, bleeding, hemorrhage, adherence, diabetes, estimated glomerular filtration rate (eGFR), and heart failure. Moreover, references from relevant identified publications and pertinent guidelines were examined. Following the exhaustive literature search and removal of duplicates, studies with the largest sample sizes that compared VKAs to the four different NOACs regarding hard endpoints were assessed. These studies are detailed separately in the text and collectively in a table.

ENGAGE AF-TIMI 48 Trial: Efficacy and Safety of Edoxaban in Stroke Prevention in AF

The pivotal phase 3, randomized, double-blind, double-dummy Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48), which involved more than 20,000 AF patients with a moderate to high risk of stroke (mean \pm Standard Deviation (SD) CHA₂DS₂ score, 2.8 \pm [1.0]), demonstrated that edoxaban was as effective as warfarin in reducing S/SEEs (Hazard Ratio (HR), 0.79; 97.5% Confidence Interval (CI), 0.63-0.99; $P < 0.001$ for edoxaban 60 mg od and HR, 1.07; 97.5% CI, 0.87-1.31; $P = 0.005$ for edoxaban 30 mg od for non-inferiority). This came with lower rates of major, life-threatening, intracranial, and major or clinically relevant non-major (CRNM) bleeding and cardiovascular (CV) mortality than warfarin, over a median follow-up of 2.8 years.²⁰ Subsequent post-hoc and subgroup analyses of the ENGAGE AF-TIMI 48 data indicated that edoxaban was consistently effective and safe across various challenging clinical conditions, including valvular heart disease,^{27,28} diabetes mellitus,^{28,29} old age (≥ 75 years),^{28,30} extremely low or high body weights (≤ 55 kg or ≥ 120 kg),^{28,31} prior stroke/transient ischemic attack (TIA),^{28,32} creatinine clearance (CrCl) ≤ 50 mL/min,^{28,33} high updated Charlson Comorbidity Index (CCI),^{28,34} and a high risk of falling.^{28,35}

RWD/RWE on Effectiveness and Safety of Edoxaban in Stroke Prevention in AF

To gather comprehensive data on the effectiveness and safety of edoxaban in AF in real-life settings, the Edoxaban Treatment in routine clinical practice in Patients with non-valvular Atrial Fibrillation (ETNA-AF) program commenced in 2019. This augmented the findings of the ENGAGE AF-TIMI 48 trial. The ETNA-AF is a registry that prospectively accumulates data from over 26,000 AF patients who have been treated with edoxaban

across several European and Asian nations.³⁶The reported findings from ETNA-AF across various regions or countries thus far confirm the beneficial effects of edoxaban in real-life treatment of AF.³⁷⁻⁴³ Our national RWE, the "Evaluation of Treatment Safety in Patients with Atrial Fibrillation on Edoxaban Therapy in Real-Life in Turkey" (ETAF-TR) study, showed that adherence to the

label-recommended dose for edoxaban use was high (> 80%) in Turkey. However, the 1-year results are not yet available.⁴⁴ Table 1 summarizes the first and second-year outcomes from the global ETNA-AF and ETNA-AF Europe studies; the key baseline characteristics of the ETAF-TR cohort are also presented.^{38,40,42-44} The consistency of ETNA-AF's findings with those of the ENGAGE

Table 1. Summary of Global ETNA-AF, ETNA-AF Europe, and ETAF-TR Studies

Study description	Participant countries	n	Key patient characteristics	Key findings
Global ETNA-AF (1-year) De Caterina et al. ³⁸ <i>J Clin Med.</i> 2021 Prospective, observational study	Austria, Belgium, Germany, Ireland, Italy, The Netherlands, Portugal, Spain, Switzerland, United Kingdom, Japan, South Korea, Taiwan	26,823	Median (IQR) age: 75 (68-80) years 58.2% male Median CHA ₂ DS ₂ -VASc (IQR) score: 3.0 (2.0-4.0) Median HAS-BLED (IQR) score: 2.0 (2.0-3.0)	MB: 1.05%/year ICH: 0.31%/year Major GIB: 0.57%/year IS: 0.87%/year CV mortality: 1.22%/year Mortality: 3.03%/year
ETNA-AF Europe (1-year) De Groot et al. ⁴⁰ <i>Eur Heart J. Cardiovasc Pharmacother.</i> 2021 Prospective, observational study	Austria, Belgium, Germany, Ireland, Italy, The Netherlands, Portugal, Spain, Switzerland, United Kingdom	13,092	Mean (SD) age: 73.6 (9.46) years 56.8% male Mean (SD) CHA ₂ DS ₂ -VASc score: 3.1 (1.4) Mean (SD) HAS-BLED score: 2.5 (1.1)	MB: 1.12%/year ICH: 0.24%/year Major GIB: 0.40%/year S/SE: 0.82%/year IS: 0.6%/year Mortality: 3.50%/year CV mortality: 1.63%/year
ETNA-AF Europe (2-year) Kirchhof et al. ⁴² <i>European Heart J - Cardiovasc Pharmacother.</i> 2022 Prospective, observational study	Austria, Belgium, Germany, Ireland, Italy, The Netherlands, Portugal, Spain, Switzerland, United Kingdom	13,133	Mean (SD) age: 73.6 (9.5) years 56.7% male Mean (SD) CHA ₂ DS ₂ -VASc score: 3.2 (1.4) Mean (SD) HAS-BLED score: 2.5 (1.1)	MB: 0.97%/year ICH: 0.20%/year Major GIB: 0.40%/year S/SE: 0.70%/year IS: 0.51%/year Mortality: 3.87%/year CV mortality: 2.14%/year
Global ETNA-AF (1st and 2nd year) Dinshaw et al. ⁴³ Presented at ESC Congress 2021 <i>Eur Heart J.</i> 42(Suppl1) Oct 2021 Prospective, observational study	Austria, Belgium, Germany, Ireland, Italy, The Netherlands, Portugal, Spain, Switzerland, United Kingdom, Japan, South Korea, Taiwan	27,617	Mean (SD) age: 73.6 (9.8) years 58.1% male Mean (SD) CHA ₂ DS ₂ -VASc score: 3.3 (1.5) Mean (SD) HAS-BLED score: 2.4 (1.1)	1st and 2nd year: MB: 1.15% vs. 0.87%/year (p=0.036) ICH: 0.31% vs. 0.26%/year Major GIB: 0.59% vs. 0.42%/year IS: 0.86% vs. 0.59%/year (p=0.015) Mortality: 3.04% vs. 3.25%/year CV mortality: 1.50% vs. 1.39%/year
ETAF-TR Türk et al. ⁴⁴ Presented at 38 th National Cardiology Congress November 10-13, 2022. <i>Anatol J Cardiol.</i> 2022;26(Suppl 1):S1-S177.	Türkiye	1,053	Mean (SD) age: 70.1 (11.3) years 41% male Mean (SD) CHA ₂ DS ₂ -VASc score: 3.5 (1.5) Mean (SD) HAS-BLED score: 1.6 (1.0)	Characteristics at baseline were presented. 82% of patients were treated with the recommended dose <i>Note: Enrollment was completed in May 2022. Results of ETAF-TR study are not available yet. Primary outcome: Any overt bleeding. Exploratory outcomes: Effectiveness, treatment persistence, and posology.</i>

CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age ≥ 65 years, sex category; CV, Cardiovascular; ETAF-TR, The Evaluation of Treatment Safety in Patients with Atrial Fibrillation on Edoxaban Therapy in Real-Life in Turkey; ETNA-AF, Edoxaban Treatment in routine clinical practice in Patients with non-valvular Atrial Fibrillation; GIB, Gastrointestinal Bleeding; HAS-BLED, hypertension, abnormal liver/renal function, stroke history, bleeding predisposition, labile INR, elderly, drug/alcohol usage score; ICH, Intracranial Hemorrhage; IS, Ischemic Stroke; MB, Major Bleeding; SD, Standard Deviation.

AF-TIMI 48 trial was assessed in a propensity score-matched sample population adjusted for key baseline characteristics. The analysis showed that real-life effectiveness results (all risks of S/SEE, IS, hemorrhagic stroke, and all-cause mortality) aligned with those reported in the ENGAGE AF-TIMI 48 study. The risks of major bleeding (MB) and CRNM bleeding were significantly reduced in real-life by 75% and 87% with the 60 mg dose of edoxaban (and by 72% and 82% with the 30 mg dose), respectively.⁴⁵

There was notable decreasing trends in the annualized event rates (AERs) of IS (from 0.86 to 0.59; $P = 0.015$) and MB (from 1.15 to 0.87; $P = 0.036$) from the first year to the second year, as observed in the global ETNA-AF second-year results.⁴³ Moreover, the AERs for intracranial hemorrhage (ICH), major gastrointestinal (GI) bleeding, and CV mortality did not rise in the second year of edoxaban treatment compared to the first year.⁴³ The evolution of these observations should be closely monitored, as they have the potential to influence clinical practice. The one and two-year results from the ETNA-AF Europe cohort also demonstrated low annualized rates of S/SSE (0.70%) and MB (0.97%) in patients treated with edoxaban in real-life settings. The AERs for all-cause death and CV death were 3.87% and 2.14%, respectively.⁴² Overall, the results aligned with those from the 1-year follow-up and the phase 3 ENGAGE AF TIMI 48 trial (Figure 2).^{20,40,42,43} Consistently, the recently reported outcomes from the Danish nationwide cohort ($n=2285$; median follow-up time ~ 1 year)⁴⁶ and from the Dresden NOAC Registry ($n = 1258$; median follow-up time ~ 2.5 years),⁴⁷ which included AF patients treated with edoxaban, also provided additional evidence on the effectiveness and safety of edoxaban in AF for real-life stroke prevention.

The 2-year follow-up of the ETNA-AF Europe cohort indicated that the strongest age-adjusted determinants of IS/SSE, MB, and CV death were previous TIA, reduced estimated CrCl (using the Cockcroft-Gault method), and a history of heart failure (HF), respectively ($P < 0.0001$ for all).⁴² Additional analyses of the ETNA-AF Europe study population shed more light on the effectiveness and safety of edoxaban in commonly encountered concomitant challenging clinical scenarios such as HF,⁴⁸ impaired renal function,⁴⁹ history of ischemic stroke,⁵⁰ diabetes,⁵¹ and dyslipidemia.⁵²

Comparative analyses of patients with and without HF in the ETNA-AF Europe study showed that pre-existing HF elevated the risk of ischemic events (i.e., IS/TIA/SEE), CV/all-cause death, and bleeding. This underlines the importance of more effective HF management in AF patients.⁴⁸

A recent real-world study comparing warfarin and NOAC users in terms of acute kidney injury (AKI) or progressive renal impairment over an average observation period of 3.3 years found that the AKI incidence was higher with warfarin than with NOACs (8.9% vs. 4.4%, $P < 0.001$ after propensity score matching). However, both groups had similar trends regarding progressive decline in renal function (assessed by eGFR change over two years).⁵³ Conversely, several studies noted a more pronounced progressive deterioration in kidney function with VKAs than with NOACs.^{54,55} Differences in study setups, patient demographics, and endpoint definitions might account for these discrepancies in real-world study results, and these factors should be considered when comparing the results. The low rate of renal function worsening (defined as a 25% decline in eGFR compared to baseline), observed in 10% of patients over a 2-year follow-up in the ETNA-AF-Europe cohort,⁴⁹ endorses edoxaban as a feasible treatment option for stroke prevention in AF patients with an elevated risk of renal dysfunction. Since NOACs undergo partial elimination through renal excretion, diminished kidney function may impact drug metabolism, necessitating a dose adjustment.^{21,23} For patients with a CrCl between 15-50 mL/min, the edoxaban dose should be reduced to 30 mg once daily to circumvent potential safety concerns.²³

The impact of having an IS history on safety and outcomes were meticulously assessed during the 2-year follow-up analysis of the global ETNA-AF program, given IS's proclivity to recur. The AERs for all types of stroke, including hemorrhagic and ischemic ones (HR, 4.23; 95% CI, 3.48-5.13; $P < 0.0001$), and for CV/all-cause death (for CV death, HR, 1.37; 95% CI, 1.11-1.70 and for all-cause death, HR, 1.50; 95% CI, 1.30-1.72; $P < 0.0001$ for both) were significantly elevated in patients with prior IS. However, the risks associated with myocardial infarction (HR, 1.24; 95% CI, 0.75-2.03; $P = 0.3993$) and SEE (HR, 2.02; 95% CI, 0.76-5.39; $P = 0.1591$) remained analogous between individuals with and without an IS history. Additionally, the frequencies of bleeding

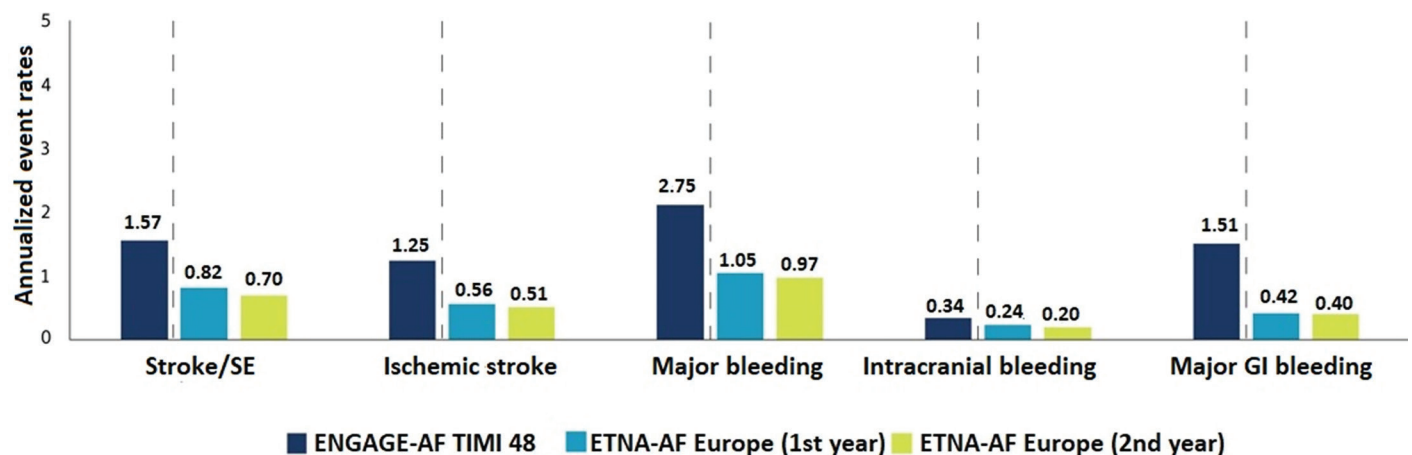


Figure 2. Annualized event rates of clinical outcomes in ENGAGE-AF TIMI 48 and ETNA-AF Europe.

incidents, including MB, major GI bleeding, ICH, and CRNM bleeding, were higher in patients with a history of IS.⁵⁰

Diabetes is an independent stroke risk factor, and patients with unregulated diabetes mellitus tend to face detrimental stroke outcomes and increased mortality rates.⁵⁶ A comparative analysis between diabetic and non-diabetic individuals in the ETNA-AF Europe cohort revealed that diabetic patients on insulin, unlike those on other treatments, exhibited a heightened risk of IS/TIA/SE, reflected by a 1.81% AER. This rate was significantly higher compared to non-diabetics ($P = 0.002$) and diabetics not using insulin ($P = 0.014$), who had 0.86% and 0.87% AERs, respectively.⁵¹ Furthermore, when comparing AF patients with insulin-dependent diabetes on edoxaban anticoagulation indirectly to AF patients with insulin-dependent diabetes on VKA anticoagulation, the latter group had an AER of 5.2% for S/SEE.⁵⁷

Given the established relationship between dyslipidemia and the risk of CV events, the impact of using lipid-lowering therapies (LLT) on ischemic event outcomes was assessed in the ETNA-AF Europe study. During the 2-year follow-up, risks of all-cause death, CV death, S/SEE, and IS were 27%, 27%, 39%, and 46% lower, respectively, for the 4,761 patients on LLT at baseline.⁵² These observations strongly emphasize the importance of better CV risk management in patients with AF to improve clinical outcomes.

In medicine, it is paramount to treat the appropriate patient with the right drug, in the correct dose, and for the optimal duration. According to the ESC AF management guidelines, Oral Anticoagulants (OACs) are recommended for men with a CHA₂DS₂-VASc (C: Congestive heart failure, H: Hypertension, A2: Age 75 years or older, D: Diabetes mellitus, S2: Prior stroke or transient ischemic attack, V: Vascular disease, A: Age 65-74 years, Sc: Sex category) score ≥ 2 (and ≥ 3 for women) and should be considered for men with a CHA₂DS₂-VASc score ≥ 1 (and ≥ 2 for women).¹³ An analysis of the global ETNA-AF population revealed that 96.7% of patients met the criteria for OAC initiation and $> 80\%$ of patients were on the correct dose of edoxaban, which is crucial for the proper management of bleeding and stroke risk.⁵⁸ Additionally, the overall adherence to the label-recommended dose was 83.1%, with even higher adherence to the standard dose of edoxaban 60 mg (88.8%) in the ETNA-AF Europe study during the 2-year follow-up.⁴² In Turkey, the approved standard dose for edoxaban is 60 mg once daily for AF. A dose of 30 mg once daily is recommended for patients with a CrCl of 15 - 50 mL/min (according to Cockcroft-Gault), those with low body weight (≤ 60 kg), or those taking strong P-glycoprotein (P-gp) inhibitors such as cyclosporine, dronedarone, erythromycin, or ketoconazole.²³ According to the 2-year follow-up results from the ETNA-AF Europe study, older age, frailty, high CHA₂DS₂-VASc, and HAS-BLED (H: Hypertension, A: Abnormal renal or liver function, S: Stroke history, B: Bleeding history or predisposition, L: Labile INR (International Normalized Ratio), E: Elderly (age >65), D: Drugs or alcohol use) scores correlated with the 30 mg once-daily dosing regimen. It is worth noting that both dosing regimens were equally effective in reducing S/SEE (HR, 1.07; 95% CI, 0.74-1.53; $P = 0.7272$) and IS (HR, 1.12; 95% CI, 0.74-1.70;

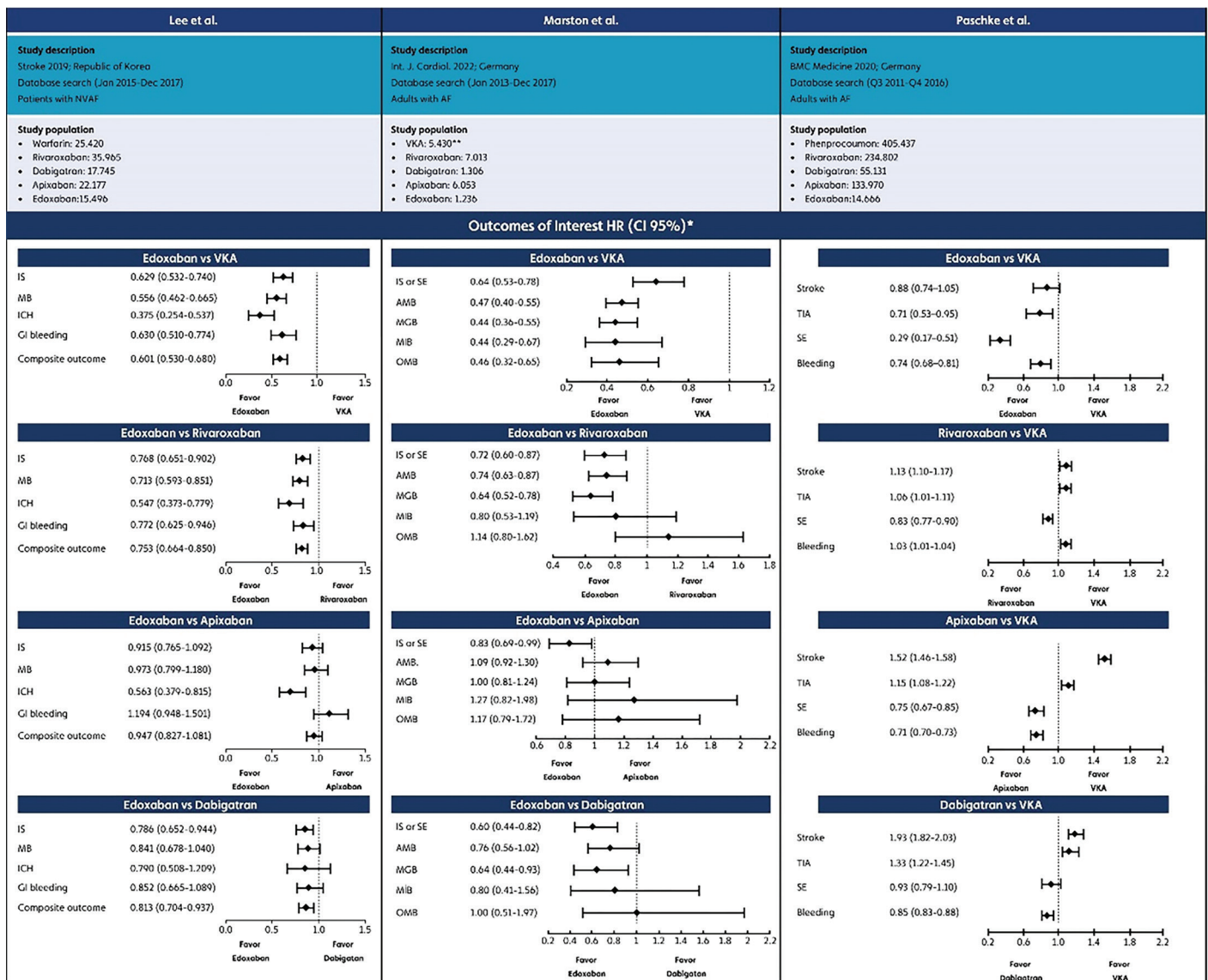
$P = 0.5862$) after adjusting for patients' baseline characteristics and calculating the risk of death.⁴²

Non-adherence to anticoagulants is an important concern that can lead to poor outcomes and, therefore, needs to be considered in clinical practice. In a retrospective, propensity-matched cohort study conducted in patients with AF, the 6-month adherence rate (proportion of days covered $\geq 80\%$) for edoxaban was significantly higher than that for apixaban, dabigatran, and VKA, and was comparable to rivaroxaban. Additionally, the 6-month persistence rate for edoxaban was significantly higher than for dabigatran, rivaroxaban, and VKA, and was similar to apixaban.⁵⁹ The twice-daily dosing regimen was reported to be an independent predictor of non-compliance (Odds Ratio (OR), 1.73; 95% CI, 1.08-2.75; $P = 0.022$) in a single-center, retrospective study ($n = 264$) that reported a 51% non-compliance rate to NOACs in patients with AF over a median period of 439 days.⁶⁰ The 2021 European Heart Rhythm Association (EHRA) practical guide also highlighted the possibility of poor compliance with twice-daily NOAC regimens. A once-daily regimen, even in patients requiring dose adjustments, may contribute to better compliance rates and improved outcomes with edoxaban treatment in clinical practice.²¹ ETAF-TR, which is the first study evaluating the safety and effectiveness of edoxaban in clinical practice in Turkey, is ongoing and will provide RWD on overt bleedings (major/CRNM bleeding and those judged by the physician as overt bleeding) and dose regimens and persistence rates of edoxaban in AF.⁶¹

To the best of our knowledge, no RCT has been conducted regarding the head-to-head comparison of different NOACs. The assessment of the comparative effectiveness and safety of edoxaban versus other NOACs relies on RWD gathered from hospital medical records, administrative and claims databases, and registries. Accordingly, a stepwise analysis of data gathered from database searches revealed three large-scale RWD/RWE studies, which included comparative results of VKAs and NOACs. An analysis of a large registry from Korea, which included $> 116,000$ patients with AF receiving OACs for stroke prevention, showed that edoxaban was associated with lower risks of IS, ICH, GI bleeding, and MB compared to VKA.⁶² The pairwise comparison of NOACs with each other revealed that the risk of IS with edoxaban was lower than with rivaroxaban (HR, 0.768; 95% CI, 0.651 - 0.902) and dabigatran (HR, 0.786; 95% CI, 0.652 - 0.944), and it was comparable to apixaban (HR, 0.915; 95% CI, 0.765 - 1.092). While patients treated with edoxaban had comparable rates of MB to those treated with dabigatran (HR, 0.841; 95% CI, 0.678 - 1.040) and apixaban (HR, 0.973; 95% CI, 0.799 - 1.180), edoxaban was associated with a lower risk of MB than rivaroxaban (HR, 0.713; 95% CI, 0.593 - 0.851). The comparison regarding the composite clinical outcome of the study (IS + MB) favored edoxaban versus rivaroxaban (HR, 0.753; 95% CI, 0.664 - 0.850) and dabigatran (HR, 0.813; 95% CI, 0.704 - 0.937), and indicated comparable safety and efficacy of edoxaban versus apixaban (HR, 0.947; 95% CI, 0.827 - 1.081). The only outcome that significantly differentiated edoxaban from apixaban was ICH, which had a lower risk in patients receiving edoxaban (HR, 0.563; 95% CI, 0.379 - 0.815) (Figure 3).⁶² A large retrospective database study from Germany ($n = 21,038$) also highlighted the beneficial effects of edoxaban versus other OACs in real-life scenarios (Figure 3). The study reported that edoxaban was more

effective in reducing the combined risk of IS/SEE compared to apixaban, rivaroxaban, dabigatran, and VKA by 17%, 28%, 40%, and 36%, respectively ($P < 0.05$ for all). The risk of MB with edoxaban was comparable to both apixaban and dabigatran but was lower than with rivaroxaban by 26% and VKA by 53%.⁶³ Furthermore, edoxaban has been found to be as effective as, and safer than, phenprocoumon in several real-life studies involving patients with AF.^{64,65} In a large retrospective study evaluating the effectiveness of all NOACs versus phenprocoumon (which was deemed effectively anticoagulated based on high TTR values ranging between 68% and 79%) in a matched population of AF patients, Paschke et al.⁶⁴ observed that all NOACs, except edoxaban, had a higher risk of stroke than phenprocoumon (HR, 0.88; 95% CI, 0.74 - 1.05 for edoxaban vs. phenprocoumon). While an increased risk of TIA was observed for other NOACs, a significant decrease in TIA risk was noted for edoxaban compared

to phenprocoumon (HR, 0.71; 95% CI, 0.53 - 0.95). The authors also reported a lower bleeding risk with edoxaban compared to phenprocoumon (HR, 0.74; 95% CI, 0.68 - 0.81) (Figure 3). In a more recent study, edoxaban was found to be as effective as phenprocoumon in reducing the risk of stroke/SE (HR, 0.85; 95% CI, 0.70 - 1.02) and had lower risks of hemorrhagic stroke (HR, 0.52; 95% CI, 0.33 - 0.83), MB (HR, 0.69; 95% CI, 0.58 - 0.81), and ICH (HR, 0.48; 95% CI, 0.35 - 0.67).⁶⁵ A systematic review and meta-analysis of real-life studies on NOACs and warfarin, which included 34 studies involving > 2,250,000 patients from various geographies focused on stroke prevention in AF, provided detailed information about the comparative effectiveness and safety of NOACs versus warfarin. Compared to warfarin, edoxaban reduced the risk of stroke by 33% (HR, 0.67; 95% CI, 0.60 - 0.76; $P < 0.01$), all-cause mortality by 48% (HR, 0.52; 95% CI, 0.31- 0.85; $P = 0.01$), MB by 45% (HR, 0.55; 95% CI,



* The graphics are adapted from relevant studies. ** 99.6% of patients treated with phenprocoumon, 0.04% with warfarin

AMB: Any major bleeding; Composite outcome: ischemic stroke + MB (ICH or CIB); GIB: Gastrointestinal bleeding; ICH: Intracranial hemorrhage; IS: Ischemic stroke; MB: Major bleeding; MGB: Major gastrointestinal bleeding; OMB: Other major bleeding; SE: Systemic emboli; TIA: Transient ischemic attack.

Figure 3. Real-life comparison of NOACs with one another and with VKAs.

0.45 - 0.66; $P < 0.01$), and ICH by 56% (HR, 0.44; 95% CI, 0.26 - 0.76; $P < 0.01$). Although the meta-analysis reported that NOACs did not significantly reduce the risk of GI bleeding versus warfarin, pairwise comparisons showed that both edoxaban and apixaban effectively reduced the risk of GI bleeding (HR, 0.62; 95% CI, 0.44 - 0.87 for edoxaban).⁶⁶ A more recent systematic review and network meta-analysis also reported that the risk of GI bleeding was lower in patients treated with edoxaban (HR, 0.74; 95% CI, 0.56 - 0.97) and apixaban than with VKA. In that meta-analysis, edoxaban did not significantly reduce the risk of all-cause mortality (HR, 0.72; 95% CI, 0.45 - 1.14) compared to VKA. However, it was superior to VKA in reducing IS (HR, 0.74; 95% CI, 0.62 - 0.90), MB (HR, 0.60; 95% CI, 0.47 - 0.77), and ICH (HR, 0.42; 95% CI, 0.31 - 0.58).⁶⁷

Conclusion

The RWD/RWE regarding the use of edoxaban for stroke prevention in AF is accumulating and being enriched with new analyses focusing on key issues to guide clinical practice. These findings are consistent with the results of the phase 3 ENGAGE AF-TIMI 48 trial and support the idea that edoxaban is an effective and safe treatment option for AF, even in challenging clinical settings.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.Ç., M.K.; Design - S.Ç., M.K.; Supervision - S.Ç., M.K.; Resource - M.K.; Materials - S.Ç., M.K.; Data Collection and/or Processing - S.Ç., M.K.; Analysis and/or Interpretation - S.Ç., M.K.; Literature Review - S.Ç., M.K.; Writing - S.Ç.; Critical Review - S.Ç., M.K.

Acknowledgment: We thank Dr. İdilhan Baloğlu Ar for compiling the feedback from the authors and providing medical writing support.

Conflict of Interest: The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Payment or honoraria for lectures, presentations, speakers from Daiichi Sankyo (SC). Daiichi Sankyo employee (MK).

Funding: This study was funded by Daiichi Sankyo.

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