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Design and rationale of the Edoxaban Treatment in routine clinical practice for patients with Atrial Fibrillation in Europe (ETNA-AF-Europe) study

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Aim Edoxaban, a nonvitamin K antagonist oral anticoagulant, is an oral factor Xa inhibitor approved for the prevention of stroke and systemic embolism in adult patients with atrial fibrillation and for the treatment and secondary prevention in adult patients with venous thromboembolism (VTE). This study details the design of the Edoxaban Treatment in routine clinical practice for patients with Atrial Fibrillation in Europe (ETNA-AF-Europe) study – a postauthorization observational study, which is part of the postapproval plan for edoxaban agreed with the European Medicines Agency.

Methods The ETNA-AF-Europe study (Clinicaltrials.gov: NCT02944019) is a multicenter, prospective, observational study that enrolled 13 980 patients with atrial fibrillation treated with edoxaban from 852 sites across 10 European countries (Austria, Belgium, Germany, Ireland, Italy, the Netherlands, Portugal, Spain, Switzerland, and the United Kingdom). Patients treated with edoxaban were prospectively enrolled and will be followed up for 4 years with yearly follow-up visits.

Assessments The primary objective of the ETNA-AF-Europe study is to assess the real-world safety of edoxaban by evaluating bleeding events, including intracranial hemorrhage; drug-related adverse events, such as hepatic events; and cardiovascular and all-cause mortality. In addition, efficacy will be assessed by recording major adverse cardiovascular events including stroke, systemic

embolic events, transient ischemic attacks, and also VTE episodes, acute coronary syndromes, and hospitalizations related to cardiovascular condition. Event rates will be compared with event rates reported in the PREvention of thromboembolic events-European Registry in Atrial Fibrillation in atrial fibrillation (PREFER in AF) and PREFER in AF Prolongation registries, and in the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48 study datasets.

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Keywords: atrial fibrillation, edoxaban, major bleeding, nonvitamin K antagonist oral anticoagulants, real-world, registry, safety outcomes, stroke prevention

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Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia in Europe, affecting approximately 2–3% of the population.^{1,2} Atrial fibrillation is associated with stroke, heart failure, dementia/cognitive impairment, sudden death, and cardiovascular morbidity and mortality.³ A significant rise in the worldwide prevalence, incidence, and overall burden of atrial fibrillation has been noted in the past few decades, along with increasing awareness, diagnostic tools, and therapies becoming available.⁴

For several decades, vitamin K antagonists (VKAs), such as warfarin, were the only oral anticoagulant drugs available for the prevention of stroke and systemic embolism in atrial fibrillation patients. However, limitations, such as the need for close monitoring and multiple food and drug interactions, prompted the search for alternative anticoagulants with a stable pharmacology and easier use in clinical practice. This resulted in the testing and approval of non-VKA oral anticoagulants (NOACs). Edoxaban is one of the four clinically available NOACs. It was approved in Europe for stroke prevention in patients

with atrial fibrillation, and also for the treatment and prevention of venous thromboembolism (VTE). Edoxaban is a highly selective, once-daily, direct, reversible inhibitor of factor Xa. The recommended edoxaban dose is 60 mg once daily. A reduced dose of 30 mg once daily is required for patients with moderate or severe renal impairment (creatinine clearance 15–50 ml/min), low body weight (≤ 60 kg), or concomitant use of strong P-glycoprotein inhibitors including cyclosporine, dronedarone, macrolide antibiotics (erythromycin, clarithromycin), or ketoconazole.⁵

The European Medicines Agency (EMA) approval of edoxaban was based on pivotal studies, including the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) and Hokusai VTE trials. The ENGAGE AF-TIMI 48 trial compared edoxaban with warfarin in 21 105 patients with atrial fibrillation, with a median 2.8 years of follow-up.⁶ Edoxaban was noninferior to warfarin for the prevention of stroke or systemic embolism, and caused less major bleeding events compared with warfarin, despite excellent time in therapeutic range in the warfarin arm. The Hokusai VTE trial compared edoxaban with warfarin in 8292 patients with deep vein thrombosis or pulmonary embolism after an initial treatment period with open-label enoxaparin or unfractionated heparin for at least 5 days. Edoxaban was noninferior to dose-adjusted warfarin for the prevention of recurrent VTE, and caused less major or nonmajor clinically relevant bleeding.⁷

The Edoxaban Treatment in routine clinical practice for patients with nonvalvular Atrial Fibrillation Europe (ETNA-AF-Europe) study was designed as part of the risk management plan of edoxaban in order to assess the risks and benefits of the drug in European patients with atrial fibrillation. The design of ETNA-AF-Europe study was agreed in close collaboration with the EMA as a single-arm prospective international observational study. The ETNA-AF-Europe registry is part of the global ETNA initiative, which is composed of three regional patient registries in Europe, East Asia, and Japan. The

ETNA-AF dataset is comparable with the earlier Prevention of thromboembolic events-European Registry in Atrial Fibrillation (PREFER in AF)⁸ and PREFER in AF Prolongation⁹ registries, and with the ENGAGE-TIMI 48 dataset. The aim of ETNA-AF-Europe study is to collect real-world data on the safety and efficacy of edoxaban in unselected patients with atrial fibrillation and to compare event rates with these potential comparator datasets.

Methods

Study design

The ETNA-AF-Europe study is a multinational, multi-center, postauthorization, observational study (ClinicalTrials.gov: NCT02944019) conducted at 852 sites from 10 European countries (Austria, Belgium, Germany, Ireland, Italy, The Netherlands, Portugal, Spain, Switzerland, and United Kingdom). The final ETNA-AF protocol was developed based on discussions with the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA, and finally approved by them. Patients will be followed up for 4 years. In line with a study collecting information in clinical routine, this observational study has broad inclusion and exclusion criteria (Table 1). Study protocol approvals were provided by Competent Authorities, and central and local Ethics Committees for each participating site in all countries involved.

Because the ETNA-AF-Europe study will be put into perspective with PREFER in AF and PREFER in AF Prolongation registries, only countries included in the PREFER registry program were allowed. Because the registry focuses on edoxaban, only countries in which edoxaban is currently reimbursed were selected.

The ETNA-AF-Europe study is part of the global ETNA program, which consists of regionally-sponsored and conducted registries, including those conducted in Japan, Europe, and South Central Asia. Each regional protocol is developed to optimally reflect the respective regulatory requirements of the regions, and therefore with specific differences, but harmonized concerning the core data to be collected. All regional core data will be therefore

Table 1 Inclusion and exclusion criteria in ETNA-AF-Europe, PREFER in AF, and ENGAGE AF-TIMI 48 studies

	ETNA-AF-Europe	PREFER in AF ⁸	ENGAGE AF-TIMI 48 ⁶
Inclusion criteria	Adult patients will be eligible for inclusion if: They provide written informed consent to participate, Are treated with edoxaban for AF according to the edoxaban summary of product characteristics, and Are not simultaneously participating in any interventional study	Adult patients were eligible for inclusion if: They gave written informed consent for participation in the registry They had a confirmed diagnosis of AF according to the 2010 ESC guidelines, ¹⁹ as documented by electrocardiography or an implanted pacemaker or defibrillator within the preceding 12 months Suspected, but unconfirmed, AF cases were not eligible	Adult patients were eligible for inclusion if They were aged ≥ 21 years and were able to provide written informed consent Had a history of AF documented by any electrical tracing within the prior 12 months and for which ACT is indicated and planned for the duration of the study Had a CHADS ₂ index score ≥ 2
Exclusion criteria	No other explicit exclusion criteria will be set to avoid selection bias and to allow documentation of routine clinical practice	No explicit exclusion criteria were defined in order to avoid selection bias and to achieve a cohort close to 'real life'	A long list of exclusion criteria were applied

ACT, anticoagulation therapy; AF, atrial fibrillation.

integrated into one global database, but will also be analyzed regionally.

Objectives and outcome measures

The primary objective of the study is to assess the real-world safety of edoxaban by evaluating bleeding events, including intracranial hemorrhage; drug-related adverse events, such as liver adverse events; and cardiovascular and all-cause mortality in atrial fibrillation patients treated with edoxaban up to 4 years, with regard to onset (relative to treatment with edoxaban) of the event, duration, severity, and outcomes. Events of special importance (major bleeding events, strokes, systemic embolic events, and deaths) will be adjudicated by an independent clinical event adjudication committee.

The results will be compared with existing datasets, namely the PREFER in AF and PREFER in AF Prolongation registries, and the ENGAGE AF-TIMI 48 trial dataset. These databases have used highly harmonized endpoint definitions, and will therefore provide comparative data for patients treated with other anticoagulants.

Secondary outcomes include the following:

- (1) Stroke (ischemic and hemorrhagic)
- (2) Systemic embolic events (SEEs)
- (3) Transient ischemic attack
- (4) Major adverse cardiovascular events (MACE), a composite endpoint of nonfatal myocardial infarction, nonfatal stroke, nonfatal SEE, and death due to cardiovascular cause or bleeding
- (5) VTE episodes
- (6) Acute coronary syndromes
- (7) Hospitalizations related to cardiovascular condition
- (8) Extent of exposure and compliance to edoxaban therapy, rate, and reasons of permanent discontinuation of edoxaban.

Results related to the secondary objectives will also be compared with external databases (PREFER in AF, PREFER in AF Prolongation and ENGAGE AF-TIMI 48 trial) along similar lines as for the data related to primary objectives. Findings from ETNA-AF-Europe after 1, 2, and 3 years, respectively, will be compared with results after 1 year (and 2 years, where applicable) from the PREFER in AF and the PREFER in AF Prolongation registries, and also with the results after 3 years from the ENGAGE AF-TIMI 48 trial.

Inclusion and exclusion criteria

Inclusion and exclusion criteria are listed in Table 1 alongside the criteria applied in the PREFER in AF registry and ENGAGE AF-TIMI 48 trial. Sites were required to complete a patient screening log of eligible patients for the registry at their treatment centers to assess the representativeness of the study population. Patients who discontinue edoxaban during the

observation period will be followed up annually for a further 2 years or until the end of the study, whichever comes first.

Study periods

The patient recruitment period is scheduled for 12 months, followed by a 48-month follow-up period per patient on edoxaban treatment. Documentation of patient data will be offered at five time-points: at baseline (at enrolment); at follow-up 1: 12 ± 2 months after baseline; at follow-up 2: 24 ± 2 months after baseline; at follow-up 3: 36 ± 2 months after baseline; and at follow-up 4: 48 ± 2 months after baseline (Fig. 1).

At baseline, the patients' medical and treatment history is collected. At each annual follow-up, changes in therapy and disease status since the last documentation will be recorded. At the time of the final assessment, the physician will be requested to enter the patient's vital status. It will be the responsibility of the investigators and their staff to enter all relevant patient data required for this study in the electronic case report form (eCRF) and patients' medical records. The final assessment will include date of final assessment, reason for final assessment (i.e. end of observational period reached – either 4 years or after two data collection points after discontinuation of edoxaban), withdrawal of consent, death, transfer to another institution, lost to follow-up), and intended further treatment for atrial fibrillation.

Patient memory aids are being distributed to patients to record all information throughout the year; these aids should support patients to recall important issues in the interval between two follow-up data collection points, as events will not trigger unplanned follow-up visits.

Definitions

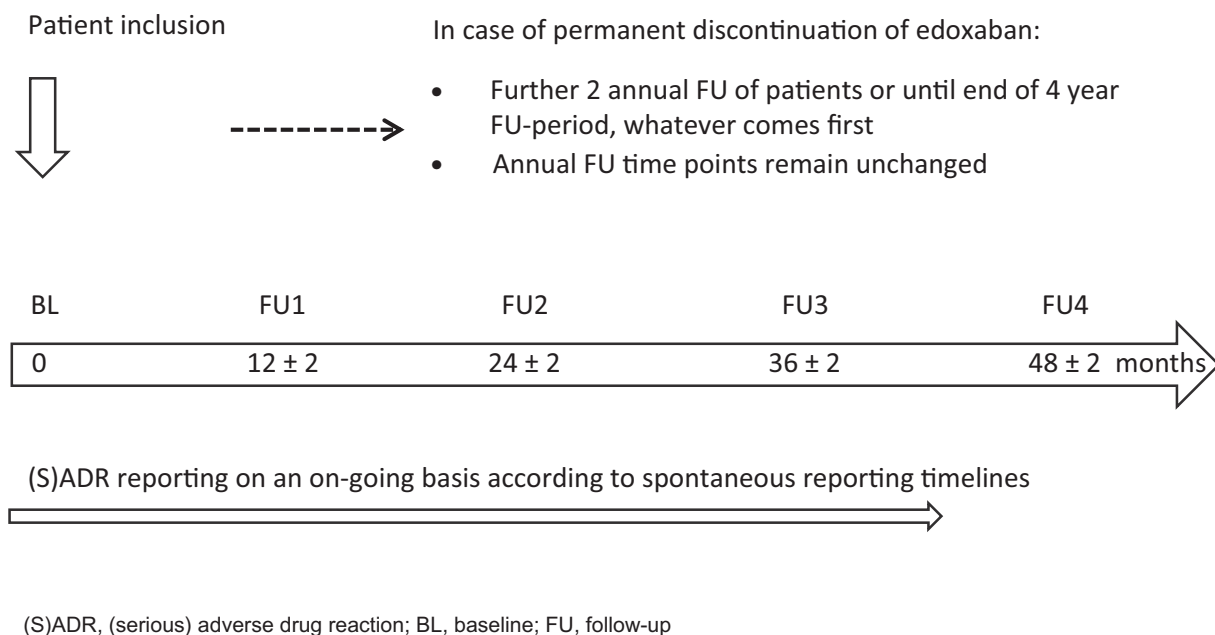
All variables in the ETNA-EU-Europe study are defined as closely as possible to those in the PREFER in AF registry program⁸ and ENGAGE AF-TIMI 48 interventional study⁶ to allow comparability of outcomes. A list of definitions is included in Supplementary Table S1 (<http://links.lww.com/JCM/A149>).

Site selection

About 1500 physicians (56.5% of hospital-based and 42.8% of office-based cardiologists, general practitioners, internists, and neurologists) are participating in the study. Different databases were used to identify a broad list of potential sites. At least three times the targeted number of active sites were contacted by sending a site qualification questionnaire to be completed.

A stepwise process for site selection was performed to allow representative regional distribution of sites and site specialties. Geographic representativeness within the country was maintained as sites were selected from each province and language region, where applicable. To

Fig. 1



Study schedule.

account for site characteristics representativeness, a ratio of 40% of cardiologists, 40% of general practitioners, and 20% of internal medicine and other specialists were specified per country. Site selection criteria are given in Table 2.

Considering that ETNA-AF-Europe is a noninterventional study, all prescriptions are solely at the discretion of the treating physicians.

Data collection

The scheduled documentation time-points are listed in Table 3. All data elements are being collected from information routinely recorded in the medical records. No additional visits or examinations, laboratory tests, or procedures are mandated as part of this study in line with the PRAC process not to influence routine clinical practice. Data from routine patient data collection points at

Table 2 Criteria for a site to be selected for participation in the study

Site selection criteria

The site should have access to patients with AF that may be treated with edoxaban
The site should be able to document the data in English language

The site should be able to complete the study in the electronic data capture system
The site should be able to conduct the study adequately, with enough time and staff to identify eligible patients, conduct the patient consent process, participate in required trainings, enter study data, and follow-up with study related activities

The site should agree to follow-up patients for a period of four years per patient according to clinical routine

AF, atrial fibrillation.

each respective site will be documented directly in the medical records and shortly thereafter updated in the eCRFs, which will be uploaded to the secure, internet-based Medidata Rave electronic data capture system.

Data management plan

The Medidata Rave EDC system will be used for data capture. Data will be collected in standardized English eCRFs. A data management plan will be created in the study start phase and will describe all functions, processes, and specifications for data collection, cleaning, and validation. The data validation includes programmed edit checks and manual checks of the following:

- (1) Checks for missing and/or incomplete data
- (2) Checks on nonconformance (e.g. a nonexistent date or a numeric field including text)
- (3) Range checks on numeric fields (e.g. a field that has to be greater than x but lower than y)
- (4) Checks for missing values (e.g. a predetermined required field)
- (5) Checks for future dates
- (6) Checks across different data items within one CRF module, between CRF modules, across visits on consistency of documentation.

Quality control

The study is being conducted according to the Good Pharmaco-epidemiology Practice and Guideline on good pharmacovigilance practices (Module VIII EMA/813938/

Table 3 Time points for data collection

	Baseline	FU1	FU2	FU3	FU4
CRFs					
Date	X	X	X	X	X
Eligibility	X				
Demographics	X				
Physical examination					
Vital signs (BP, HR, height, and weight)	X	X	X	X	X
AF disease					
Medical history (relevant comorbidities)	X				
Disease history (first diagnosis, events) ^a	X				
AF diagnosis as available ^a	X	X	X	X	X
Laboratory parameters as available	X	X	X	X	X
AF symptoms	X	X	X	X	X
AF related clinical events and hospitalisations ^b	X	X	X	X	X
AF-related interventions ^a		X	X	X	X
AF therapy					
AF-related previous therapy (medications, interventions) ^c	X				
Edoxaban therapy (history/current/since last data collection point) ^c	X	X	X	X	X
Nonedoxaban AF-related therapy	X	X	X	X	X
Physician judgement on compliance to edoxaban therapy ^d	(X) ^e	X	X	X	X
ADR reporting for edoxaban	Continuously				
Final assessment ^f	At final FU or early study termination				

ADR, adverse drug reaction; AF, atrial fibrillation; BL, baseline; BP, blood pressure; CRFs, case report forms; FU, follow-up; HR, heart rate. ^aType of AF, date of first diagnosis, symptoms at first diagnosis and current, ECHO; type of interventions, date and number of interventions. ^bEvent date, type, location if applicable, severity, outcomes of stroke, transient ischaemic attack, other bleeding events, acute coronary syndrome, chronic heart failure, systemic embolism, venous thromboembolic event, malignancies, others. ^cPast and current therapy; start and stop dates, dosage and frequency. ^dOptional data, reported by investigator and patient. ^eIf patient is not edoxaban naïve. ^fThe final assessment includes date of final assessment, reason for final assessment [i.e. end of observational period reached (either 4 years or after two data collection points after discontinuation of edoxaban), withdrawal of consent, death, transfer to another institution, lost to follow-up] and intended further treatment for AF.

2011 Rev 1). Related quality control mechanisms, including data plausibility checks and monitoring of data, will be performed accordingly. Onsite monitoring is being performed in randomly selected sites (30%) including 100% check of informed consents and source data verification of up to three patients per visited site. Remote quality checks will be done using both automated and manual queries. Data quality checks will be performed on an ongoing basis. Particular attention will be given to the completeness and correctness of safety data. These processes are homologous to the quality control in PREFER in AF.

Sample size calculations

The sample size calculations are based on the incidence rate of intracranial hemorrhages (ICHs), as this has the lowest incidence amongst the event rates of interest (major bleeding, ischemic stroke, and ICH). Taking the real-life situation into account, the event rate for ICH was assumed at 0.35% per year. Over 4 years, this results in a rate of 1.4%. To estimate the 95% confidence interval (CI) with a precision range from $\pm 0.25\%$ for the rate at 1.4% (corresponding to a relative precision of 17.8%), 8485 patients are needed. Assuming a dropout rate of approximately 35% over the 4 years, approximately 13 100 patients were estimated as needed to be enrolled for a reasonable estimation of the event rate.

To increase the study power for the primary safety analysis and to address the spectrum of indications for edoxaban, the ETNA-AF-Europe data will be combined with the safety data from the parallel edoxaban study

ETNA-VTE-Europe, which plans to recruit 2700 patients to be followed up for 18 months.¹⁰ Together, these studies will enroll approximately 15 800 patients, with a combined expected 18-month dropout rate of 20%. Consequently, data for approximately 12 640 patients should be available at 18 months to assess the incidence rates of interest [i.e. major bleeding, mortality and adverse drug reactions (ADRs)]. This combined analysis should provide sufficient statistical power to capture uncommon ADRs with low incidence rates. For example, for those with incidence rates between 0.1 and 1.0%, the corresponding 95% CIs will range between ± 0.06 and 0.17%.

Statistical analysis

All analyses will be defined prospectively in a statistical analysis plan. The following analyses are planned: a final analysis of ETNA-AF-Europe; a comparison of ETNA-AF-Europe with the results of the PREFER in AF and the ENGAGE AF-TIMI 48 datasets; a combined safety analysis of ETNA-AF-Europe and ETNA-VTE-Europe based on the 18-month safety data of both the studies. Five data snapshots will be performed after approximately 1, 2, 3, and 4 years of mean enrolment: quarter (Q) 4 2017, Q4 2018, Q4 2019, Q4 2020, and Q4 2021.

All computations and generations of tables will be performed using the SAS version 9.3 or higher (SAS Institute, Cary, North Carolina, USA). Exploratory/descriptive statistics will be used to perform the analyses. Categorical variables will be summarized by the number and percentage (%) of patients in each category.

Continuous variables will be summarized using number of nonmissing/missing observations, mean, standard deviation (SD), median, first and third quartile, and minimum/maximum values. The 95% CIs will also be provided for selected variables. Whenever applicable, Kaplan–Meier analysis will be performed to illustrate risk over time.

Time-to-event variables will be analyzed by a Cox proportional-hazard regression model, presenting hazard ratios, and corresponding 95% CIs and *P* values for comparisons of the predefined subgroups. All Cox models will include the CHA₂DS₂-VASc score as an additional covariate. Based on the results in the PREFER in AF registry program and the ENGAGE AF-TIMI 48 trial, no further confounders are considered upfront. Nevertheless, if any relevant differences in baseline characteristics are detected, these variables will be added to the model as additional covariates.

All comparisons between ETNA-AF data and the data from the PREFER in AF disease registry program and the contextualization of outcomes versus ENGAGE AF-TIMI 48 trial will be explorative.

Study status

The enrolment started in May 2015 in Switzerland and in August 2015 in Germany; however, in agreement with the newly formed PRAC, it was stalled to integrate the input from PRAC. The study protocol was revised according to the guidance received from the PRAC, mandated by changes in EMA legislation and a revised PRAC process that was notified in July 2015. This process delayed enrollment by approximately 1 year. Patient enrollment resumed in Germany, Ireland, The Netherlands, Switzerland, and United Kingdom in November 2016, and in Austria, Belgium, Italy, Portugal, and Spain in Q1 of 2017.

Discussion

The ETNA-AF-Europe and the global ETNA program will provide ‘real-world’ efficacy and safety data on edoxaban use in a wide range of European countries and diverse clinical settings mandated by EMA. Findings from this registry will complement the results of pivotal trials through the use of unselected real-world patient population. The design of ETNA-AF-Europe study will be put into perspective with the data from the PREFER in AF and PREFER in AF Prolongation registries, with highly harmonized sites and methods of data collection. Because the PREFER registries enrolled patients treated with a range of oral anticoagulants, analyses on different treatments including NOACs, VKAs, and antiplatelet agents as monotherapy or in combinations (for Europe and per country) can be conducted. In addition, the results obtained in the ETNA-AF-Europe study will be put in relation with the results of the ENGAGE AF-TIMI 48 study to reflect similarities and differences between noninterventional and interventional settings of

the two studies. These will include the discontinuation rates experienced in the PREFER in AF registry and ENGAGE AF-TIMI trial, which may be useful for a comparison with the real-life patient adherence in the ETNA-AF registry. In all, the variables and approaches used for ETNA-AF-Europe are defined as close as possible to the ones used in PREFER in AF/ENGAGE AF-TIMI 48 and as feasible in a noninterventional trial to allow a meaningful comparison.

In addition, the design of the Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation (XANTUS) study was also taken into consideration while designing ETNA-AF-Europe.¹¹ The XANTUS study – a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation – was similar in design (noninterventional, nonrandomized, single-arm postauthorization safety study) and size (~7000 patients), and investigated similar objectives, namely the safety and efficacy of rivaroxaban in a real-world setting.

Collection of real-world data for anticoagulants, as for any new drug in general, is vital because of the need for obtaining valuable information additional to what is collected in the setting of clinical trials. The latter select patients using stringent inclusion and exclusion criteria, and patients are followed up very closely to ensure adherence to drug regimens, which does not occur once the drug is released in the market. In addition, the spectrum of patients effectively treated once the drug is released in the market is wider than that used in the registered trials, because of the off-label use for a variety of patients.

Regarding oral anticoagulants, many countries are seemingly on the verge of a large shift from VKAs to NOACs as the preferred choice for thrombosis prophylaxis, with NOACs now being highly adopted into practice and already becoming prescribed more frequently than VKAs.^{12,13} Notably, data available from other registries, such as Global Anticoagulant Registry in the FIELD–Atrial Fibrillation¹⁴ and Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation,¹⁵ have provided insights into the evolution of global anticoagulation practice and the increasing use of NOACs. This raises important questions that can only be addressed in datasets that are close to routine practice, for example, attrition and discontinuation rates on therapy, adequacy of dosing and relationship of inadequate dosing to outcomes, and regional patterns of NOAC use, including effects of different healthcare systems and socioeconomic environments. Initial data from Europe suggest that the treatment benefits of NOAC therapy are preserved in routine care.^{11,16–18} The ETNA-AF-Europe study will further contribute important information on the management of atrial fibrillation patients in routine care, NOACs in general, and the risks and benefits associated with edoxaban.

The strengths of the ETNA-AF-Europe noninterventional registry include the prospective design, large sample size, inclusion of patients from different clinical settings, predefined endpoints, rigorous data collection, prolonged follow-up, and that it ‘nests’ within a global registry program with harmonized outcome definitions. The independent adjudication of events of special importance is expected to reduce reporting and misclassification bias. While the PRAC process delayed the start of ETNA-AF, the stringent planning will add to the quality of the data coming from its analysis.

Some limitations common to noninterventional studies are, however, present, mostly related to the nonrandomized nature of the study. Because patients treated with edoxaban before baseline, but not receiving the drug at baseline, are not eligible for inclusion in this study, a possible ‘selection bias’ of patients cannot be excluded. However, it must be noted that this bias cannot be excluded in any other noninterventional study focusing on a new drug category, including all registries with NOACs. For the success of the study, it is vital that all sites have sufficient recruitment capability, the capacity to participate in this postauthorization observational study, and are then able to follow-up patients for 4 years. Due to the long time between two data collection points, it is possible that some data may be under-reported by participating patients, or there may be potential chances of misclassification of treatment changes and concomitant drug exposure. However, this risk is considered to be low, as relevant treatment changes are usually precisely documented in medical records, the eCRF, and often in patient memory aids. Finally, there will be a need to take the regional differences into consideration while evaluating the persistence of edoxaban.

Conclusions

The ETNA-AF-Europe registry will provide valuable data on the real-world use of edoxaban in Europe. Moreover, the safety of edoxaban and some clues to its efficacy in the general population of atrial fibrillation patients will be assessed over a period of 4 years. International trends of edoxaban usage and persistence may be of interest and may determine the value of the latest once a day NOAC to be approved for stroke prevention in patients with AF.

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References

- Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 study. *Circulation* 2014; **129**:837–847.
- Lane DA, Skjoth F, Lip GYH, Larsen TB, Kotecha D. Temporal trends in incidence, prevalence, and mortality of atrial fibrillation in primary care. *J Am Heart Assoc* 2017; **6**; doi: 10.1161/JAHA.116.005155.
- Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016; **18**:1609–1678.
- Chugh SS, Roth GA, Gillum RF, Mensah GA. Global burden of atrial fibrillation in developed and developing nations. *Glob Heart* 2014; **9**: 113–119.
- European Medicines Agency. Lixiana: summary of product characteristics. 2015. Available from: https://www.ema.europa.eu/documents/product-information/lixiana-epar-product-information_en.pdf. [Accessed 2 November 2018]
- Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369**:2093–2104.
- Buller HR, Decousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013; **369**:1406–1415.
- Le Heuzey JY, Ammentorp B, Darius H, et al. Differences among western European countries in anticoagulation management of atrial fibrillation. Data from the PREFER IN AF registry. *Thromb Haemost* 2014; **111**: 833–841.
- Purmah Y, De Caterina R, Le Heuzey J-Y, et al. Evolution of symptoms, rate, and rhythm control therapy in AF patients in Europe: a comparison of the PREFER in AF and PREFER in AF prolongation data sets. *Eur Heart J* 2016; **37**:287; (abstract supplement) Abstract: P1533.
- Edoxaban Treatment in Routine Clinical Practice in Patients With Venous Thromboembolism in Europe (ETNA-VTE: NCT02943993). Clinicaltrials.gov: U.S. National Library of Medicine. <https://clinicaltrials.gov/ct2/show/NCT02943993?id=NCT02943993&rank=1>. [Accessed 12 December 2017]
- Camm AJ, Amarencu P, Haas S, et al. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J* 2016; **37**:1145–1153.
- Steinberg BA, Shrader P, Thomas L, et al. Factors associated with nonvitamin K antagonist oral anticoagulants for stroke prevention in patients with new-onset atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II). *Am Heart J* 2017; **189**:40–47.
- Huisman MV, Rothman KJ, Paquette M, et al. The changing landscape for stroke prevention in AF: findings from the GLORIA-AF Registry phase 2. *J Am Coll Cardiol* 2017; **69**:777–785.
- Ten Cate V, Ten Cate H, Verheugt FW. The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF): exploring the changes in anticoagulant practice in patients with nonvalvular atrial fibrillation in the Netherlands. *Neth Heart J* 2016; **24**:574–580.
- Huisman MV, Lip GY, Diener HC, et al. Design and rationale of Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation: a global registry program on long-term oral antithrombotic treatment in patients with atrial fibrillation. *Am Heart J* 2014; **167**: 329–334.
- Lip GY, Laroche C, Popescu MI, et al. Improved outcomes with European Society of Cardiology guideline-adherent antithrombotic treatment in high-risk patients with atrial fibrillation: a report from the EORP-AF General Pilot Registry. *Europace* 2015; **17**:1777–1786.
- Boriani G, Proietti M, Laroche C, et al. Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: a report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry. *Europace* 2018; **20**:747–757.
- Steinberg BA, Gao H, Shrader P, et al. International trends in clinical characteristics and oral anticoagulation treatment for patients with atrial fibrillation: results from the GARFIELD-AF, ORBIT-AF I, and ORBIT-AF II registries. *Am Heart J* 2017; **194**:132–140.
- Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010; **31**:2369–2429.