Received: 23 May 2018 | Revised: 24 July 2018 | Accepted: 25 July 2018

DOI: 10.1002/clc.23037

PREVENTION WILEY CLINICAL CARDIOLOGY

TRIAL DESIGNS

Edoxaban Management in Diagnostic and Therapeutic Procedures (EMIT-AF/VTE)—Trial design

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Non-vitamin K dependent oral anticoagulants (NOAC) are now widely used in patients with nonvalvular atrial fibrillation (NVAF) for stroke prevention and in patients with venous thromboembolism (VTE) for the treatment and secondary prevention of the disease. Among NOAC, edoxaban demonstrated noninferiority to warfarin for stroke prevention in NVAF and for VTE treatment, with superior safety. EMIT-AF/VTE (Edoxaban Management in Diagnostic and Therapeutic Procedures) (NCT02950168) is a multicenter, prospective, and noninterventional registry study designed to collect detailed information on the periprocedural management of patients with NVAF and VTE receiving edoxaban. The primary objective of EMIT-AF/VTE is to document the periprocedural management of patients receiving edoxaban and to collect data on safety and other outcomes in these patients. The primary safety outcome is the rate of major bleeding. Other assessments include the evaluation of efficacy outcomes, periprocedural dosing, and timing of edoxaban. The observation period will start 5 days prior to the procedure and end 30 days post-procedure. EMIT-AF/VTE will aim to prospectively enroll up to approximately 1400 procedures from Europe. Enrollment commenced in December 2016 and will be completed in July 2018. As of July 2018, before database lock and with several procedure forms still temporarily inserted, a preliminary number of 1204 patients have been enrolled, who underwent a total of 1453 procedures. The prospective EMIT-AF/VTE registry program will expand the knowledge of periprocedural management of patients with NVAF and VTE receiving edoxaban in clinical practice.

KEYWORDS

bleeding, edoxaban, non-vitamin K antagonist oral anticoagulants, oral anticoagulation, periprocedural management

1 | INTRODUCTION

Non-vitamin K dependent oral anticoagulants (NOAC) are increasingly used in patients with nonvalvular atrial fibrillation (NVAF) for stroke prevention and in patients with venous thromboembolism (VTE) for the treatment and secondary prevention of the disease. NOAC administration is a long-term treatment for the majority of these patients.[1,2]

Annually, at least 10% of patients receiving anticoagulation therapy undergo diagnostic and therapeutic procedures.[3] The bleeding risks of these procedures vary from minimal (eg, colonoscopy) and minor (eg, phacoemulsification) to high (eg, major surgery). Given the wide range in bleeding risk and the plethora of therapeutic options for anticoagulation, including vitamin K antagonists (VKAs), heparin, and NOAC, different treatment recommendations will inevitably emerge.[1,4]

Bridging with low-molecular-weight heparin (LMWH) could benefit patients receiving VKAs due to the late onset of action of VKAs and its long-lasting anticoagulation effect following discontinuation; however, in patients receiving NOAC, bridging with LMWH may be associated with

higher risks of bleeding.[4] The short half-lives of NOAC of 5 to 15 hours and their rapid onset of action with maximum plasma concentrations achieved in 1 to 4 hours after administration may allow for brief periods of treatment interruption without the need for heparin bridging.[5–7] Current evidence suggests that if the bleeding risk is low to intermediate, interruption of anticoagulation therapy may not be necessary.[8] On the other hand, in patients receiving NOAC undergoing procedures with intermediate to high bleeding risk, data on safety and management of anticoagulation therapy are still limited.[5,7,8] Secondary analyses of the safety and efficacy of NOAC in patients enrolled in the phase 3 studies who underwent procedures have been reported on several thousands of patients and events (Table 1). However, these secondary analyses are limited by the paucity of detailed information on management of patients who undergo invasive diagnostic/therapeutic procedures, and are retrospective and do not allow for any causality to be established between drug management and endpoint.[8–10] On the other hand, the advantages of prospective studies specifically addressing this question are typically hampered by smaller patient numbers.[5,7]

Among NOAC, edoxaban—a direct factor Xa inhibitor—demonstrated noninferior efficacy to warfarin for stroke prevention in NVAF and for VTE treatment/secondary prevention and was associated with significantly reduced major or clinically relevant nonmajor (CRNM) bleeding rates.[11,12] Currently, periprocedural management data are only available from post hoc analyses of edoxaban[13]; therefore, there is the need for prospective outcomes information. The EMIT-AF/VTE (Edoxaban Management in Diagnostic and Therapeutic Procedures) study (NCT02950168) is designed to prospectively collect detailed information on the periprocedural management of patients receiving edoxaban in its approved indications, with an emphasis on patients undergoing major surgical procedures at increased risk of bleeding.

2 | METHODS

2.1 | Study design and objectives

EMIT is a multicenter, prospective, and noninterventional study conducted in Europe (NCT02950168). Several prespecified sub-analyses will include stratification by country, by specialty of procedure (separate analysis for dentistry, ophthalmology, cardiothoracic and cardiac surgery, gastrointestinal), by under- or overdosing of edoxaban, by emergency vs planned procedure, by patients with single or multiple procedures, by type of VTE, and by type of AF (paroxysmal, persistent, or permanent). There have been no major protocol amendments since the first patient was enrolled.

This study was funded by Daiichi Sankyo, Inc. Assistance in editorial support for this manuscript was provided by AlphaBioCom, LLC (King of Prussia, Pennsylvania), and funded by Daiichi Sankyo, Inc. All authors materially participated in the design and/or drafting and editing of the paper and approved its final content. The Executive Committee is responsible for the study design, conduct, and supervision. The Steering Committee, in addition to supporting the Executive Committee in the overall oversight of the study, assures the study's implementation to optimize the quality of the data and study integrity. The steering Committee will make the decision to submit the paper for publication, and that the funding source has no role in this decision. See Appendix S1 (Supporting information) for the listing members of the Executive and Steering Committees, as well as the Principal Investigators.

The primary objective of this registry is to document the periprocedural management of patients receiving edoxaban and to collect data on safety and other outcomes in these patients. The primary safety outcome is the rate of major bleeding from 5 days prior to the

TABLE 1 Key published data from subanalyses of phase 3 trials on the periprocedural management of patients with the indication for chronic oral anticoagulation therapy

Name Oral anticoagulant	RE-LY[9] Dabigatran vs warfarin	ARISTOTLE[8] Apixaban vs warfarin	ROCKET AF[10] Rivaroxaban vs warfarin	ENGAGE AF-TIMI 48[13] Edoxaban vs warfarin
Published (year)	2012	2014	2014	2015
Type of analysis and study design	Prespecified subanalysis from phase 3 RCT	Prespecified subanalysis from phase 3 RCT	Post hoc subanalysis from phase 3 RCT	Prespecified subanalysis from phase 3 RCT
Number of procedures by drug and dose	1487 (D110 mg) 1546 (D150 mg); 1558 (W)	4679 (A); 4581 (W)	1297 (R); 1683 (W) for procedures	2379 (E60 mg); 2446 (E30 mg); 2368 (W)
CrCL reflected in analyses	Yes	Yes	Unknown[a]	N/A
"No interruption" defined	No	Yes	No	Yes
Unit of time from last dose until procedure	Hour/Day	Day	N/A	Day
Unit of time to first dose after procedure	N/A	N/A	N/A	N/A
Periprocedural bridging by drug and dose (%)	15.3 (D110 mg) 17.0 (D150 mg); 28.5 (W)	11.7 (A); 11.7 (W)	8.2 (R); 4.9 (W)[b]	N/A
Definition of major procedure	Procedures lasting >1 hour	Required general anesthesia	N/A	N/A
Major procedures by drug and dose (%)	31.8 (D110 mg) 33.1 (D150 mg); 32.0 (W)	10.2	N/A	N/A
Unscheduled surgeries by drug and dose (%)	7.2 (D110 mg); 9.1 (D150 mg); 7.1 (W)	2.9	N/A	N/A

Abbreviations: A, apixaban; CrCL, creatinine clearance; D110 mg, dabigatran 110 mg; D150 mg, dabigatran 150 mg; E30 mg, lower-dose edoxaban regimen (30/15 mg); E60 mg, higher-dose edoxaban regimen (60/30 mg); N/A, not applicable; RCT, randomized controlled trial; W, warfarin.
[a] Among patients with temporary interruption of therapy.
[b] Information available for patients with temporary interruption of therapy.

procedure to 30 days postprocedure using the International Society of Thrombosis and Hemostasis (ISTH) definition[14,15] (Table S1). Other safety outcomes include the rates of CRNM bleeding, minor bleeding, all bleeding, and death from any cause. CRNM bleeding events are defined as overt bleeding that requires medical attention and that does not fulfill the criteria for a major bleeding event. A complete list of all procedures divided by European Heart Rhythm Association bleeding risk are listed in **Table S2**.

Secondary objectives include the evaluation of the periprocedural dosing of edoxaban and the efficacy outcome, defined as the composite of acute coronary syndrome, nonhemorrhagic stroke, transient ischemic attack (TIA), systemic embolic events (SEE), deep vein thrombosis (DVT), pulmonary embolism (PE), and cardiovascular (CV) mortality, and its individual components. The additional parameters recorded during the observational period are listed in Table S3.

The observation period of the study will start 5 days prior to the procedure and end 30 days postprocedure in all patients. The study design is shown in Figure 1. Since this is a noninterventional study, only data on routine clinical practice will be documented. In order to enhance the quality of data by capturing important details of the diagnostic and therapeutic procedures, and medication adherence/compliance, patients may will receive a memory aid (a booklet to complete) at enrollment into the study. This booklet is the basis of data capturing during the follow-up phone call at 30 days.

2.2 | Patient population and eligibility

EMIT is planned to include approximately 1400 procedures from Europe (Belgium, Germany, Italy, the Netherlands, Spain, Portugal, and the UK). Enrollment and data collection commenced in December 2016 and will complete in July 2018. As of July 2018, before database lock and with several procedure forms still temporarily inserted, a preliminary number of 1204 patients were enrolled, who underwent a total of 1453 procedures.

Patients ≥18 years of age will be eligible to enroll if they have AF or VTE treated with edoxaban, according to local label, prior to enrollment into this registry, with a scheduled or unscheduled diagnostic/therapeutic procedure (see Table **S2** for full listing of procedures), and if they are not enrolled in any other interventional study. Multiple procedures are allowed if they are at least 31 days apart, allowing for a clear attribution of events to a procedure. Patients in the elective surgery/procedure group may or may not have interruption of edoxaban. Since EMIT is enrolling prospective unselected patients, an exclusion list was not planned.

2.3 | Assessments

Baseline demographics and clinical characteristics including age, gender, and comorbidities will be recorded for all patients. Concomitant medications, bleeding risk, HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly) score, CHA_2DS_2-VASc (Cardiac failure, Hypertension, Age ≥ 75 [doubled], Diabetes, Stroke [doubled]-Vascular disease, Age 65-74 years, and sex category [female]) score, details of edoxaban treatment, diagnostic/therapeutic procedures, and clinical outcomes will be documented at baseline and updated with any new information for each procedure recorded. Date of visit, details of edoxaban treatment, and clinical outcomes will be documented at 30 days after each procedure.

All safety measures that occur between enrollment and final follow-up will be recorded. These include major, CRNM, minor, and all bleeding, and death from any cause. Similarly, all efficacy measures—which include acute coronary syndrome, nonhemorrhagic stroke, TIA, SEE, DVT, PE, and CV mortality—will be recorded.

2.4 | Data management

All clinical data will be documented using the Medidata Rave Electronic Data Capture system (New York, New York). In the start-up phase, a data management plan has been created that describes all functions, processes, and specifications for data collection, cleaning, and validation. Automated plausibility checks at data entry are performed to obtain immediate feedback if data are missing, out of range, illogical, or potentially erroneous allowing for correction

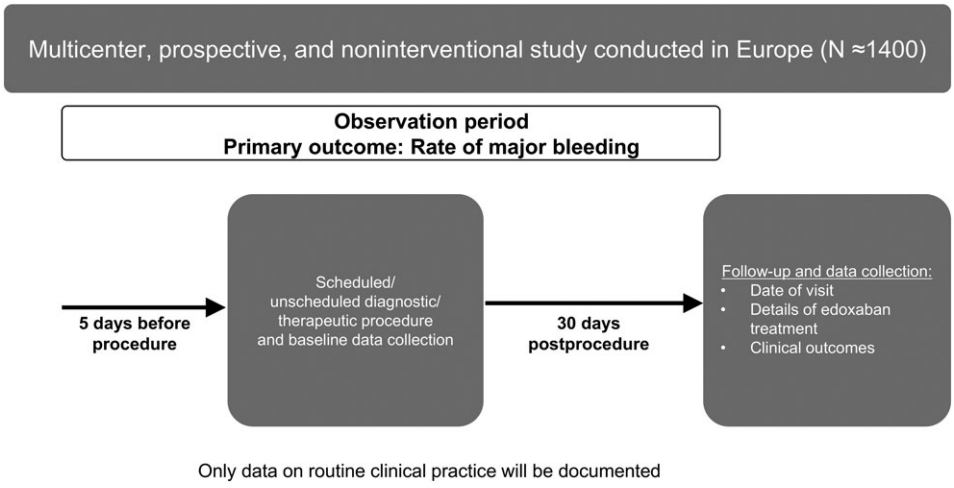

FIGURE 1 Design of the EMIT registry program. This flow chart will be repeated for any further procedures for a patient

or confirmation by the site. Concurrent manual data review will also be performed based on parameters defined in the data management plan.

2.5 | Sample size estimation

EMIT intends to document 1415 procedures within Europe, acknowledging regional therapeutic practices. This assumption is based on recent published data from the Dresden NOAC registry investigating the periprocedural management of NOACs in daily care.[5] In this registry, 2179 patients were enrolled. A total of 595 (27.3%) patients underwent 863 surgical or therapeutic procedures. Ten major bleeding complications (1.2%) occurred during the follow-up period of 30 ±5 days. Another cohort study reported 10 major bleedings (1.8%) in 541 procedures occurring during the 30-day follow-up.[7]

The sample size estimation for EMIT is based on the rate of major bleeding at 30 days and is assumed to be 1.5% based on the above studies. To estimate the 95% confidence interval (CI) with an acceptable precision range, the width of confidence limit should be half of the above expected rate of major bleeding, less than 0.75%. Therefore, the Executive Committee set the distance from proportion to limit as 0.65%, less than the acceptable 0.75%, with a calculated sample size of 1344 procedures. Assuming a 5% dropout rate, 1415 procedures should allow for a reasonable estimation of the event rate.

It should be noted, that the 1.5% bleeding rate is based on NOAC-treated patients who had an elective not urgent surgery/procedure. In urgent surgery the incidence of bleeding may be higher.

2.6 | Statistical analysis

Binary, categorical, and ordinal parameters will be summarized by means of absolute and percentage numbers. Numerical data will be described by standard statistics. The statistical analyses will be performed using SAS version 9.3 or higher (SAS Institute, Cary, North Carolina). Two-sided 95% CI and/or *P* values will be presented for important parameters. Additional selection criteria for patients (eg, subgroup analyses) will be considered for variables of interest, if arising as useful during the statistical analyses. The purpose of all analyses will be descriptive and exploratory.

2.7 | Quality control and ethics

Data quality checks will be performed on a regular basis to ensure that the patient rights are protected, the reported data are accurate and complete, and the conduct of the study is in compliance with the observational plan and regulatory requirements. The study will be conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practice, Good Pharmacovigilance Practices, and the ethical principles specified in the Declaration of Helsinki. Informed consent will be obtained from the participants prior to enrollment.

All study sites will be remotely monitored and there will also be on-site monitoring in 17% of randomly selected study sites; the monitor will verify 100% of informed consent documentation and perform source data verification against the patient's medical records in randomly selected patients (three per site). Particular attention will be paid to the completeness and correctness of safety data during monitoring activities.

3 | DISCUSSION

Annually, approximately 10% of patients receiving anticoagulation therapy undergo diagnostic or therapeutic procedures.[3] Nevertheless, many large prospective registries such as GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment In Patients With Atrial Fibrillation),[16] and GARFIELD-AF (The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation),[17] did not systematically collect any efficacy and safety data on periprocedural management of anticoagulation therapy. In ORBIT AF (The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) a comparison between bridged and nonbridged patients was previously reported.[18] Subanalyses of the large phase 3 studies of NOAC have provided insight into the topic[8–11] (Table 1); however, extrapolation to medical practice is limited. Recognizing the differences between clinical study protocol-driven and real world daily medical practice-driven oral anticoagulant treatment decisions, researchers have initiated a series of prospective registries and controlled studies (Table 2).

To fill the data gap on periprocedural management of patients on edoxaban, the ongoing EMIT study was devised. It is the first international, prospective, and noninterventional study of patients receiving edoxaban designed to document the periprocedural management by analyzing the safety of edoxaban according to different classifications of periprocedural bleeding risk. EMIT will provide precise information useful to national and international guidelines. A key objective of EMIT is to obtain information on routine clinical practice from diverse medical care institutions such as primary and secondary care centers across all medical specialties and, thus, to identify possible treatment challenges in real world patient care. One particular focus of the study will be high-bleeding-risk procedures, which lack data from previous post hoc analyses, published studies, or registries. Another focus of the study will be to analyze the extent to which renal function might affect preprocedural discontinuation of the drug. Hence, the study will capture the period of edoxaban interruption (ie, the hours elapsed from the last dose to the procedure and from the procedure to the first dose thereafter). Determination of creatinine clearance as calculated by the Cockroft-Gault formula will clarify whether edoxaban was dosed according to the dose reduction criteria as described in the Summary of Product Characteristics.

Other observational studies have also addressed, or are planning to address, the periprocedural management of patients with the indication for oral anticoagulation therapy. The Dresden NOAC registry reported efficacy and safety data on NVAF, DVT, or PE patients treated with NOAC prospectively.[5] Relevant efficacy and safety data and information on the periprocedural management of anticoagulant therapy—including interruption of NOAC treatment, possible bridging, and restart of NOAC administration—were collected from 5 days before to 30 days after the procedure. According to the American

TABLE 2 Key published data from pivotal observational studies on the periprocedural management of patients with the indication for chronic oral anticoagulation therapy

Name	Perioperative dabigatran study[7]	Dresden registry[5]	PAUSE	EMIT
Published (year)	2015	2014	Recruiting (NCT02228798)	Recruiting (NCT02950168)
Oral anticoagulant	Dabigatran	NOAC	Dabigatran, rivaroxaban, or apixaban	Edoxaban
Study design	Prospective cohort study	Prospective registry	Prospective cohort study	Prospective registry
Number of procedures	541	863	3291 (target sample size)	2000 (target sample size)
CrCL reflected in analyses	Yes	N/A	Yes	Yes
"No interruption" defined	No	Yes	Only patients who required treatment interruption were studied	Yes
Units of time from last dose until procedure	Day	N/A	Unknown	Hour
Unit of time to first dose after procedure	Hour/Day	N/A	Unknown	Hour
Periprocedural bridging (%)	1.7	29.8	Ongoing	Ongoing
Definition of major procedure	Investigator's judgment based on prespecified procedures with high risk of bleeding	Bleeding risk categories per ACCP and EHRA guidelines	Ongoing	Ongoing
Major procedures (%)	40.1	10.1	Ongoing	Ongoing
Unscheduled surgeries (%)	0	N/A	0	Ongoing

Abbreviations: ACCP, American College of Clinical Pharmacology; CrCL, creatinine clearance; EHRA, European Heart Rhythm Association; N/A, not applicable; NOAC, non-vitamin K oral anticoagulants.

College of Chest Physicians guidelines ninth edition[14] and the European Heart Rhythm Association Practical Guide,[19] the categories of minimal, minor, and major procedures were created. Major procedures are procedures with relevant tissue trauma and high bleeding risk such as open pelvic, abdominal, thoracic, brain, major orthopedic, or vascular surgery. Similarly, a Canadian prospective cohort study was conducted to evaluate the safety of periprocedural management of dabigatran.[7] The protocol specified the time points as the last dose before the procedure, the first dose after the procedure, and the time of the procedure. This specification was based on patients' creatinine clearance with the corresponding estimated half-life of dabigatran and procedure-related bleeding risk. The timing and dosing resumption of dabigatran after procedure was recommended according to patients' bleeding risk, which was classified as "high" or "standard." The study demonstrated that perioperative dabigatran administration was safe, as reflected by the low rate of major bleeding. However, it is not possible to extrapolate these results to any other NOAC since they have different pharmacokinetic profiles.

The ongoing PAUSE (Perioperative Anticoagulant Use for Surgery Evaluation) study (NCT02228798) includes AF patients who receive either dabigatran, rivaroxaban, or apixaban. Edoxaban was not included in the study, since it became available in Canada after the study had started enrolling. The objective of this study is to establish a safe and standardized perioperative management approach for NOAC in AF patients undergoing elective surgeries/procedures. The perioperative protocol of each NOAC is adjusted based on patients' renal function and procedure-related bleeding risk.

In addition to postmarketing registries of NOAC, the BRIDGE (Bridging Anticoagulation in Patients Who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery) trial randomized NVAF patients after perioperative interruption of warfarin therapy to receive bridging therapy with dalteparin or matching placebo.[20] Warfarin treatment was stopped 5 days before procedure and dalteparin (100 IU/kg administered subcutaneously twice daily) was started 3 days before procedure. Outcomes were observed for 30 days after the procedure. The primary outcomes were arterial thromboembolism and major bleeding as defined by the ISTH criteria[14] (see Table S1). The limitations of this study encompass the need for a full therapeutic dose of dalteparin starting early after surgery, the overlap with the restart of warfarin, and the small percentage of patients undergoing high-risk procedures. Moreover, the definition of high-risk surgeries per se is questionable since these included procedures that usually do not have a high risk of bleeding (eg, pacemaker or internal defibrillator insertion, biopsy of kidney or prostate, and any other procedure lasting ≥1 hour).

In patients with AF receiving edoxaban, periprocedural adverse outcomes are available from a prespecified post hoc subanalysis from the ENGAGE-AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) study.[12] In this analysis, "noninterruption" was defined as either continuation or discontinuation of edoxaban for ≤3 days presurgery, whereas "interruption" was defined as stopping edoxaban 4 to 10 days presurgery.[11] Although the difference in outcomes when interrupting edoxaban for 1, 2, or 3 days is not reported in the study, the half-life of edoxaban (10-14 hours) suggests that an interval of 24 to 48 hours might be a reasonable approach to reduce plasma concentrations to safe levels allowing for surgical procedures at low risk of bleeding. Another unknown in the study is the time from the end of procedure until the administration of the first dose. It is also unknown if patients were bridged with LMWH during the period of anticoagulation interruption and if bridging could have influenced the adverse outcomes. Therefore, the available data do not provide specific management guidance for patients on edoxaban undergoing diagnostic or therapeutic

procedures, especially when the bleeding risk is high. In another secondary analysis of the ENGAGE-AF-TIMI 48 trial, interruption of study drug for >3 days was associated with an increased risk of stroke/SEE and major cardiac and cerebrovascular events (MACCE) over the ensuing 30 days vs those who never interrupted (15.42% vs 0.26% and 60.82% vs 0.36% per 100 patient-years, respectively).[21] Rates of clinical events after interruption of warfarin and edoxaban were similar. Interruption for adverse events was associated with an increased risk of MACCE but not stroke/SEE vs interruptions for other reasons. Invasive procedures accounted for 29.4% of study drug discontinuations, however, event rates in patients discontinuing due to invasive procedures were not reported.

In EMIT, as with any observational study, the question arises whether to incorporate comparator drugs. However, there is no gold standard in the periprocedural management of anticoagulation in patients with AF or VTE who are undergoing diagnostic or therapeutic procedures. Furthermore, it might be unethical to use comparator drugs that, despite their widespread use, are associated with bleeding profiles inferior to edoxaban. Although it is possible to power such a study sufficiently and to execute it diligently, such a study would entail an endeavor that may delay the availability of clinically relevant results.

4 | CONCLUSIONS

Regarding the periprocedural management of anticoagulation therapy, in particular with oral agents, in patients with AF or VTE, the relevant guidelines (eg, American College of Cardiology, the American Heart Association, and the European Heart Rhythm Association) are inconsistent.[4,19,22] EMIT will provide data on the use of the direct factor Xa inhibitor edoxaban in real world clinical practice to support further alignment of the above guidelines.

ACKNOWLEDGMENTS

Medical writing and editorial support was provided by Senem Kurtoglu, PhD, of AlphaBioCom, LLC (King of Prussia, Pennsylvania), and funded by Daiichi Sankyo, Inc. (Basking Ridge, New Jersey). The authors would like to thank Paul-Egbert Reimitz for his contribution to sample size determination; Christopher Helfer for data management; Petra Laeis and Diana Wolpert for implementation of the study; and Cathy ZL Chen for her significant contribution to the preparation of the manuscript.

Conflict of interest

Paolo Colonna, Christian von Heymann, and Amparo Santamaria-Ortiz participate in Daiichi Sankyo, Inc.-funded research. Paolo Colonna is a coauthor of ESC guidelines on AF (versions 2010 and 2012) and received institutional research grants from Bayer, Boehringer, and Daiichi Sankyo, Inc.; and speaker honoraria from Bayer, Boehringer Ingelheim, Pfizer-BMS, and Daiichi Sankyo, Inc. Christian von Heymann has received honoraria for lectures, consultancy work, and travel reimbursements from Bayer AG; Boehringer Ingelheim; Pfizer GmbH; Bristol Myers Squibb; Daiichi Sankyo, Inc.; CSL Behring; Baxter; NovoNordisk; Ferring; Stago; Octapharma; Leo Pharma; Haemonetics; Mylan Healthcare GmbH; Sanofi-Aventis; and HICC GbR. Amparo Santamaria Ortiz has received advisory fees for conferences from Daiichi Sankyo, Inc.; Bayer; Boehringer Ingelheim; Bristol Myers Squibb; and Pfizer. Yasuyuki Matsushita and Martin Unverdorben are full-time employees of Daiichi Sankyo, Inc.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Colonna P, von Heymann C, Santamaria A, Matsushita Y, Unverdorben M. Edoxaban Management in Diagnostic and Therapeutic Procedures (EMIT-AF/VTE)—Trial design. *Clin Cardiol*. 2018;41:1123–1129. https://doi.org/10.1002/clc.23037