

# Perioperative Management in Patients with Atrial Fibrillation Treated with Non-Vitamin K Antagonist Oral Anticoagulants Undergoing Minor Bleeding Risk Procedure: Rationale and Protocol for the PERIXa Study

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**Background:** While treatment interruption of non-vitamin K antagonist oral anticoagulants (NOACs) for elective surgery or procedures among patients with atrial fibrillation (AF) is becoming more prevalent, there remains insufficient evidence regarding the optimal perioperative management of NOACs, particularly procedures with minor bleeding risks.

**Objective:** This study aims to evaluate the safety and effectiveness of a simplified, standardized protocol for perioperative management of direct factor Xa inhibitors in patients, with AF undergoing procedures associated with minor bleeding risk.

**Methods:** This multicenter, prospective single-arm registry study plans to enroll patients undergoing procedures with minor bleeding risk who were prescribed direct factor Xa inhibitors for AF. The procedures with minor bleeding risk will include gastrointestinal endoscopy for diagnostic purposes, selected dental procedures, and ocular surgery for cataracts or glaucoma. For apixaban, patients will withhold the last evening dose and resume either from the evening dose of the procedure day or the following morning, depending on the bleeding risk of the patient. For edoxaban or rivaroxaban, patients will withhold only a single dose on the procedure day. The primary outcome is the occurrence of major bleeding events within 30 days. Secondary outcomes include systemic thromboembolism, all-cause mortality, and a composite of major and clinically relevant non-major bleeding events.

**Conclusion:** This study has the potential to generate evidence regarding the safety of perioperative management for patients, with AF undergoing procedures associated with minor bleeding risk.

**Trial Registration:** Clinicaltrials.gov: NCT05801068.

**Keywords:** atrial fibrillation, direct factor Xa inhibitor, bleeding, oral anticoagulant, perioperative care

## Introduction

An oral anticoagulant (OAC) is pivotal for the prevention and treatment of thromboembolism in patients with atrial fibrillation (AF).<sup>1</sup> While warfarin has historically been the sole available OAC, the introduction of non-vitamin K antagonist oral anticoagulants (NOACs) has significantly influenced clinical practice.<sup>2</sup> NOACs offer enhanced convenience compared to warfarin, as they eliminate the need for routine blood tests to monitor therapeutic effectiveness. Moreover, the efficacy and safety of NOACs have been consistently demonstrated across multiple trials,<sup>3-6</sup> and real-world clinical studies, even in

clinically complex patients.<sup>7,8</sup> Compared to warfarin, NOACs exhibit either a comparable or lower risk of stroke, coupled with a substantial reduction in the incidence of intracranial hemorrhage (ICH), which is a major complication associated with warfarin, by nearly 50%.<sup>9</sup> Consequently, NOACs have not only rapidly replaced warfarin but have also contributed to addressing the under-utilization of OACs.<sup>10</sup>

With the rising prevalence of patients on OAC therapy, the instances where these individuals need to interrupt OAC therapy for elective procedures or surgery temporarily are also increasing. Continuation of NOAC therapy without unnecessary interruption is crucial to maximize the prevention of thromboembolic events.<sup>11</sup> However, approximately one out of six patients with AF receiving NOACs experience therapy interruptions annually due to procedures or surgery.<sup>12</sup> Considering that NOACs have a shorter half-life than warfarin, it is recommended to omit bridging therapy during perioperative periods in patients on NOACs unless there is a high risk of thromboembolic events.<sup>1</sup>

## Perioperative Factor Xa Inhibitor Discontinuation in AF Patients Who Undergoing Minor Bleeding Risk Elective Procedure or Surgery

One previous study reported that the majority of procedures undertaken by patients on OACs were gastrointestinal endoscopy (diagnostic purposes), dental procedures (i.e., teeth extraction, periodontitis, implants), and ocular surgery (i.e., cataract or glaucoma surgery), which have minor bleeding risk.<sup>13</sup> According to current guidelines, it is recommended to omit the last evening dose of NOACs preoperatively and resume it six hours after the procedure when minor bleeding risk is present.<sup>1</sup> In this case, NOACs used once a day (rivaroxaban and edoxaban) will not be interrupted, while drugs used twice a day (dabigatran and apixaban) will require single-dose omission.

However, more evidence is needed to support the recommendation, which remains an unmet need. The specific management of stopping and resuming NOACs during the perioperative period depends not only on the type of NOAC received by the patient but also on the bleeding risk of the procedure.<sup>1,14</sup> Moreover, the definition of minor bleeding risk in procedures varies across specialties and societies. Therefore, a practical, standardized protocol for perioperative management of NOACs is needed for procedures with minor bleeding risk.

This prospective single-arm study aims to investigate the safety and effectiveness of a standardized, simplified protocol for the perioperative management of factor Xa inhibitors in patients with AF undergoing elective procedures or surgery with minor bleeding risk. The study will focus on procedures including gastrointestinal endoscopy, dental procedures, and ocular surgery. A brief review of the current status of related studies and guidelines across the specialties is provided before illustrating the study design and protocol.

## Current Guidelines on Perioperative Management of NOAC for Minor Bleeding Risk Procedures or Surgery

### Endoscopic Procedures

Table 1 summarizes the recommendations for the periprocedural use of NOACs in patients undergoing gastrointestinal endoscopy across academic societies. Cardiology and gastroenterology societies have varied definitions of low or minor bleeding risk in procedures. According to the 2021 European Heart Rhythm Association (EHRA) and the 2017 American Heart Association (AHA) guidelines,<sup>1,14</sup> only endoscopic procedures without biopsy are defined as low-bleeding-risk procedures. Even within the gastroenterology societies, detailed definitions of low-bleeding-risk procedures vary across countries.<sup>15–19</sup> In Japan, only endoscopic procedures without biopsy are classified as low-bleeding-risk procedures (The Japanese guidelines use the terminology “low-bleeding-risk”, and no definition for “minor-bleeding-risk” was found).<sup>17</sup>

Another challenge associated with gastrointestinal endoscopic procedures is that while they are primarily diagnostic, they often involve the possibility of performing biopsies. Endoscopic biopsies have a low risk of bleeding, whereas diagnostic endoscopy without biopsy is classified as having a minor risk of bleeding. Consequently, it is often difficult to determine the actual bleeding risk beforehand, as it remains to be determined whether a biopsy will be required during the procedure.

Recommendations for the periprocedural use of NOACs for low-bleeding-risk endoscopic procedures also differ across guidelines. The 2021 EHRA guideline recommends omitting the evening dose of the day before the procedure and resuming the medication six hours after the procedure,<sup>1</sup> while the 2017 AHA guideline recommends continuing the

**Table 1** Summary of Guidelines/Recommendations/Expert Consensus on Periprocedural Management of NOAC for Minor/Low Bleeding Risk Interventions – Focused on Endoscopic Procedures

References	Year	Minor or Low Bleeding Risk Procedures	Recommendations
EHRA guideline <sup>1</sup>	2021	Endoscopy without biopsy or resection	May omit Day-1 evening dose of NOAC, may resume 6 hrs after the intervention (Expert consensus)
AHA guideline <sup>14</sup>	2017	Endoscopy without biopsy	Continuing NOAC in the peri-endoscopic period (Expert consensus)
BSG/ESGE guideline <sup>15</sup>	2021	Diagnostic procedures ± biopsy, biliary or pancreatic stenting, device-assisted enteroscopy without polypectomy, esophageal, enteral or colonic stenting, EUS without sampling or interventional therapy	Continue warfarin. Omit DOAC on the morning of the the procedure (Low-quality evidence, weak recommendation)
ASGE guideline <sup>18</sup>	2016	Diagnostic procedures ± mucosal biopsy, ERCP with stent (biliary or pancreatic) placement or papillary balloon dilation without sphincterotomy, push enteroscopy and diagnostic balloon-assisted enteroscopy, capsule endoscopy, enteral stent deployment, argon plasma coagulation, Barrett's ablation	Continuing NOAC in the peri-endoscopic period (Low-quality evidence)
APAGE/APSDE guideline <sup>19</sup>	2018	Diagnostic endoscopy with biopsy, endoscopic ultrasound without fine needle aspiration, ERCP with biliary or pancreatic stenting, diagnostic push or device-assisted enteroscopy, video capsule endoscopy, esophageal, enteral and colonic stenting, argon plasma coagulation	Continuing NOAC in the peri-endoscopic period (Low-quality evidence, weak recommendation)
Korean guideline <sup>16</sup>	2020	Diagnostic endoscopy including mucosal biopsy, endoscopic ultrasonography without needle aspiration or biopsy ERCP with stent (biliary or pancreatic) placement, papillary balloon dilation without sphincterotomy, diagnostic push or device-assisted enteroscopy, video capsule endoscopy, esophageal, gastric, enteral, and colonic stenting	Continuing NOAC in the peri-endoscopic period (Low-quality evidence, weak recommendation)
Japanese guideline <sup>17</sup>	2018	Diagnostic gastroenterological endoscopic procedures without biopsy, upper gastroenterological endoscopy (including transnasal endoscopy), lower gastroenterological endoscopy, endoscopic ultrasonography, capsule endoscopy, ERCP, endoscopic mucosal biopsy (excluding endoscopic ultrasonography-guided fine-needle aspiration: EUS-FNA), balloon-assisted endoscopy, marking (including clipping, electrocoagulation, tattooing), gastroenterological, pancreatic duct, biliary duct stenting (without incision before treatment), endoscopic papillary balloon dilation	(1) Diagnostic gastroenterological endoscopy without biopsy can be carried out without DOAC withdrawal (Weak evidence, strong recommendation)(2) For endoscopic mucosal biopsy and gastroenterological endoscopic procedures with low bleeding risk during DOAC treatment, withdrawal is not required. However, the procedures should be carried out at a time avoiding the peak DOAC blood concentration estimated from the time of administration (Weak evidence, strong recommendation)
ACG/CAG guideline <sup>20</sup>	2022	<Low/moderate bleeding risk procedures>EGD/ colonoscopy/sigmoidoscopy with/without biopsy, ERCP with stent placement or papillary balloon dilation without sphincterotomy, EUS without FNA, push enteroscopy, diagnostic balloon-assisted enteroscopy, enteral stent deployment, argon plasma coagulation, balloon dilation of luminal stenoses, polypectomy (<1 cm), marking, and video capsule endoscopy	For patients on DOACs who are undergoing elective/ planned endoscopic gastrointestinal procedures, we suggest temporarily interrupting DOACs rather than continuing DOACs (conditional recommendation, very low certainty of evidence).  In patients who are undergoing elective endoscopic GI procedures whose DOAC was interrupted, we could not reach a recommendation for or against resuming the DOAC on the same day of the procedure vs 1–7d after the procedure.

(Continued)

**Table 1** (Continued).

References	Year	Minor or Low Bleeding Risk Procedures	Recommendations
CHEST guideline <sup>21</sup>	2022	<Low-to-moderate bleeding risk procedures> surgery/procedure (30-day risk of major bleed 0–2%): GI endoscopy ± biopsy Colonoscopy ± biopsy	Withholding DOACs for 1 full day before the procedure, which corresponds to a 30- to 36-hour interruption interval (or approximately three DOAC half-lives), should result in a residual anticoagulant effect which is acceptable clinically for lower bleed risk procedures. In all patients, no DOAC is taken on the day of the surgery/procedure. (Conditional Recommendation, Very Low Certainty of Evidence) Apixaban: 1 day off before low-to-moderate-bleed-risk Dabigatran: 1 day off before low-to-moderate-bleed-risk if CrCl ≥ 50 mL/min, 2 days off before low-to-moderate-bleed-risk if CrCl < 50 mL/min. Edoxaban: 1 day off before low-to-moderate-bleed-risk Rivaroxaban: 1 day off before low-to-moderate-bleed-risk Resume NOAC at least 24 hours after low-to-moderate-bleed-risk
Review article <sup>22</sup>	2023	Endoscopy or colonoscopy without polypectomy	May not require interruption of anticoagulation
Review article <sup>23</sup>	2023	Gastrointestinal endoscopy ± biopsy, colonoscopy ± biopsy	1 day off the DOAC before the surgery/procedure, which corresponds to a 30- to 36-hour interruption interval between the last dose and the procedure. Resuming DOAC is flexible to allow variability in surgery/procedure site hemostasis, whereby DOACs can be resumed approximately 24 hours after a low/moderate-bleed-risk procedure.

**Abbreviations:** AHA, American Heart Association; APAGE, Asian Pacific Association of Gastroenterology; APSDE, Asian Pacific Society of Digestive Endoscopy; ASGE, American Society for Gastrointestinal Endoscopy; BSG, British Society of Gastroenterology; EHRA, European Heart Rhythm Association; ERCP, endoscopic retrograde cholangiopancreatography; ESGE, European Society of Gastrointestinal Endoscopy; EUS, Endoscopic ultrasound-guided; FNA, fine needle aspiration; NOAC, non-vitamin K oral anticoagulant; ACG, American College of Gastroenterology; CAG, Canadian Association of Gastroenterology; CrCl, Creatinine clearance; DOAC, direct oral anticoagulant.

NOACs without interruption.<sup>14</sup> Both guidelines made the recommendations at the level of expert consensus due to insufficient evidence. In the gastroenterology societies, the 2021 British Society of Gastroenterology/European Society of Gastrointestinal Endoscopy (BSG/ESGE) guideline recommends omitting NOACs on the procedure day,<sup>15</sup> while the 2016 American Society for Gastrointestinal Endoscopy (ASGE),<sup>18</sup> 2018 Asian Pacific Association of Gastroenterology/Asian Pacific Society of Digestive Endoscopy (APAGE/APSDE),<sup>19</sup> and Asian guidelines<sup>16,17</sup> recommend continuing NOACs without interruption. Most guidelines had weak recommendations based on low-quality evidence.

In summary, there exists a discrepancy across the academic societies in the guidelines for the periprocedural use of NOACs for low-bleeding-risk endoscopic procedures, and all recommendations had low-quality evidence.

## Dental Procedures

Although no relevant international guidelines were found from dental societies, some review articles defined dental procedures as low-bleeding-risk (Table 2). According to the reviews, teeth extraction and implant placement were coherently defined as low-bleeding-risk procedures.<sup>24,25</sup> The definition also holds in the 2021 EHRA guidelines,<sup>1</sup> while the 2017 AHA guidelines do not offer detailed lists of low-bleeding-risk dental procedures.<sup>14</sup>

The 2021 EHRA guidelines include the number of teeth extracted during dental procedures as a factor to assess the severity of bleeding risk, which is not commonly considered in other literature. Moreover, while some literature

**Table 2** Summary of Guidelines/Recommendations/Expert Consensus on Periprocedural Management of NOAC for Minor/Low Bleeding Risk Interventions – Focused on Dental Procedures

References	Year	Minor or Low Bleeding Risk Procedures	Recommendations
EHRA guideline <sup>1</sup>	2021	Dental extractions (1–3 teeth), periodontal surgery, implant positioning, subgingival scaling/cleaning	May omit Day-1 evening dose of NOAC, may resume 6 hours after the intervention
AHA guideline <sup>14</sup>	2017	Minor dental procedures (no detailed descriptions)	Continuing NOAC in the peri-procedural period (Expert consensus)
Review article <sup>24</sup>	2019	Surgical teeth extraction, implant surgery, excision of cystic formations	Continue NOAC with cautions with local hemostatic agents (Expert opinion)
Review article <sup>25</sup>	2019	Dental scaling, dental restorations that involve soft-tissue manipulation, dental extractions that are not surgically complex (fewer than 3 teeth), soft-tissue biopsy, endodontic procedures, implant placement, prosthodontic procedures (fixed and removable dentures, crowns, bridges)	Continue NOAC with cautions with local hemostatic agents (Expert opinion)
Review article <sup>26</sup>	2023	Scaling and/or root planing, restorative treatment, non-surgical endodontic treatment, simple extractions, or minor surgery	Continue NOAC in subjects with normal kidney function. Interrupting NOAC 12–24 hours before surgery in patients with comorbidities favoring the accumulation of the drug (kidney disease, advanced age, etc.), and NOAC can be resumed six to eight hours after the intervention if complete hemostasis has been achieved.
CHEST guideline <sup>21</sup>	2022	Minimal-bleed-risk surgery/procedure (30-day risk of major bleed approximately 0%): Minor dental procedures (dental extractions, restorations, prosthetics, endodontics), dental cleanings, fillings	Minimal-bleed-risk procedures and selected surgeries are those in which anticoagulants may be continued perioperatively without any or with minimal (i.e., day of procedure only) interruption. Selected minimal-bleed-risk procedures may require 1 to 2 days of anticoagulant interruption if there is concern about bleeding; for example, a dental extraction may be more complex in a patient with poor dentition or compromised gingival integrity.
Review article <sup>22</sup>	2023	Minor dental procedures	May not require interruption of anticoagulation.
Review article <sup>23</sup>	2023	Minor dental procedures (dental extraction, restorations, prosthetics, endodontics), dental cleanings, fillings	Continue DOAC. Resume the delayed dose for once-daily DOACs and omit the morning dose for twice-daily DOACs.

**Abbreviations:** AHA, American Heart Association; DOAC, direct oral anticoagulant; EHRA, European Heart Rhythm Association; NOAC, non-vitamin K oral anticoagulant.

differentiates between bleeding risks associated with dental scaling and implant procedures, others categorize both as having a similarly low risk of bleeding (Table 2).

Within the cardiology societies, there exists a discrepancy in the recommendations between Europe and America. The European guidelines recommend omitting the day-1 evening dose of NOACs and resuming them six hours after the procedure, as in the endoscopic procedures.<sup>1</sup> Conversely, the American guidelines recommend continuing NOACs.<sup>14</sup> Dental reviews suggest continuing NOACs with caution and using local hemostatic agents.<sup>24,25</sup> In conclusion, regardless of the guidelines or reviews, most recommendations remained at the level of expert consensus.

## Ocular Surgery

Table 3 summarizes the current guidelines or reviews focused on ocular surgery. Similar to dental societies, ophthalmology societies do not provide relevant international guidelines, although some reviews exist. Ophthalmologists categorized

**Table 3** Summary of Guidelines/Recommendations/Expert Consensus on Periprocedural Management of NOAC for Minor/Low Bleeding Risk Interventions – Focused on Ocular Surgery

References	Year	Minor or Low Bleeding Risk Procedures	Recommendations
EHRA guideline <sup>1</sup>	2021	Cataract or glaucoma intervention	May omit Day-1 evening dose of NOAC, may resume 6 hrs after the intervention
AHA guideline <sup>14</sup>	2017	Ocular surgery (no detailed descriptions)	Continuing NOAC in the peri-endoscopic period (Expert consensus)
Review article <sup>28</sup>	2019	Sub-Tenon/topical cataract surgery, corneal surgery, oculoplastic: chalazion, eyelid cyst/lesion removal, strabismus	Omit dose 2 days pre-operatively (depending on renal function) and restart 1–2 days post-operatively if adequate hemostasis is achieved (Proposal)
Review article <sup>27</sup>	2015	Very-low bleeding risk surgery: Cataract removal Low-moderate risk surgery: Vitreoretinal surgery, oculoplastic surgery	Low hemorrhagic risk: Stop NOAC 24 hours before and resume 24 hours after the operation Moderate/high hemorrhagic risk: Stop NOAC 48 hours before and resume when there is no evidence of active bleeding
CHEST guideline <sup>21</sup>	2022	Minimal bleeding risk surgery/procedure (30-d risk of major bleed approximately 0%): Ophthalmologic (cataract) procedures	Minimal-bleed-risk procedures and selected surgeries are those in which anticoagulants may be continued perioperatively without any or with minimal (i.e., day of procedure only) interruption. Selected minimal-bleed-risk procedures may require 1 to 2 days of anticoagulant interruption if there is concern about bleeding
Review article <sup>22</sup>	2023	Cataract removal	May not require interruption of anticoagulation
Review article <sup>23</sup>	2023	Ophthalmological (cataract) procedures	Continue DOAC. Resume the delayed dose for once-daily DOACs and omit the morning dose for twice-daily DOACs.

**Abbreviations:** AHA, American Heart Association; DOAC, direct oral anticoagulant; EHRA, European Heart Rhythm Association; NOAC, non-vitamin K oral anticoagulant.

cataract surgery as a low-bleeding-risk surgery.<sup>27,28</sup> In one review article, other surgeries for sub-tenon, cornea, strabismus, oculoplastics, and eyelid cyst removal were also categorized as low-bleeding-risk surgery.<sup>28</sup> However, the 2021 EHRA guidelines defined only cataract or glaucoma surgery as low-bleeding-risk ocular surgery.<sup>1</sup> In the 2017 AHA guidelines, a detailed definition of low-bleeding-risk ocular surgery was not provided.<sup>14</sup> The 2021 EHRA guidelines provide the same recommendations for the low-bleeding-risk procedures regardless of endoscopic, dental, or ocular interventions.<sup>1</sup> However, the evidence is insufficient to support the recommendations.

## Perioperative Use of NOAC – Minor-Bleeding-Risk Procedures

Four pivotal randomized controlled trials (RCTs) for each type of NOAC involving patients who underwent minor bleeding-risk procedures were evaluated.<sup>3–6</sup> Table 4 compares the results of the sub-analysis of each RCT, which focused on the patients who received periprocedural management of NOACs.<sup>29–32</sup> In a sub-study of the RE-LY trial, which investigated dabigatran, 3033 patients underwent periprocedural management, and only 8.9–10.1% had either gastrointestinal endoscopy, ophthalmology, or dental surgery.<sup>29</sup> The incidence of ischemic stroke or thromboembolism 30 days after the procedure was 0.6%, and the incidence of major bleeding was 1.9–3.2%. Since this value was observed from all types of procedures, the incidence may be lower for low-bleeding-risk procedures. In the case of rivaroxaban (in a sub-study of the ROCKET AF trial), the incidence of stroke or thromboembolism 30 days after the procedure was 0.27%, and the incidence of major bleeding was 0.99%.<sup>32</sup> In this study, the proportion of minor-bleeding-risk procedures was only 8–17% of all procedures. Although a sub-study of the ARISTOTLE trial investigated the incidences from a composite population of both warfarin and apixaban users, the proportion of low-bleeding-risk was only 8–17.5% of the total



**Table 4** Comparison of Results and Characteristics of Selected Studies Investigated Peri-Procedural Outcomes of NOAC for Low-Bleeding-Risk Interventions

References	PAUSE Registry <sup>33</sup>	MARK Registry <sup>34</sup>	Dresden Registry <sup>13</sup>	Periop Dabigatran Study <sup>35</sup>	RE-LY Substudy <sup>29</sup>	ROCKET AF Substudy <sup>32</sup>	ARISTOTLE Substudy <sup>31</sup>	ENGAGE AF-TIMI Substudy <sup>30</sup>
Study design	Prospective cohort	Prospective cohort	Prospective cohort	Prospective cohort	Subanalysis of RCT	Subanalysis of RCT	Subanalysis of RCT	Subanalysis of RCT
NOAC types	Dabigatran, rivaroxaban, and apixaban	Pooled NOAC	Pooled NOAC	Dabigatran	Dabigatran	Rivaroxaban	Edoxaban	Edoxaban
The number of patients received NOAC and underwent perioperative management	3007	351	595	541	3033	968	5439	4825
The proportion of patients having surgeries or procedures with minor bleeding risks, %	66.5	52.7	74.3	26.6	DI10: 27.4 DI50: 28.2	42	40.1	36.7
Age (mean or median, according to study), yr	73	73 <sup>a</sup>	75	72	72	73	71	73
The proportion of surgeries/procedures with minor bleeding risks								
Gastrointestinal endoscopic procedures, %	20.9	34.9	19.9 <sup>b</sup>	21.8 <sup>b</sup>	DI10: 9.6 DI50: 8.9	17	17.5 <sup>c</sup>	12.3
Ocular surgery, %	0.7	NA	7	3.9	DI10: 8.3 DI50: 10.1	8	8.0 <sup>c</sup>	11.2
Dental surgery, %	0.3	5.6	13.4	1.7	DI10: 9.5 DI50: 9.2	17	14.6 <sup>c</sup>	13.2
Was perioperative use of bridging therapy used?	Yes	Either	Either	No	Either	Either	Either	Either
Perioperative incidence of stroke or systemic thromboembolism, %	Apixaban: 0.16 Dabigatran: 0.60 Rivaroxaban: 0.37	Continued: 0 Interrupted: 0.8	0.8 (only data for MACE was available)	0.2	DI10: 0.6 DI50: 0.6 (specific data for minor surgery was N/A)	Continued: N/A Interrupted: 0.27	Continued: 0.4 Interrupted: 0.3	1. E60 Continued: 0.7 Interrupted: 0.5 2. E30 Continued: 0.9 Interrupted: 0.9
Perioperative incidence of major bleeding, %	Apixaban: 1.4 Dabigatran: 0.9 Rivaroxaban: 1.9	Continued: 1.2 Interrupted: 3.0	0.5	1.8	DI10: 1.9 DI50: 3.2 (for minor surgery only)	Continued: N/A Interrupted: 0.99	Continued: 1.6 Interrupted: 1.7	1. E60 Continued: 2.6 Interrupted: 1.2 2. E30 Continued: 2.4 Interrupted: 1.1

**Notes:** <sup>a</sup>Including both patients with NOAC and warfarin. <sup>b</sup>Including both gastrointestinal endoscopy and bronchoscopy. <sup>c</sup>Including both patients with apixaban and warfarin.

**Abbreviations:** DI10/150, dabigatran 110/150 mg; E30/60, edoxaban 30/60 mg; MACE, major adverse cardiovascular event; N/A, not available; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial.

procedures.<sup>31</sup> The incidence of stroke or thromboembolism was 0.3–0.4%, and the incidence of major bleeding risk was 1.6–1.7%. Lastly, in a sub-study of the ENGAGE AF-TIMI trial, the proportion of low-bleeding risk procedures was only 11.2–13.2% of the total procedures, and the incidence of stroke or thromboembolism was 0.5–0.7%, and the incidence of major bleeding was 1.1–2.6%.<sup>30</sup>

Summarizing the above clinical trial sub-studies, it is expected that the risk of major bleeding could be reduced without significantly increasing the risk of stroke or thromboembolism, even if NOACs are temporarily stopped during the periprocedural procedures.

Conversely, there are also results from prospective registries investigated the outcomes of periprocedural use of NOAC. Table 4 summarizes the results of selected studies. The PAUSE trial investigated the safety of a standardized protocol for the perioperative management of NOAC using 3007 patients with AF.<sup>33</sup> In this study, the proportion of endoscopic procedures accounted for 20.9% of the total procedures, while the proportions of ocular and dental surgeries were only 0.7% and 0.3%, respectively. The study reported that the incidence of stroke or thromboembolism was 0.2–0.6%, and the incidence of major bleeding was 0.9–1.9%. The MARK registry, the Dresden registry, and the Periop Dabigatran Study are also prospective registries and investigated the outcomes of perioperative management of NOAC.<sup>13,34,35</sup> According to the studies, endoscopic procedures accounted for 19.9–34.9% of total procedures, while ocular or dental surgery accounted for only 3.9–13.4%. Overall, the incidence of stroke or thromboembolism and major bleeding were reported to be similar to those of other studies.

In summary, there remains insufficient data on the safety and effectiveness of the perioperative management of NOAC for minor bleeding-risk procedures.

## Study Design and Protocols

NOACs have been widely used in patients with AF, and in any given year, one in six patients with AF taking OAC will have to stop their medication due to a procedure or surgery.<sup>12</sup>

One large registry study has been reported on perioperative NOAC discontinuation and resumption in low and high bleeding-risk procedure/surgery.<sup>33</sup> In the latter study, the safety of a protocol that included one or two days of NOAC discontinuation before surgery and resumption of NOAC the day after surgery or the next day, depending on the bleeding risk of the procedure, was examined in nearly 3000 patients with AF taking NOACs. Existing literature indicates that dental procedures categorized as minor bleeding-risk (tooth extraction, gingival treatment such as periodontitis or abscess, dental implants), eye surgery (cataract and glaucoma surgery), and gastrointestinal endoscopy for diagnostic purposes are reported to be more common in real-world practice setting (90% of all procedures) than these low or high bleeding-risk procedures.<sup>13</sup>

Although guidelines recommend not discontinuing OAC for minor bleeding-risk procedures and note that they can be performed 12 to 24 hours after the last dose of NOAC,<sup>1</sup> a more practical recommendation in real-world practice may be to take the last dose of NOAC 18 to 24 hours before the procedure and resume 6 hours after the procedure.<sup>1</sup> However, there is a discrepancy between the basic principles of not recommending discontinuation and practical guidelines that recommend single-dose discontinuation depending on the specific type of NOAC (ie, apixaban or dabigatran) and there is a lack of prospective evidence to support this recommendation. Smaller reports suggest a trend toward a lower risk of bleeding with discontinuation compared to continuation of anticoagulation without a clear increase in stroke or systemic embolism risks.<sup>13,36–39</sup>

This prospective study aimed to determine the safety and effectiveness of a simplified protocol for the perioperative management of a factor Xa inhibitor for stroke prevention in patients with AF.

## Ethical Statements

This study conformed to the ethical guidelines of the Declaration of Helsinki (revised in 2013) and was approved by the Institutional Review Board of Seoul National University Hospital (no. H-2005-151-1125).

## Study Population, Inclusion, and Exclusion Criteria

Patients with non-valvular AF taking rivaroxaban, apixaban, or edoxaban who are at least 20 years of age and scheduled for a minor bleeding-risk procedure will be enrolled. They will provide informed consent to participate in the study. Minor bleeding-risk procedures/surgeries are defined as follows: (1) dental procedures (1–3 extractions, periodontal surgery, drainage incisions, or dental implants); (2) cataract or glaucoma surgery; and (3) diagnostic gastroduodenoscopic/



colonoscopic procedures.<sup>1</sup> The following patients are excluded from this study: patients younger than 20 years of age, pregnant women, or other vulnerable subjects; those taking once a daily agent (rivaroxaban or edoxaban) regularly in the afternoon schedule; those with severe psychiatric or cognitive impairment who are expected to have poor adherence to this study; (4) those with contraindications for rivaroxaban, apixaban, or edoxaban according to the local marketing authorization/summary of medicinal products characteristics; those with diagnosis of moderate or severe mitral stenosis or who have undergone prosthetic valve replacement surgery; those with indications for OACs other than AF (ie, pulmonary artery thrombus or deep vein thrombus); those who are scheduled for another procedure or surgery with a minor bleeding-risk or greater bleeding-risk within 30 days of an index minor bleeding-risk procedure or surgery; those taking OACs or antiplatelet agent(s) other than rivaroxaban, apixaban, or edoxaban; those with major bleeding, systemic embolism, or those who experienced stroke in the past 12 months; and those with a planned therapeutic endoscopic procedure.

## Study Hypothesis and Sample Size Determination

This study plans to enroll 2500 participants. This study aims to determine the effectiveness and safety of a simplified protocol for the discontinuation and resumption of factor Xa inhibitor (rivaroxaban, apixaban, and edoxaban) periprocedurally in patients with non-valvular AF who are scheduled to undergo minor bleeding-risk procedures or surgery. For this purpose, the primary outcome is defined as the 30-day major bleeding event, and the following assumptions are made to calculate the number of subjects to meet the study objectives.

- I. Primary outcome: A 30-day major bleeding event (major bleeding: according to the International Society on Thrombosis and Haemostasis [ISTH] criteria)<sup>40</sup>
- II. Level of significance,  $\alpha = 0.05$
- III. The power of the test = 80%
- IV. Superiority design based on a single-arm proportional test

The rationale for calculating the number of subjects according to the primary outcome was based on bleeding events.<sup>33,37,41,42</sup> The incidence of the primary outcome of discontinuing factor Xa inhibitors for minor bleeding-risk procedures varies across reporters, with dental procedure accounting for 5.6%, 2.5% for cataract surgery, and (2.9%/7.9%) for low-/high-risk gastrointestinal endoscopic procedures.<sup>13,42</sup> Based on the literature, we assumed an average primary outcome rate of 3.6% for all procedures. In contrast, the primary outcome rate when factor Xa inhibitors were maintained was assumed to be 4.8%, based on the existing literature, and because it is conventionally expected to be higher than when factor Xa inhibitors are discontinued.<sup>13</sup> This study aimed to show that the bleeding rate would be lower when factor Xa inhibitors were discontinued than when they were maintained. Moreover, the number of subjects was calculated based on the existing literature, which showed a 4.8% bleeding rate when factor Xa inhibitors were maintained and a 3.6% bleeding rate when they were discontinued. The bleeding rate, when maintained, was set as the null hypothesis ( $H_0: p = p_0$ , primary outcome rate of 4.8%), and the bleeding rate, when discontinued, was set as the alternative hypothesis ( $H_1: p = p_1 \neq p_0$ ), primary outcome rate of 3.6%. Based on the above assumptions, the required number of subjects is expected to be 2303, and considering the dropout rate of 8%, the final number of subjects is set to be 2500.

## Study Outcomes

The study outcomes are summarized in Table 5. The primary outcome of this study is defined as the major bleeding events that will occur within 30 days according to the ISTH criteria.<sup>40</sup> Major bleeding includes fatal bleeding; and/or symptomatic bleeding in a vital site or organ, such as intracranial, intrathecal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular bleeding with compartment syndrome; and/or bleeding that causes hemoglobin level to drop more than 20 g/L (1.24 mmol/L) or requires transfusion of more than two units of whole blood or red blood cells. Secondary outcomes include stroke within 30 days or systemic embolism including ischemic stroke, transient ischemic attack, acute myocardial infarction, deep vein thrombosis, pulmonary thromboembolism, and other venous thromboembolism events; all-cause death within 30 days, a 30-day composite of major bleeding and clinically relevant nonmajor bleeding (CRNMB), and any type of bleeding. The definition of CRNMB encompasses any sign or symptom of

**Table 5** Study Outcomes and Definitions

Minor bleeding risk procedures	(1) Dental procedures (1–3 teeth extraction, periodontal procedures, implantation) (2) Ocular surgery (Cataract phacoemulsification, glaucoma) (3) Diagnostic endoscopy ± biopsy <sup>a</sup>
Primary outcome	30-day major bleeding event according to the ISTH definitions <sup>40</sup>
Secondary outcomes	(1) 30-day stroke or systemic embolism <sup>b</sup> (2) 30-day composite of all-cause death, stroke, or systemic embolism (3) 30-day composite of major bleeding and clinically relevant nonmajor bleeding according to the ISTH definitions, <sup>43</sup> and any bleeding
Other measurements	(1) Protocol adherence (2) Anti-factor Xa plasma level

**Notes:** <sup>a</sup>Diagnostic esophagogastroduodenoscopy, colonoscopy, sigmoidoscopy, and biopsy, except for polypectomy, endoscopic mucosal resection, endoscopic submucosal dissection, and endoscopic variceal ligation, endoscopic hemostasis, pneumatic or bougie dilation, endoscopic ultrasound-guided fine-needle aspiration, percutaneous endoscopic gastrostomy, percutaneous endoscopic jejunostomy, and therapeutic balloon-assisted enteroscopy (including esophageal, enteral, and colonic stenting). <sup>b</sup>Systemic embolism included ischemic stroke, transient ischemic attack, acute myocardial infarction, deep vein thrombosis, pulmonary thromboembolism, and other venous thromboembolic events.

**Abbreviation:** ISTH, the International Society on Thrombosis and Haemostasis.

hemorrhage (ie, more bleeding than would be expected for a clinical circumstance, including bleeding found solely through imaging) that does not fit the criteria for the ISTH definition of major bleeding but meets at least one of the following criteria: requiring medical intervention by a healthcare professional, hospitalization or increased level of required care, and prompt need for a face-to-face evaluation.<sup>43</sup>

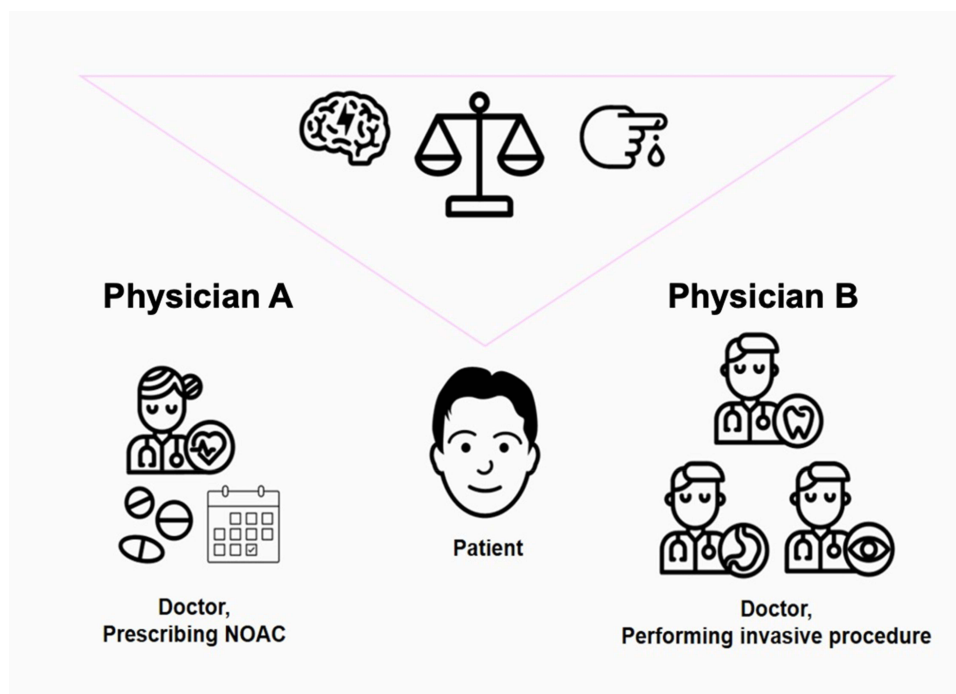
Moreover, protocol adherence is assessed, whether the proposed instructions for discontinuing or resuming a factor Xa inhibitor as per the study protocol were followed. If a subject did not adhere to the study protocol, the reasons (i.e., unclear physician instructions, need for additional post-procedure hemostasis, participant inattention) for the study protocol violation are collected and analyzed through communication with the patient and/or the physician (through in-office questionnaire or telephone consultation).

# Study Flow and Peri-Procedural Management Protocol

When a patient with AF who is prescribed a factor Xa inhibitor for stroke prevention presents to the prescribing physician (Physician A) for consultation regarding discontinuation of a factor Xa inhibitor due to a scheduled procedure with minor bleeding risk (Figure 1), Physician A will outline the protocol for discontinuing or resuming the direct factor Xa inhibitor before and after the procedure (Figure 2). Accordingly, patients taking apixaban at doses of 2.5 mg or 5 mg twice daily (BID) will discontinue the medication, beginning with the evening dose before the day of the procedure and the morning and evening doses on the day of the procedure. Resumption of therapy will begin with the morning dose on the day following the procedure. However, for procedures or surgeries performed in the morning, apixaban may be resumed from the evening of the procedure day if there is no risk of bleeding and hemostasis is deemed to be completed (denoted by “X” in Figure 2). Patients taking edoxaban 60 mg once daily (QD) or 30 mg QD, rivaroxaban 20 mg QD, or 15 mg QD should continue taking the medication until the day before the procedure, discontinuing it on the day of the procedure. Resumption will commence the day after the procedure (Figure 2). The physician performing the actual procedure or surgery (Physician B) will be informed of the patient’s participation in the study and will be instructed to complete a survey related to the procedure to obtain information regarding the type of procedure and severity of any associated bleeding. Furthermore, a follow-up with the patient will be conducted to collect the survey and gather information (Supplementary Material).

A patient will be instructed to discontinue or resume the factor Xa inhibitor according to the instructed protocol before and after the procedure unless a significant event prevents patient adherence to the study protocol. After the procedure, the survey will be verified by communicating with the patient via telephone or outpatient visit(s), and evaluation of all bleeding and thromboembolic events 30 days after the procedure will be performed.

Information will be collected through two patient contacts. Visit 1 (Day 7) will be conducted by phone or in person to determine (1) whether the primary and secondary endpoints occurred, (2) the subjective degree of bleeding experienced



**Figure 1** The overview of the study.

**Abbreviation:** NOAC, non-vitamin K oral anticoagulant.

	Day-2		Day-1		Procedure day		Day+1		Day+2	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
A5/2.5 bid				×	×	(×)				
E60/30 qd, R20/15 qd					×					

**Figure 2** The protocol for stopping and resuming direct factor Xa inhibitors during the perioperative period.

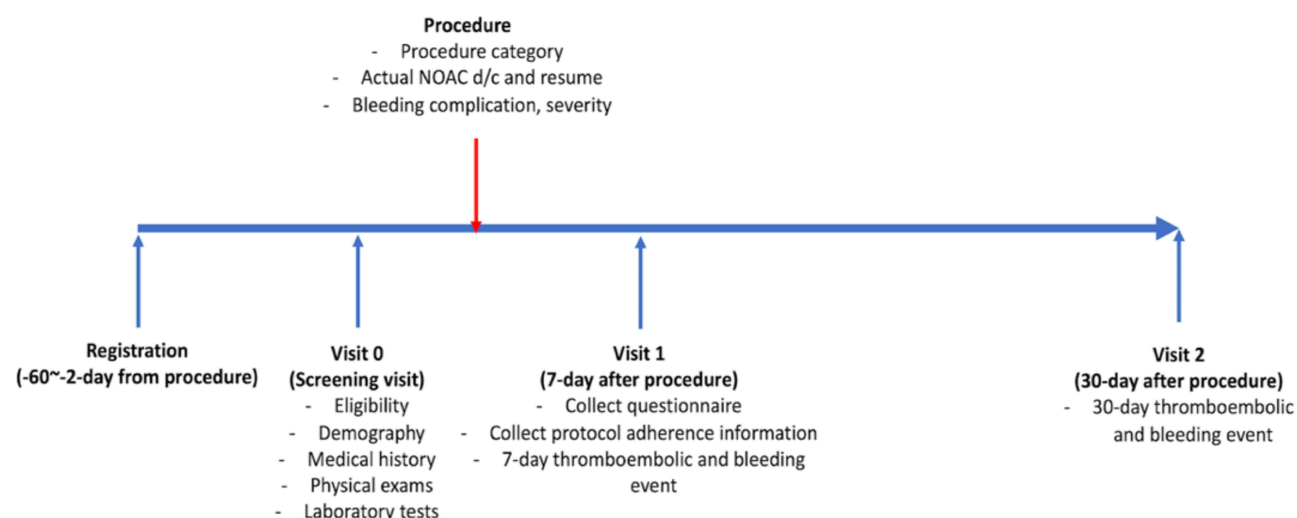
**Abbreviations:** A5/2.5, apixaban 5 mg or 2.5 mg; E60/30, edoxaban 60 or 30 mg; R20/15, rivaroxaban 20 or 15 mg.

during the procedure (none, little, moderate, or heavy), (3) actual adherence to pre- and post-procedure factor Xa inhibitor medication, and (4) collection of the study survey. At Visit 2 (Day 30), the primary and secondary endpoints since Visit 1 are reconfirmed by phone or outpatient visit (Figure 3).

As smartphone use has become universal in recent years, mobile technologies have increasingly been accepted as effective tools for conducting clinical trials.<sup>44,45</sup> In our study, telephone communication is actively used in cases where study participants find it difficult to visit the clinics for follow-ups. Utilizing telephone communications may help decrease dropout rates due to the loss of follow-ups, enhance the availability of study data, and increase statistical power.

## Statistical Analysis Plan

The proportion of primary and secondary outcomes will be presented through descriptive analysis. Intention-to-treat and per-protocol analyses will be performed based on adherence to the study protocol, allowing for a comparison of the occurrence of the primary outcome between these two analyses. Additionally, we will evaluate how these rates differ



**Figure 3** The flowchart of the study.

**Abbreviations:** NOAC, non-vitamin K oral anticoagulant; d/c, discontinuation.

from previously reported data. Survival analysis will be performed for both the primary and secondary endpoints related to efficacy and safety, as outlined earlier, aiming to assess bleeding risk and cardiac events following perioperative factor Xa inhibitor discontinuation for procedures or surgeries with minor bleeding risk.

## Study Limitations

Although the study was meticulously designed, it has several limitations. Firstly, this study does not compare the efficacy and safety of various periprocedural oral anticoagulant (OAC) management strategies. A comparison of different strategies might offer more clinical benefits and impacts on AF management. However, this would necessitate at least a two-arm study design and a more extensive study population to achieve sufficient statistical power. Such conditions diminish the feasibility of the study. Secondly, the evaluation of study outcomes is based on surveys completed by physicians who performed procedures with a minor risk of bleeding rather than on the researchers' direct verification of the outcomes. Consequently, the reported outcomes might be biased due to the physicians' subjective assessments. Nevertheless, given the study's feasibility constraints, we determined that this evaluation method was appropriate. Furthermore, assessments by experts with relevant procedural expertise might yield more accurate results than those conducted by researchers. Thirdly, the study primarily focused on Korean populations. Although its findings might be extrapolated to other Asian groups, these results may not be directly applicable to Western populations.

## Conclusions

This study represents a multicenter, prospective registry trial that investigates the optimal standardized perioperative management of direct factor Xa inhibitors in patients, with AF undergoing procedures with minor bleeding risk. The study will assess the safety and effectiveness of a simplified protocol for discontinuing and resuming NOACs during periprocedural periods. This study is expected to generate evidence concerning the safety and effectiveness of a simplified protocol for the perioperative management of OACs in patients with AF undergoing procedures associated with low bleeding risk.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

EKC: Research grants or speaking fees from Abbott, Bayer, BMS/Pfizer, Biosense Webster, Chong Kun Dang, Daewoong Pharmaceutical Co., Daiichi-Sankyo, DeepQure, Dreamtech Co., Ltd., Jeil Pharmaceutical Co., Ltd., Medtronic, Samjinpharm, Seers Technology, and Skylabs. GYHL: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Anthos and Daiichi-Sankyo. No personal fees were received. The co-principal investigator of the AFFIRMO project on multimorbidity in AF received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No. 899871. The authors report no conflicts of interest in this work.

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