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Full Length Article

# Design and rationale for REVERXaL: A real-world study of patients with factor Xa inhibitor–associated major bleeds

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ABSTRACT

*Background:* The prevalence of anticoagulation treatment is increasing as an aging global population faces a high burden of cardiovascular comorbidities. Direct oral anticoagulants, including factor Xa inhibitors (FXai), are replacing vitamin K antagonists as the most commonly prescribed treatment for reducing risk of thrombotic events. While the risk of FXai-associated spontaneous bleeds is established, less is understood about their management and the effect of treatment on clinical and patient-reported outcomes. The primary objectives of the REVERXaL study are to describe patient characteristics, health care interventions during the acute-care phase, in-hospital outcomes, and associations between timing of reversal/replacement agent administration and in-hospital outcomes. Secondary/exploratory objectives focus on clinical assessments and patient-reported outcome measures (PROMs) at 30 and 90 days.

*Methods:* REVERXaL is a multinational, observational study of hospitalized patients with FXai-associated major bleeds in Germany, Japan, the United Kingdom, and the United States. The study includes 2 cohorts of approximately 2000 patients each. Cohort A is a historic cohort for whom medical chart data will be collected from hospitalization to discharge for patients admitted for major bleeds during FXai use within 2 years prior to enrollment of Cohort B. Cohort B will prospectively enroll patients administered any reversal/replacement agent during hospitalization to manage FXai-associated major bleeds and will include the collection of clinical outcomes and PROMs data over 3 months.

*Conclusions:* REVERXaL will generate insights on patient characteristics, treatment approaches, and associated outcomes in patients hospitalized with FXai-associated major bleeds. These data may inform clinical practice and streamline treatment pathways in this population.

*Registration:* URL: https://www.clinicaltrials.gov; unique identifier: NCT06147830.

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**Abbreviations**

| | |
|---|---|
| 3F-PCC | 3-factor prothrombin complex concentrate |
| 4F-PCC | 4-factor prothrombin complex concentrate |
| AE | adverse event |
| CI | confidence interval |
| CRF | case report form |
| CT | computed tomography |
| DOAC | direct oral anticoagulant |
| EQ-5D-5L | 5-level EuroQol 5-dimension |
| FXai | factor Xa inhibitor |
| Hct | hematocrit |
| Hgb | hemoglobin |
| HRQoL | health-related quality of life |
| ICH | intracranial hemorrhage |
| ICU | intensive care unit |
| OAC | oral anticoagulant |
| PRBC | packed red blood cells |
| PRO | patient-reported outcome |
| PROM | patient-reported outcome measure |
| SAE | serious AE |
| SF-36v2 | Short Form-36 health survey, version 2 |
| VKA | vitamin K antagonist |

## 1. Introduction

Oral anticoagulant (OAC) use is common and increasing with an aging population that faces a high burden of cardiovascular conditions, including atrial fibrillation and venous thromboembolism [1,2]. The incidence of such cardiovascular events has risen over the last half century, with the estimated prevalence of atrial fibrillation among adults between 2 % and 4 %, and an expected increase of >2-fold over the next several decades due to increasing life expectancies and the prevalence of comorbidities [1,2]. OACs are indicated for the treatment and prevention of these cardiovascular conditions; however, the benefit of treatment needs to be tempered against the increased risk of potentially life-threatening bleeding events [1,2].

There has been a paradigm shift with direct oral anticoagulants (DOACs), including factor Xa inhibitors (FXai), replacing vitamin K antagonists (VKAs) as FXai may reduce the risk of stroke and other thromboembolic events, with reduced risk of bleeding, compared with VKAs [3,4]. Among US Medicare beneficiaries, OAC use increased from 9.2 % in 2011 to 11.5 % in 2019, with DOACs accounting for 7.4 % and 66.8 % of OAC use in 2011 and 2019, respectively [5]. While FXai use is associated with fewer major bleeding events than VKA use, the rapid rise in the use of FXai would be expected to result in an overall increased prevalence of major bleeding events globally [2,6]. Major bleeding events related to FXai use are associated with significant clinical burden and morbidity and result in high mortality [7–9].

Treatment for FXai-associated bleeds has evolved substantially over the last decade, including the introduction of andexanet alfa, a specific reversal agent for FXai [10]. In the prospective, single-arm ANNEXA-4 study, treatment with andexanet alfa was associated with a marked reduction in anti-FXa activity and a hemostatic efficacy rate of 82 % among patients with FXai-associated acute major bleeds [11]. Several guidelines now recommend the use of andexanet alfa for FXai–associated bleeds; in many settings, however, 3-factor prothrombin complex concentrate (3F-PCC) and 4-factor prothrombin complex concentrate (4F-PCC) continue to be used off-label for treatment of FXai-associated bleeds [12–14].

Real-world evidence can provide valuable information about patient characteristics, treatment patterns, and clinical outcomes from routine practice, which may complement data from clinical trials. However, previous studies of patients with FXai-associated bleeds in clinical practice were generally small, were predominantly based in a single center or single health system (largely in the United States), had data collected retrospectively with no or minimal follow-up, or did not adjust for important variables making comparisons between treatments difficult to interpret [15–27]. Moreover, not all studies collected clinically relevant data (e.g., time since last dose of FXai) that would ensure that patients who were included in the study were therapeutically anticoagulated. Notably, these studies do not include patient-reported outcome measures (PROMs) [15–29], such as assessments of health-related quality of life (HRQoL), which are increasingly valued by the clinical community, regulators, payers, and policy makers [30,31]. Further, previous studies have not thoroughly explored the impact of timing of different treatments, the restart of anticoagulation, the occurrence of rebleeding events, and postdischarge outcomes [15–29].

Here, we describe the design and rationale of REVERXaL (ClinicalTrials.gov Identifier: NCT06147830), a multinational observational study of patients with FXai-associated major bleeds from Germany, Japan, the United Kingdom, and the United States. By leveraging both retrospective (historic) and prospective data collection, the overarching goal of REVERXaL is to describe the patient characteristics, health care interventions provided, and clinical and self-reported health outcomes of patients with FXai-associated acute major bleeds. By providing a broad multicountry overview of the real-world clinical presentation, management, and long-term outcomes for patients hospitalized with FXai-associated acute major bleeding, the REVERXaL study will fill a key evidence gap for these patients. In particular, by incorporating assessments of both clinical outcomes and PROMs, the study will provide a comprehensive view of the patient experience with these types of bleeds.

## 2. Methods

### 2.1. Study design

REVERXaL is a multinational, observational, longitudinal, cohort study focusing primarily on hospitalized patients with FXai-associated acute major bleeding events in Germany, Japan, the United Kingdom, and the United States. This study will mainly be descriptive in nature, without any prespecified statistical hypotheses. In the context of this study, acute major bleeding is defined as any of the following: life-threatening or potentially life-threatening bleeding (according to the treating physician); acute bleeding associated with hemodynamic compromise; or bleeding occurring in an anatomically critical site, requiring transfusion (≥2 units of packed red blood cells), or resulting in a hemoglobin drop ≥2 g/dL or death, consistent with consensus definitions from the International Society on Thrombosis and Haemostasis [14,32].

Two cohorts will be included in this study. Cohort A is a historic cohort of approximately 2000 patients admitted at participating institutions with an FXai-associated bleeding event during a period of ≤2 years preceding the start of enrollment for Cohort B. Patients enrolled in Cohort A may or may not have received treatment with a reversal or replacement therapy and will be followed from the time of admission for an FXai-associated bleed (Cohort A index date) until death or hospital discharge (Fig. 1). Patients who develop an FXai-associated bleed while already admitted to the hospital will also be included; for these patients, the index date will be defined as the date of the onset of the bleeding event. Cohort B will include approximately 2000 patients administered any reversal or replacement therapy during hospitalization for an FXai-associated bleeding event (Cohort B index date) at participating sites. Patients enrolled in Cohort B will be enrolled as soon as possible

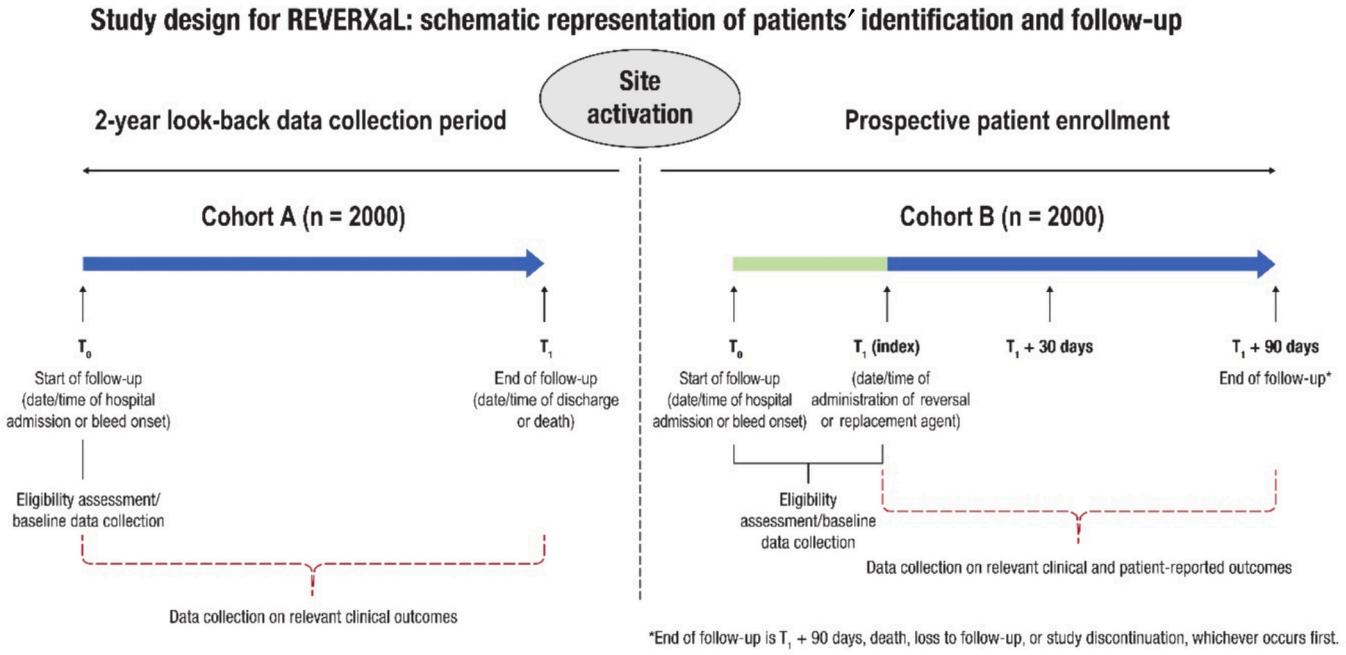


**Fig. 1.** Study design for REVERXaL.

upon hospitalization after being stabilized from the acute bleeding, then followed for 3 months postindex or until study discontinuation, loss to follow-up, or death (Fig. 1). The study is projected to run until the end of 2025, depending on the patient enrollment rate.

This study will leverage hybrid data collection, including both primary and secondary data collection. Cohort A will involve secondary data extraction from medical records for patients presenting at participating institutions. Cohort B will involve primary collection of certain data (PROMs and adverse events [AEs]), as well as secondary data extraction from health records. This study is noninterventional in nature and, as such, patients will receive standard medical care as determined by their treating physicians without receiving any experimental disease management intervention or treatment. No additional site visits, invasive clinical tests, or procedures are mandated per the study protocol. Ethics approval will be sought from relevant local authorities for both Cohorts A and B, and informed consent will be obtained from all patients recruited to Cohort B.

### 2.2. Study population

Study sites are selected to represent the range of health care facilities managing different types of acute major bleeds, which include, but are not limited to, intracranial hemorrhage [ICH] and gastrointestinal bleeds, and will include small and large medical centers and hospitals in the participating countries. The study is intended to include 80–100 sites overall, with site selection ongoing at the time of the writing of this manuscript. The study population will be composed of adult patients with FXai-associated acute major bleeding events who meet the inclusion and exclusion criteria summarized in Table 1.

### 2.3. Study objectives

The primary objectives to be assessed in both Cohorts A and B are to describe: 1) patient characteristics, 2) health care interventions during the acute-care phase and in-hospital outcomes, and 3) associations between timing of reversal/replacement agent administration since admission/bleed onset and in-hospital outcomes (Table 2). The secondary objectives of this study (to be assessed in Cohort B) are to describe clinical outcomes and PROMs at 30 days postindex and to assess any associations between timing of reversal agent administration and clinical outcomes and PROMs at the 30-day postindex visit (Table 2). Additional, exploratory objectives of this study will include describing the clinical outcomes and PROMs at 90 days postindex with consideration of the impact of timing of interventions and different treatments.

**Table 1**
Inclusion and exclusion criteria.

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Aged ≥18 years on the index date<br>• Admitted to the hospital with acute major bleeding or developed acute bleeding while already in the hospital<br>• Ongoing treatment[a] with an FXai before the index date[b]<br>• Provided signed and dated informed consent or able to obtain a waiver[c]<br>• In addition, for Cohort B:<br>  ○ Administered reversal or replacement therapy | • Pregnant women<br>• Patients enrolled in any interventional trial that includes reversal/replacement agents<br>• In addition, for Cohort B:<br>  ○ Use of PCCs or recombinant factor VII, or transfusion of whole blood or plasma within the preceding 7 days of the index event<br>  ○ As judged by the investigator, if it is deemed undesirable for the participant to participate in the study or participant is unlikely to comply with study procedures, and requirements<br>  ○ Involvement in the planning and/or conduct of the study |

FXai, factor Xa inhibitor; PCC, prothrombin complex concentrate.
[a] Ongoing treatment/use refers to: 1) patient was taking apixaban, rivaroxaban, or edoxaban prior to index bleeding event, 2) patient started taking FXai ≥5 days prior to index event, 3) last FXai dose was ≤24 h prior to index bleed onset, or 4) the treating physician believes the major bleeding event to be related to FXai use (as documented in the medical record).
[b] Ongoing treatment with an FXai excludes treatment with vitamin K antagonists and dabigatran (within 7 days prior to the index date for Cohort B).
[c] Waiver of informed consent applies only to Cohort A. In Japan, an "opt-out" method will be adopted.

### 2.4. Study measurements

This hybrid study design leverages both primary and secondary data collection. Primary data collection will be done by direct-to-patient

**Table 2**
Primary and secondary objectives and descriptive variables.

| | Descriptive variables |
|---|---|
| Primary objectives | Cohorts A and B |
| To describe the characteristics of patients with FXai-associated major bleeding | • Demographics and lifestyle factors<br>• Medical history, comorbidities, and medication history<br>• Clinical presentation, vital signs, chemical and hematology parameters, and hemodynamic status<br>• Health care system characteristics |
| To describe the health care interventions provided during the acute-care phase and in-hospital outcomes in patients with FXai-associated major bleeding | • Health care interventions: reversal/replacement therapy,[a] transfusion of any blood products and/or rescue therapy, surgical procedures/interventions, and imaging at admission<br>• In-hospital outcomes<br>○ Hemostatic effectiveness[b]<br>○ ICU stay and length of ICU or hospital stay<br>○ Resumption of anticoagulant therapy and thrombotic events<br>○ Functional status at discharge and discharge disposition<br>○ All-cause mortality<br>○ Time to bleed cessation (*Cohort B only*)<br>○ PROs at discharge (*Cohort B only*) |
| To describe the association of timing of administration of reversal/replacement agents since admission/bleed onset with in-hospital outcomes | • Adjusted effect measures characterizing the impact of timing of administration of reversal/replacement agents on the following outcomes:<br>○ Hemostatic effectiveness[b]<br>○ Length of ICU or hospital stay<br>○ Resumption of anticoagulant therapy and thrombotic events<br>○ Functional status at discharge<br>○ All-cause mortality<br>○ Time to bleed cessation (*Cohort B only*)<br>○ PROs at discharge (*Cohort B only*) |
| Secondary objectives | Cohort B |
| To describe clinical outcomes and PROs at 30 days postindex in patients with FXai-associated major bleeding who were administered reversal/replacement therapy | • Resumption of anticoagulant therapy and thrombotic events<br>• All-cause rehospitalization, rehospitalization for rebleeds, and health care visits<br>• Functional status<br>• PROs<br>• All-cause mortality |
| To describe the association of timing of administration of reversal/replacement therapy since admission/bleed onset with clinical outcomes and PROs at 30 days postindex | • Adjusted effect measures characterizing the impact of timing of administration of reversal/replacement therapy on the following outcomes:<br>○ Resumption of anticoagulant therapy and thrombotic events<br>○ All-cause rehospitalization, rehospitalization for rebleeds, and health care visits<br>○ Functional status<br>○ PROs<br>○ Residential status<br>○ All-cause mortality |

CT, computed tomography; FXai, factor Xa inhibitor; Hct, hematocrit; Hgb, hemoglobin; ICH, intracranial hemorrhage; ICU, intensive care unit; PRBC, packed red blood cells; PRO, patient-reported outcome.

[a] The data on reversal/replacement therapy collected included: class, dose, frequency, time from admission to first dose administration of reversal/replacement therapy.

[b] Hemostatic effectiveness was categorized as excellent, good, or poor. For all bleed types, if patients required >2 units of blood products (excluding PRBC) or additional coagulation factors within 12 h after infusion of primary drug had finished, they will be considered to have poor hemostasis. For ICH, hemostasis is considered good/excellent if the hematoma volume, or thickness (for subarachnoid hemorrhages and subdural hematomas), increases by ≤20 %; good for a >20 % but ≤35 % increase; and poor for a >35 % increase on repeat imaging (within 12 h; time window 6–24 h after index CT). For non-ICH bleeding, hemostasis is considered excellent for an Hgb/Hct decrease of ≤10 % at 12 h, good for a >10 % but ≤20 % decrease, and poor for a >20 % decrease. Both Hgb and Hct will be corrected based on the amount of PRBC administered (for every 1 unit of PRBC given, 1 g/dL will be subtracted from the Hgb level and 3 % from the Hct level).

approaches, where possible, to capture PROMs. Secondary data collection will include data extracted from patients' medical records by physicians/site personnel. All data collected for enrolled patients will be captured via a standardized case report form (CRF) and identified by a unique CRF-generated participant identifier. Data extracted from medical records will include demographic information (e.g., age, race), health care system characteristics (e.g., hospital type), lifestyle factors (e.g., nicotine or alcohol use), medical history and comorbidities, medication history (e.g., use of FXai, type of FXai, indication, length of use, time since last dose), clinical presentation (e.g., bleed type, bleed location, bleed recurrence, hemodynamic status), and in-hospital outcomes (e.g., hemostatic effectiveness, length of stay, discharge disposition [home, nursing home, other destination]). Local adaptations to the variables may be required due to differential data availability and format in each country.

Primary data will be collected directly from consented patients in Cohort B at the index hospitalization and during follow-up at the 30-day and 90-day postindex visits. Data on health care resource use, comorbidities, and clinical health outcomes will be collected from routine health care visits that take place within a defined time frame for each of these follow-up time points. Collected data will include the type of reversal/replacement therapy agents, time from bleed onset to reversal/replacement administration, and time from admission to reversal/replacement administration.

Cohort B will also include the collection of PROMs, such as the Short Form-36 health survey, version 2 (acute recall; SF-36v2) and the 5-level EuroQol 5-dimension (EQ-5D-5L) questionnaire. These will be prospectively collected using a Web link (or app) at index visit (within 7 [±7] days after administration of reversal/replacement therapy) and at 30 (±14) days and 90 (±30) days postindex date. The SF-36 v2 is a standardized, patient-administered instrument that has been translated and validated in multiple countries and assesses 8 domains: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health [33]. The scores for these 8 domains are summarized as Physical and Mental Component Summary scores [33]. The EQ-5D-5L questionnaire measures generic HRQoL and has been translated and validated in numerous countries [34]. The EQ-5D-5L contains questions on 5 dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety/depression, each of which are scored based on 5 levels of severity (no problems, slight problems, moderate problems, severe problems, and extreme problems). These dimension scores can also be converted into a single numeric score. Use of both HRQoL instruments allows for more comprehensive coverage of key aspects of quality of life and dimensions of health [35].

In this study, AEs and serious AEs (SAEs), including those not reported to health care providers, will be collected as primary data (i.e., directly from consented patients). All nonserious AEs that are assessed to be possibly related to andexanet alfa and all SAEs, regardless of causality, will be recorded in the electronic CRF. The timing of data collection for different data elements is summarized in Supplemental Table 1.

### 2.5. Statistical analysis

The sample size for Cohort B is based on precision assumptions that should be obtained in terms of confidence intervals within geographic locations and/or bleed types. The sample size of Cohort A was chosen to

mirror that of Cohort B (see full statistical analysis plan in Supplemental Material). Analyses will be separately conducted for each cohort and will be based on the full analysis set, which will include all patients enrolled in the study with no important protocol deviations. The baseline value for descriptive summaries and statistical analyses is defined as the last non-missing observed measurement prior to admission or bleed onset for Cohort A and prior to administration of reversal/replacement therapy for Cohort B. Change from baseline endpoints will be quantified as change from baseline to postadmission/bleed onset value. For any endpoint subjected to log transformation, the change from baseline calculated and summarized on the log scale ratio will be back-transformed.

Continuous variables will be summarized using descriptive statistics (mean, standard deviation, median, 25th and 75th percentile, minimum, and maximum), and the number of missing observations will be reported. If data are available for <3 patients, summary statistics will not be presented, aside from minimum, maximum, and number of observations. Categorical variables will be summarized by frequencies and percentages at all time points using the most appropriate denominator; missing data may be included as a separate category, depending on the nature of the variable.

Logistic regression will be explored to model binary outcomes (yes/no; e.g., resumption of anticoagulant therapy), linear regression will be employed for continuous measures (e.g., time to bleed cessation and length of intensive care unit stay), and linear mixed models will be used for repeated assessments of continuous outcomes (e.g., PROMs). For outcomes for which time to event may be available (e.g., in-hospital all-cause mortality), the crude incidence rate of the outcome will be computed during follow-up. Incidence rates will be calculated as the total number of patients who ever had an event divided by the total person-time. Kaplan-Meier methods will be used to examine the median time (along with 95 % confidence intervals [CIs]) until the outcome. Cox proportional hazards models will be used to estimate unadjusted and adjusted hazard ratios and 95 % CIs.

For association analyses between groups (e.g., effectiveness comparison between early [≤90 min] and late [>90 min] initiation of reversal/replacement therapy since admission/bleed onset; andexanet alfa vs usual care), a multivariable regression model will be used to account for demographic and clinical characteristics of patients in different comparison groups when estimating the risk of certain outcomes of interest or PROMs data. Results will be presented for each of the cohorts and will be stratified by country, bleed type, and reversal/replacement agent. For specific outcomes, data may be pooled from Cohort A and Cohort B prior to the analysis (e.g., in-hospital outcome measures, such as hemostatic effectiveness, anticoagulant resumption, and mortality). Assuming different event rates (5 %, 10 %, 20 %, 30 %, and 40 %) and margins of error (1 %, 2 %, and 3 %) for an event of interest under the 95 % CI, a sample size of approximately 2000 patients should provide adequate precision in the point estimation.

## 3. Discussion

The introduction of FXai was welcomed as a major advancement in anticoagulant management due to the challenges associated with therapeutic use of VKAs, such as warfarin. However, when pivotal clinical trials reported the occurrence of major bleeding events following FXai use [36–38], the lack of a specific reversal agent for treatment of these bleeds emerged as a key concern for health care providers. Thus, the introduction of andexanet alfa as a specific FXai reversal agent in 2018 was seen as a practice-changing moment. Nonetheless, in many settings, 3F-PCC and 4F-PCC continue to be used off-label for the reversal of FXai-associated major bleeds despite their efficacy having not been established. For example, in 2020 a wide discrepancy was found in the availability of specific DOAC reversal agents across 4276 US hospitals, with andexanet alfa available in only approximately 12 % of sites that year [39].

The profiles of patients experiencing FXai-associated bleeds and receiving different reversal/replacement agents are not well understood, and the variation in clinical practices across different health care systems and countries has not been well studied. Previous studies of characteristics, treatment patterns, and outcomes for patients with FXai-associated bleeds in clinical practice have predominantly been limited to a single center or single country, included a relatively small patient population (<100 patients), were retrospective in nature, and/or did not evaluate long-term outcomes (Supplemental Table 2) [15–29,40–45]. These previous studies were focused predominantly on patients with ICH, resulting in limited insights into patients with other FXai-associated bleed types (e.g., non-ICH traumatic bleeds). Moreover, as nearly all prior observational studies did not collect information on PROMs, including those assessing HRQoL, this remains a critical evidence gap for these patients.

REVERXaL aims to address these key evidence gaps by generating insights on patient characteristics, treatment approaches, and associated outcomes in hospitalized patients with FXai-associated major bleeds across Germany, Japan, the United Kingdom, and the United States. This multicountry study also includes PROMs, and the longer-term assessment of PROMs and other clinical outcomes will provide insights into the treatment patterns for different bleed phenotypes from different health care systems. The inclusion of both historic and prospective cohorts will generate data on the changing patterns in clinical care as novel treatments have become available and will allow for a more comprehensive view of the broad population of patients with FXai-associated bleeds presenting at participating study sites. The longer follow-up included in this study provides an opportunity to assess both short- and long-term outcomes (e.g., mortality, functional status, and health care resource use) of this patient population. The outcomes of this long-term real-world study will complement and help to contextualize prospective clinical trial data on reversal and replacement agents, such as the ANNEXA-4 and ANNEXA-I clinical trials of andexanet alfa [11,46,47]. Additionally, data gathered from PROMs across patients with a variety of FXai-associated bleed types may provide valuable evidence to support payers' drug coverage decisions and health care provider discussions with patients regarding their choice of treatment.

### 3.1. Strengths and limitations

A key strength of this study is the extensive collection of clinical data and PROMs over a 3-month follow-up period across multiple countries. In addition, the analysis of health care interventions will provide insights on treatment approaches, including administration of reversal/replacement therapies in a real-world clinical setting, with a broader patient population and greater variations in the dosing and timing of reversal/replacement treatment administration than in a clinical trial. Further, the combined primary and secondary data approach used in the current study will provide a more comprehensive view of the patient journey, without interfering unnecessarily with clinical practice, since data collection will occur outside of physician-patient interaction and without demanding additional physician time.

This study may be subject to several limitations. Since this study leverages routinely collected medical data, there is a possibility of the occurrence of missing data for critical clinical and/or laboratory measures, and patients with missing data may be systematically different from patients without missing data, potentially introducing a bias. Further, the recruitment of Cohort B is prospective, and acquiring adequate participation in a timely manner may be difficult. Patient loss to follow-up in a study lasting 3 months posthospitalization is expected and could also impact recruitment and participation. However, Cohort A will help to understand the broader population of patients experiencing FXai-associated bleeds who present in the included sites and may provide a basis for identification of bias. While the study will include patients with different bleed types, it is possible that the number of patients with any specific bleed type may be too small to draw meaningful conclusions.

The collection of PROMs may be subject to error bias, which may affect the reliability or generalizability of findings. One such potential

source of bias is that patients who are the most severely compromised may not be able to report PROs. However, quality control of data collection methodology and proper statistical consideration will limit the possible impact of this challenge. Additionally, immortal time bias is a potential limitation of observational or noninterventional studies [48]; in the current study, every effort will be made to recruit patients as early as possible after hospital admission and collect information on all eligible patients. In general, given the observational and descriptive nature of the study, it may not be possible to establish causality on the findings. However, the descriptive nature of the study objectives and the incorporation of methodologic approaches to minimize potential confounding would help to improve the validity of findings.

## 4. Conclusions

REVERXaL will generate insights into the characteristics of hospitalized patients with FXai-associated major bleeds and will provide a broad view of the full spectrum of patient care and outcomes for these types of bleeds. These data may inform clinical guidelines and initiatives to streamline treatment pathways for patients experiencing acute major bleeding while taking FXai.

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## CRediT authorship contribution statement

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## Declaration of competing interest

MN and SY have no conflicts of interest to disclose. RA has received fees for consulting work from AstraZeneca, Alexion, Bristol Myers Squibb, Pfizer, Bayer, and Daiichi. RO-A, SA-C, HC, and BK are employees of AstraZeneca. MY has received lecture, advisory, and travel fees from AstraZeneca, Bristol Myers Squibb, Nippon Boehringer Ingelheim, Bayer, Daiichi Sankyo, and CSL Behring; and scholarship funds or nonrestricted grants from Nippon Boehringer Ingelheim. VS has served as a consultant for Apollo Endosurgery, Pentax, Medtronic, Pharmacosmos, Microtech, and AstraZeneca; has served on advisory boards for Pharmacosmos and Microtech; and has received educational grants from Apollo Endosurgery, Pentax, and Medtronic. AT has received consulting fees from Bayer, Biomarin, Biotest, Chugai, Roche, Takeda, CSL Behring, Novo Nordisk, Octapharma, Pfizer, and Sobi; has received payment or honoraria for lectures, presentations, speakers bureaus, or educational events from Bayer, Biomarin, Biotest, Chugai, Roche, Takeda, CSL Behring, Novo Nordisk, Octapharma, Pfizer, and Sobi; and has received support for attending meetings and/or travel from Bayer, Biomarin, Biotest, Chugai, Roche, Takeda, CSL Behring, Novo Nordisk, Octapharma, Pfizer, and Sobi. BDC has served as a consultant for AstraZeneca. MM has received lecture honoraria, payment for participation in expert and advisory panels, and financial support for scientific meeting participation from AstraZeneca, Baxter, Bayer, Biotest, CSL Behring, IL-Werfen/TEM-International, LFB Biomedicaments France, Octapharma, and Portola. AJS has served on an advisory board for Alexion and AstraZeneca; has served on the speakers bureau of Alexion and AstraZeneca; and his institution has received research funding from Alexion.

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## References

[1] D.J. Kumbhani, C.P. Cannon, C.J. Beavers, D.L. Bhatt, A. Cuker, T.J. Gluckman, J. E. Marine, R. Mehran, S.R. Messe, N.S. Patel, B.E. Peterson, K. Rosenfield, S. A. Spinler, V.H. Thourani, 2020 ACC expert consensus decision pathway for anticoagulant and antiplatelet therapy in patients with atrial fibrillation or venous thromboembolism undergoing percutaneous coronary intervention or with atherosclerotic cardiovascular disease: A report of the American College of Cardiology Solution Set Oversight Committee, J. Am. Coll. Cardiol. 77 (2021) 629–658, https://doi.org/10.1016/j.jacc.2020.09.011.

[2] G. Hindricks, T. Potpara, N. Dagres, E. Arbelo, J.J. Bax, C. Blomstrom-Lundqvist, G. Boriani, M. Castella, G.A. Dan, P.E. Dilaveris, L. Fauchier, G. Filippatos, J. M. Kalman, M. La Meir, D.A. Lane, J.P. Lebeau, M. Lettino, G.Y.H. Lip, F.J. Pinto, G. N. Thomas, M. Valgimigli, I.C. Van Gelder, B.P. Van Putte, C.L. Watkins, 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC, Eur. Heart J. 42 (2021) 373–498, https://doi.org/10.1093/eurheartj/ehaa612.

[3] A. Chen, E. Stecker, B.A. Warden, Direct oral anticoagulant use: a practical guide to common clinical challenges, J. Am. Heart Assoc. 9 (2020) e017559, https://doi.org/10.1161/JAHA.120.017559.

[4] K.N. Aronis, E.M. Hylek, Evidence gaps in the era of non-vitamin K oral anticoagulants, J. Am. Heart Assoc. 7 (2018) e007338, https://doi.org/10.1161/JAHA.117.007338.

[5] A. Troy, T.S. Anderson, National trends in use of and spending on oral anticoagulants among US Medicare beneficiaries from 2011 to 2019, JAMA Health Forum 2 (2021) e211693, https://doi.org/10.1001/jamahealthforum.2021.1693.

[6] T.J. Milling Jr., J. Frontera, Exploring indications for the use of direct oral anticoagulants and the associated risks of major bleeding, Am. J. Manag. Care 23 (2017) S67–S80.

[7] T. Inohara, Y. Xian, L. Liang, R.A. Matsouaka, J.L. Saver, E.E. Smith, L. H. Schwamm, M.J. Reeves, A.F. Hernandez, D.L. Bhatt, E.D. Peterson, G. C. Fonarow, Association of intracerebral hemorrhage among patients taking non-vitamin k antagonist vs vitamin k antagonist oral anticoagulants with in-hospital mortality, JAMA 319 (2018) 463–473, https://doi.org/10.1001/jama.2017.21917.

[8] J.M. Williams, B. Lovelace, M.J. Christoph, S. Li, H. Guo, M. Hoover, C.I. Coleman, Clinical and health care resource use burden of hospitalizations for oral factor Xa inhibitor-associated major bleeding: A real-world analysis of Medicare beneficiaries, J. Am. Coll. Emerg. Physicians Open 4 (2023) e12956, https://doi.org/10.1002/emp2.12956.

[9] D. Wilson, D.J. Seiffge, C. Traenka, G. Basir, J.C. Purrucker, T. Rizos, O. A. Sobowale, H. Sallinen, S.J. Yeh, T.Y. Wu, M. Ferrigno, R. Houben, F.H.B. M. Schreuder, L.A. Perry, J. Tanaka, M. Boulanger, R. Al-Shahi Salman, H.R. Jager, G. Ambler, C. Shakeshaft, Y. Yakushiji, P.M.C. Choi, J. Staals, C. Cordonnier, J.

S. Jeng, R. Veltkamp, D. Dowlatshahi, S.T. Engelter, A.R. Parry-Jones, A. Meretoja, D.J. Werring, Outcome of intracerebral hemorrhage associated with different oral anticoagulants, Neurology 88 (2017) 1693–1700, https://doi.org/10.1212/WNL.0000000000003886.
[10] ANDEXXA® (coagulation factor Xa (recombinant), inactivated-zhzo), Lyophilized Powder for Solution for Intravenous Injection [Package Insert], Portola Pharmaceuticals, Inc., South San Francisco, CA, 2018.
[11] S.J. Connolly, M. Crowther, J.W. Eikelboom, C.M. Gibson, J.T. Curnutte, J. H. Lawrence, P. Yue, M.D. Bronson, G. Lu, P.B. Conley, P. Verhamme, J. Schmidt, S. Middeldorp, A.T. Cohen, J. Beyer-Westendorf, P. Albaladejo, J. Lopez-Sendon, A. M. Demchuk, D.J. Pallin, M. Concha, S. Goodman, J. Leeds, S. Souza, D.M. Siegal, E. Zotova, B. Meeks, S. Ahmad, J. Nakamya, T.J. Milling Jr., Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors, N. Engl. J. Med. 380 (2019) 1326–1335, https://doi.org/10.1056/NEJMoa1814051.
[12] C.W. Baugh, M. Levine, D. Cornutt, J.W. Wilson, R. Kwun, C.E. Mahan, C. V. Pollack Jr., E.G. Marcolini, T.J. Milling Jr., W.F. Peacock, R.P. Rosovsky, F. Wu, R. Sarode, A.C. Spyropoulos, T.C. Villines, T.D. Woods, J. McManus, J. Williams, Anticoagulant reversal strategies in the emergency department setting: recommendations of a multidisciplinary expert panel, Ann. Emerg. Med. 76 (2020) 470–485, https://doi.org/10.1016/j.annemergmed.2019.09.001.
[13] H. Christensen, C. Cordonnier, J. Korv, A. Lal, C. Ovesen, J.C. Purrucker, D. Toni, T. Steiner, European Stroke Organisation guideline on reversal of oral anticoagulants in acute intracerebral haemorrhage, Eur. Stroke J. 4 (2019) 294–306, https://doi.org/10.1177/2396987319849763.
[14] G.F. Tomaselli, K.W. Mahaffey, A. Cuker, P.P. Dobesh, J.U. Doherty, J. W. Eikelboom, R. Florido, T.J. Gluckman, W.J. Hucker, R. Mehran, S.R. Messe, A. C. Perino, F. Rodriguez, R. Sarode, D.M. Siegal, B.S. Wiggins, 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Solution Set Oversight Committee, J. Am. Coll. Cardiol. 76 (2020) 594–622, https://doi.org/10.1016/j.jacc.2020.04.053.
[15] C.S. Brown, A.E. Mattson, D. Cabrera, N. Coelho-Prabhu, A.A. Rabinstein, T. Dettling, R.D. McBane 2nd, F. Bellolio, Real world utilization of Andexanet alfa in the management of oral factor Xa inhibitor-associated gastrointestinal bleeding, Am. J. Emerg. Med. 73 (2023) 1–6, https://doi.org/10.1016/j.ajem.2023.07.042.
[16] A.J. Singer, M. Concha, J. Williams, C.S. Brown, R. Fernandes, H.C. Thode Jr., M. Kirchman, A.A. Rabinstein, Treatment of factor-Xa inhibitor-associated bleeding with Andexanet alfa or 4 factor PCC: a multicenter feasibility retrospective study, West J. Emerg. Med. 24 (2023) 939–949, https://doi.org/10.5811/westjem.60587.
[17] G. Pon, B. Pelsue, S.T. Reddy, K. Parsha, X. Zhang, B. Gulbis, A. Barreto, S.I. Savitz, M. Escobar, T.A. Allison, Hemostatic efficacy of four factor prothrombin complex concentrate in intracerebral hemorrhage patients receiving warfarin vs. factor Xa inhibitors, Thromb. Res. 229 (2023) 46–52, https://doi.org/10.1016/j.thromres.2023.06.021.
[18] M. Lipski, S. Pasciolla, K. Wojcik, B. Jankowitz, L.A. Igneri, Comparison of 4-factor prothrombin complex concentrate and andexanet alfa for reversal of apixaban and rivaroxaban in the setting of intracranial hemorrhage, J. Thromb. Thrombolysis 55 (2023) 519–526, https://doi.org/10.1007/s11239-022-02752-z.
[19] C. Troyer, W. Nguyen, A. Xie, D. Wimer, Retrospective review of Andexanet alfa versus 4-factor prothrombin complex concentrate for reversal of DOAC-associated intracranial hemorrhage, J. Thromb. Thrombolysis 55 (2023) 149–155, https://doi.org/10.1007/s11239-022-02715-4.
[20] P.M. Whaley, C. Franco-Martinez, A.E. Lock, D. Ramaswamy, E.H. Young, S. M. Allen, C.A. Barthol, Hemostatic efficacy and safety of 4-factor prothrombin complex concentrate in DOAC-associated intracranial hemorrhage, J. Pharm. Pract. (2022) 8971900221148034, https://doi.org/10.1177/08971900221148034.
[21] L. Milioglou, K. Liao, J. Traeger, C. McKenzie, C. Burrelli, A.K.B. Khunayfir, J. Makii, A. Hoffer, Reversal of factor Xa inhibitors associated intracranial haemorrhage at a tertiary medical centre, Blood Coagul. Fibrinolysis 33 (2022) 261–265, https://doi.org/10.1097/MBC.0000000000001128.
[22] H. Pham, W.G. Medford, S. Horst, M. Levesque, D. Ragoonanan, C. Price, H. Colbassani, K. Piper, K. Chastain, Andexanet alfa versus four-factor prothrombin complex concentrate for the reversal of apixaban- or rivaroxaban-associated intracranial hemorrhages, Am. J. Emerg. Med. 55 (2022) 38–44, https://doi.org/10.1016/j.ajem.2022.02.029.
[23] M. Hormese, A. Littler, B. Doane, N. Glowacki, A. Khimani, N. Vivacqua, K. Rudenberg, Comparison of high- and low-dose 4-factor prothrombin complex concentrate for the emergent reversal of oral factor Xa inhibitors, J. Thromb. Thrombolysis 52 (2021) 828–835, https://doi.org/10.1007/s11239-021-02412-8.
[24] E.A. Highsmith, C. Morton, S. Varnado, K.R. Donahue, S. Sulhan, A. Lista, Outcomes associated with 4-factor prothrombin complex concentrate administration to reverse oral factor Xa inhibitors in bleeding patients, J. Clin. Pharmacol. 61 (2021) 598–605, https://doi.org/10.1002/jcph.1779.
[25] M.J. Korobey, F. Sadaka, M. Javed, M. Moynihan, A. Alsaei, Efficacy of 4-factor prothrombin complex concentrates in factor Xa inhibitor-associated intracranial bleeding, Neurocrit. Care 34 (2021) 112–120, https://doi.org/10.1007/s12028-020-00968-6.
[26] C.J. Nederpelt, L. Naar, K.W. Sylvester, M.E. Barra, R.J. Roberts, G.C. Velmahos, H. M.A. Kaafarani, M.G. Rosenthal, D.R. King, Evaluation of oral factor Xa inhibitor-associated extracranial bleeding reversal with andexanet alfa, J. Thromb. Haemost. 18 (2020) 2532–2541, https://doi.org/10.1111/jth.15031.
[27] A. Giovino, E. Shomo, K.V. Busey, D. Case, A. Brockhurst, M. Concha, An 18-month single-center observational study of real-world use of andexanet alfa in patients with factor Xa inhibitor associated intracranial hemorrhage, Clin. Neurol. Neurosurg. 195 (2020) 106070, https://doi.org/10.1016/j.clineuro.2020.106070.
[28] P.P. Dobesh, G.J. Fermann, M.J. Christoph, B. Koch, E. Lesen, H. Chen, B. Lovelace, T. Dettling, M. Danese, J. Ulloa, S. Danese, C.I. Coleman, Lower mortality with andexanet alfa vs 4-factor prothrombin complex concentrate for factor Xa inhibitor-related major bleeding in a U.S. hospital-based observational study, Res. Pract. Thromb. Haemost. 7 (2023) 102192, https://doi.org/10.1016/j.rpth.2023.102192.
[29] S.S. Sutton, J. Magagnoli, T.H. Cummings, T. Dettling, B. Lovelace, M.J. Christoph, J.W. Hardin, Real-world clinical outcomes among US veterans with oral factor xa inhibitor-related major bleeding treated with andexanet alfa or 4-factor prothrombin complex concentrate, J. Thromb. Thrombolysis 56 (2023) 137–146, https://doi.org/10.1007/s11239-023-02820-y.
[30] Center for Drug Evaluation and Research, Center for Devices and Radiological Health, Center for Biologics Evaluation and Research, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Guidance for Industry, 2009 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims (Accessed February 13, 2024).
[31] S. Cruz Rivera, C. McMullan, L. Jones, D. Kyte, A. Slade, M. Calvert, The impact of patient-reported outcome data from clinical trials: perspectives from international stakeholders, J Patient Rep Outcomes 4 (2020) 51, https://doi.org/10.1186/s41687-020-00219-4.
[32] S. Schulman, U. Angeras, D. Bergqvist, B. Eriksson, M.R. Lassen, W. Fisher, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis, Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients, J. Thromb. Haemost. 8 (2010) 202–204, https://doi.org/10.1111/j.1538-7836.2009.03678.x.
[33] L. Lins, F.M. Carvalho, SF-36 total score as a single measure of health-related quality of life: scoping review, SAGE Open Med 4 (2016) 2050312116671725, https://doi.org/10.1177/2050312116671725.
[34] C. Gerlinger, L. Bamber, F. Leverkus, C. Schwenke, C. Haberland, G. Schmidt, J. Endrikat, Comparing the EQ-5D-5L utility index based on value sets of different countries: impact on the interpretation of clinical study results, BMC. Res. Notes 12 (2019) 18, https://doi.org/10.1186/s13104-019-4067-9.
[35] A. Vaidya, M.C. Kleinegris, J.L. Severens, B.L. Ramaekers, A.J. Ten Cate-Hoek, H. Ten Cate, M.A. Joore, Comparison of EQ-5D and SF-36 in untreated patients with symptoms of intermittent claudication, J Comp Eff Res 7 (2018) 535–548, https://doi.org/10.2217/cer-2017-0029.
[36] R.P. Giugliano, C.T. Ruff, E. Braunwald, S.A. Murphy, S.D. Wiviott, J.L. Halperin, A.L. Waldo, M.D. Ezekowitz, J.I. Weitz, J. Spinar, W. Ruzyllo, M. Ruda, Y. Koretsune, J. Betcher, M. Shi, L.T. Grip, S.P. Patel, I. Patel, J.J. Hanyok, M. Mercuri, E.M. Antman, Edoxaban versus warfarin in patients with atrial fibrillation, N. Engl. J. Med. 369 (2013) 2093–2104, https://doi.org/10.1056/NEJMoa1310907.
[37] M.R. Patel, K.W. Mahaffey, J. Garg, G. Pan, D.E. Singer, W. Hacke, G. Breithardt, J. L. Halperin, G.J. Hankey, J.P. Piccini, R.C. Becker, C.C. Nessel, J.F. Paolini, S. D. Berkowitz, K.A. Fox, R.M. Califf, Rivaroxaban versus warfarin in nonvalvular atrial fibrillation, N. Engl. J. Med. 365 (2011) 883–891, https://doi.org/10.1056/NEJMoa1009638.
[38] C.B. Granger, J.H. Alexander, J.J. McMurray, R.D. Lopes, E.M. Hylek, M. Hanna, H. R. Al-Khalidi, J. Ansell, D. Atar, A. Avezum, M.C. Bahit, R. Diaz, J.D. Easton, J. A. Ezekowitz, G. Flaker, D. Garcia, M. Geraldes, B.J. Gersh, S. Golitsyn, S. Goto, A. G. Hermosillo, S.H. Hohnloser, J. Horowitz, P. Mohan, P. Jansky, B.S. Lewis, J. L. Lopez-Sendon, P. Pais, A. Parkhomenko, F.W. Verheugt, J. Zhu, L. Wallentin, Apixaban versus warfarin in patients with atrial fibrillation, N. Engl. J. Med. 365 (2011) 981–992, https://doi.org/10.1056/NEJMoa1107039.
[39] Z. Kanjee, M.L. McCann, J.A. Freed, Availability of specific direct oral anticoagulant reversal agents in US hospitals, JAMA Netw. Open 4 (2021) e2110079, https://doi.org/10.1001/jamanetworkopen.2021.10079.
[40] S. Rauch, H.P. Muller, J. Dreyhaupt, A.C. Ludolph, J. Kassubek, K. Althaus, Andexanet alfa for reversal of factor Xa inhibitors in intracranial hemorrhage: observational cohort study, J. Clin. Med. 11 (2022), https://doi.org/10.3390/jcm11123399.
[41] A.A. Ammar, M.A. Ammar, K.A. Owusu, S.C. Brown, F. Kaddouh, A.A. Elsamadicy, J.N. Acosta, G.J. Falcone, Andexanet alfa versus 4-factor prothrombin complex concentrate for reversal of factor Xa inhibitors in intracranial hemorrhage, Neurocrit. Care 35 (2021) 255–261, https://doi.org/10.1007/s12028-020-01161-5.
[42] H.A. Wilsey, A.M. Bailey, A. Schadler, G.A. Davis, M. Nestor, K. Pandya, Comparison of low- versus high-dose four-factor prothrombin complex concentrate (4F-PCC) for factor Xa inhibitor-associated bleeding: a retrospective study, J. Intensive Care Med. 36 (2021) 597–603, https://doi.org/10.1177/0885066620916706.
[43] R. Castillo, A. Chan, S. Atallah, K. Derry, M. Baje, L.L. Zimmermann, R. Martin, L. Groysman, S. Stern-Nezer, A. Minokadeh, A. Nova, W. Huang, W. Cang, K. Schomer, Treatment of adults with intracranial hemorrhage on apixaban or rivaroxaban with prothrombin complex concentrate products, J. Thromb. Thrombolysis 51 (2021) 151–158, https://doi.org/10.1007/s11239-020-02154-z.
[44] M.N. Smith, L. Deloney, C. Carter, K.A. Weant, E.A. Eriksson, Safety, efficacy, and cost of four-factor prothrombin complex concentrate (4F-PCC) in patients with factor Xa inhibitor-related bleeding: a retrospective study, J. Thromb. Thrombolysis 48 (2019) 250–255, https://doi.org/10.1007/s11239-019-01846-5.
[45] M. Sheikh-Taha, Treatment of apixaban- and rivaroxaban-associated major bleeding using 4-factor prothrombin complex concentrate, Intern. Emerg. Med. 14 (2019) 265–269, https://doi.org/10.1007/s11739-018-1977-9.
[46] T.J. Milling Jr., S. Middeldorp, L. Xu, B. Koch, A. Demchuk, J.W. Eikelboom, P. Verhamme, A.T. Cohen, J. Beyer-Westendorf, C. Michael Gibson, J. Lopez-

Sendon, M. Crowther, A. Shoamanesh, M. Coppens, J. Schmidt, P. Albaladejo, S. J. Connolly, ANNEXA-4 Investigators, Final study report of andexanet alfa for major bleeding with factor Xa inhibitors, Circulation 147 (2023) 1026–1038, https://doi.org/10.1161/CIRCULATIONAHA.121.057844.

[47] S.J. Connolly, M. Sharma, A.T. Cohen, A.M. Demchuk, A. Członkowska, A. G. Lindgren, C.A. Molina, D. Bereczki, D. Toni, D.J. Seiffge, D. Tanne, E.C. Sandset, G. Tsivgoulis, H. Christensen, J. Beyer-Westendorf, J.M. Coutinho, M. Crowther, P. Verhamme, P. Amarenco, R.O. Roine, R. Mikulik, R. Lemmens, R. Veltkamp, S. Middeldorp, T.G. Robinson, T.J. Milling Jr., V. Tedim-Cruz, W. Lang, A. Himmelmann, P. Ladenvall, M. Knutsson, E. Ekholm, A. Law, A. Taylor, T. Karyakina, L. Xu, K. Tsiplova, S. Poli, B. Kallmünzer, C. Gumbinger, A. Shoamanesh, ANNEXA-I Investigators, Andexanet for factor Xa inhibitor-associated acute intracerebral hemorrhage, N. Engl. J. Med. 390 (2024) 1745–1755, https://doi.org/10.1056/NEJMoa2313040. https://www.nejm.org/doi/10.1056/NEJMoa2313040.

[48] K. Yadav, R.J. Lewis, Immortal time bias in observational studies, JAMA 325 (2021) 686–687, https://doi.org/10.1001/jama.2020.9151.