Bleeding Complications in Patients on New Oral Anticoagulants for Venous Thromboembolism in Kenya

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Research Article

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Abstract

Background:

The purpose of this study is to determine the rates of bleeding associated with NOAC use.

Methods:

Patients diagnosed with venous thromboembolism (VTE) and treated with NOACs at a tertiary referral hospital in Kenya from January 2014 to December 2019 were recruited. They were followed up from commencement of oral anticoagulation to completion of therapy, the first major bleed, clinically relevant non-major bleed (CRNM), or minor bleeding. Data on bleeding was obtained from the hospital database and through telephone interviews. Unadjusted rates of the first major bleeding event or clinically relevant non-major bleeding (CRNM) were calculated as the number of bleeding events per 100 patient-years.

Results:

Two hundred forty-three patients with VTE were recruited. 222 (91.4%) were initiated on rivaroxaban, 12 (4.9%) on dabigatran, 9 (3.7%) on apixaban with a median follow-up of 213 (119,477) days. The median age of the patients was 57 (45, 71) years. A total of 64 bleeding events were identified in 41 (16.9%) patients, 18.8% were major, 17.2% were clinically relevant non-major (CRNM), and 64.1% were minor. The incidence rate for bleeding events was 22.1 per 100 patient-years. Gastrointestinal (GIT) bleeding was the most common major bleeding site. There were more females with bleeding events (70.7%) compared to males.

Conclusions:

In our cohort, most bleeding events were minor, with the GIT being the most common site of major bleeding and menorrhagia being the commonest cause of bleeding. Females had more major and CRNM than men.

Key Points

- Most of the patients were initiated on rivaroxaban
- Incidence rate of bleeding was 22.1 per 100 patient-years
- Gastrointestinal bleeding was the most common major bleeding site
- Females had more bleeding events than males
- Future clinical trials should include outcomes stratified by sex, and further trials are needed to investigate the clinical impact of this sex-related safety difference.
Introduction

Venous thromboembolism (VTE) (comprising deep-vein thrombosis (DVT), or pulmonary embolism (P.E.), or both) is the third most common cardiovascular disorder [1] with an incidence of one to two cases per 1000 people in the general population. VTE is associated with a high mortality rate, substantial healthcare costs, and a high recurrence rate [2].

Until the advent of newer agents, the standard treatment of VTE included parenteral anticoagulants and vitamin K antagonists (primarily warfarin) with a target International Normalized Ratio (INR) of 2.0–3.0. The use of warfarin for long-term treatment of VTE has been associated with a significant risk of bleeding. A pooled analysis of the EINSTEIN-DVT and P.E. study revealed that a first major or non-major clinically relevant bleeding event occurred in 388 (9.4%) rivaroxaban patients compared with 412 patients (10.0%) in the standard therapy group (heparin combined with vitamin K antagonists); hazard ratio, 0.93 [3]. Furthermore, the use of warfarin is associated with several drug and food interactions that could either increase or decrease its metabolism, and its use requires frequent monitoring of INR, which is both costly and cumbersome. The introduction of new oral anticoagulants (NOACs) has revolutionized the treatment of both VTE. These agents have a wider therapeutic window, a reduced need for monitoring, and fewer interactions.

Several phase 3 trials have highlighted the benefit of using NOACs versus warfarin [4] to treat VTE. Data on real-life patients in Sub-Saharan Africa are anecdotal. Although less compared to warfarin, bleeding complications still occur and are associated with high morbidity and mortality. The new oral anticoagulants apixaban, dabigatran, edoxaban, and rivaroxaban are efficacious in phase 3 randomized trials for acute and long-term treatment of venous thromboembolism [3, 5, 6]. In the RE-COVER and RECOVER II trials, dabigatran etexilate 150mg had comparable efficacy to dose-adjusted warfarin for the treatment of DVT and PE [7]. Dabigatran's efficacy was comparable to that of warfarin with much fewer bleeding events for extended treatment of VTE in the RE-MEDY trial[8]. The phase 3 EINSTEIN DVT study showed that major bleeding occurred less often with rivaroxaban and with less severity than with low molecular weight (LMWH)/ vitamin K antagonists (VKA) therapy [3], and it was equally as efficacious in the treatment of VTE [6, 7]. In the AMPLIFY trial of apixaban use in VTE, apixaban is non-inferior to conventional therapy in VTE treatment, and the rate of major bleeding was significantly lower in the apixaban group [9].

XALIA, a large-scale, prospective study of rivaroxaban in patients with VTE, showed a low rate of major bleeding (0.8% vs. 2.1%) and recurrent VTE in the treatment of deep-vein thrombosis (DVT) [4]. Similar real-world studies, including from European PREFER and the REMOTEV study, showed low rates of major bleeding (The major and clinically relevant bleeding rate was 5.4% (15/280) in the rivaroxaban group 9.4%/(9/96) in the VKA group and 7.2% (5/69) in the heparin/fondaparinux group) [10, 11]. These results are consistent with those of the phase 3 EINSTEIN-DVT and P.E. trials [3] and confirm that these studies' results can be translated to patients typically treated in routine clinical practice.
ETNA-VTE Europe, a prospective, non-interventional study conducted in eight European countries, assessed the real-world benefits and risks of edoxaban for the treatment of VTE during the first three months. The rate of major bleeding was few, occurring in 0.97% of the patients. This study further reaffirms the safety of NOACs in contemporary clinical practice[12].

There are some data from East Africa, but they are very scarce. XALIA-LEA was conducted in regions not included in XALIA (Latin America, Eastern Europe, the Middle East, Africa, and the Asia-Pacific) and enrolled patients with isolated pulmonary embolism (P.E.). It included 12 patients on rivaroxaban from Kenya, 145 from Egypt, and 32 from Algeria [13]. This study reaffirmed the findings of XALIA.

NOACs have a higher incidence of gastrointestinal bleeding (GIB) compared with VKA [14]. In the RE-LY trial, dabigatran at 150mg twice a day was associated with a higher incidence of gastrointestinal bleeding than warfarin (1.51% vs. 1.02%). Holster et al. [15] summarized the risk of GIB associated with NOACs in a meta-analysis and noted 1.5% GIB events, with 89% being major GIB (defined by International Society on Thrombosis and Haemostasis (ISTH) criteria).

Methods

Study design and population

This was a single-center, retrospective cohort study of patients diagnosed with VTE and treated with NOACs. All patients with a confirmed VTE diagnosis who had been on treatment with NOACs were eligible for inclusion if ≥18 years. The index date of diagnosis was defined as the date of the first prescription of the NOAC. Patients were followed from the index date to the first major or first CRNM bleeding event, date of discontinuation of NOAC, a switch to VKA (commonly warfarin), or LMWH end of the study period, or interruption in continuous enrolment, whichever occurred earlier.

Data collection procedures

A hospital database medical chart search of patients with VTE was carried out. Files for patients with VTE diagnosed between January 2014 and December 2019 were retrieved. The observation period ended three months from the final patient enrolment date, ensuring that each patient was followed up for at least three months. Demographic and clinical characteristics, relevant concomitant medication was obtained from the medical records. Comorbidities, including heart failure, acute coronary syndromes, peripheral vascular disease, hypertension, renal insufficiency, cancer, stroke, alcohol, and tobacco use, were identified based on the diagnosis. A questionnaire was used to record data on bleeding. Patients were advised to seek medical attention if they developed any bleeding complications.

Outcome Parameters

The primary outcome was minor, major, or CRNM bleeding per the ISTH (International Society on Thrombosis and Hemostasis) criteria [16].
Data Analysis

Categorical data were presented as frequencies and percentages and continuous data as means and standard deviations or medians and interquartile ranges. Unadjusted rates of the first major bleeding event or CRNM bleeding were reported as the number of bleeding events per 100 person-years. Univariate analyses were performed using the Kruskal Wallis test for continuous variables and Fishers Exact test for categorical variables. A p-value of less than 0.05 was considered significant.

Results

Study Cohort

A total of 608 patients were assessed for eligibility; 288 did not meet the inclusion criteria. Three hundred twenty were enrolled, of whom 77 were excluded (unavailable or declined to participate). A total of 243 patients were included in the final analysis, as shown in Figure 1.

Baseline Patient Characteristics

Among 243 eligible patients, 222 (91.4%) were initiated on rivaroxaban, 12 (4.9%) on dabigatran, and 9 (3.7%) on apixaban with a median follow-up of 213 (IQR: 119 - 477) days. The median age of the patients was 57 (IQR: 45 - 71) years, mean 57.9(16.09)

Of the comorbidities investigated, hypertension, diabetes mellitus, dyslipidemia, cancer, and renal dysfunction affected >10% of the patients at baseline. Table 1 describes the baseline patient characteristics.

Bleeding Incidence

The median follow-up time was 213 (IQR: 119 - 477) days, and the total follow-up was 105,872 days. A total of 64 bleeding events were identified in 41 patients (16.9%) with a bleeding event rate of 22.1/100 patient-years (Table 3). Of these, 18.8% were major, 17.2% were CRNM, and 64.1% were minor (Figure 2). The most common anatomical site for major bleeding was the GIT with 1.7 events per 100 patient-years. (Table 2)

Major Bleeding Events

Ten patients (4%) had a major bleeding event. The overall incidence rate for major bleeding events was 4.1 per 100 patient-years. G.I. bleeding was the most common major bleeding site, with 1.7 major events per 100 patient-years, followed by muscle bleeding with 1.03 events per 100 patient-years. Table 2 illustrates the proportions of the different forms of bleeding.

Factors associated with bleeding
The median age of the patients with bleeding events was 47 years, while the non-bleeding population had a median age of 60. There were more females (70.7%) with bleeding events than males (46.5%). (Table 4)

Furthermore, a logistic regression was analysed to identify independent associations and younger age, female gender and those with dyslipidemia were associated with bleeding (Age: odds ratio [OR], 0.93; 95% CI, 0.90-0.96; P <0.001; Females: OR, 2.97; 95% CI, 1.30-6.80; P =0.010; Dyslipidemia: OR, 9, 87; 95% CI, 3.51-27.76; P <0.001) (Table 5)

**Discussion**

This was a single-center retrospective review of VTE patients on NOACs assessing bleeding outcomes in a Sub-Saharan African setting. The study found that the incidence rate for bleeding was 22.1 per 100 patient-years, with the most common site of major bleeding being the gastrointestinal system. Female sex was associated with a higher risk of major and clinically relevant non-major bleeding.

The major bleeding rate was 4.1 per 100 patient-years, similar to the Dresden NOAC registry (a large, prospective registry in the administrative district of Dresden, Germany) study, which found major bleeding rates of 4.1 per 100 patient years[17]. More than 80% of all the NOAC associated bleeding was non-major bleeding, with major bleeds accounting for 17.2% of all the events. The most common site of major bleeding was the gastrointestinal system (2.1%). These G.I. bleeds required blood transfusions and endoscopic interventions to stop the bleeding, and one case was fatal. One case of major GI bleeding occurred in a patient with gastrointestinal cancer, necessitating conversion to LMWH. These findings are similar to a meta-analysis by Holster et al., which reported a higher tendency to GIB among patients receiving NOACs than standard therapy with VKA[15]. A retrospective review of patients with G.I. malignancy and VTE treated with rivaroxaban or LMWH revealed a higher GIB incidence among rivaroxaban users (19).

Menorrhagia was the most common form of non-major bleeding, accounting for 35.9% of all bleeding. More than 90% were managed conservatively, mainly by a dose reduction or temporary interruption of NOAC therapy, use of antifibrinolytic agents, or insertion of an intrauterine device (IUD). The high rates of menorrhagia reported in this study may reflect that the study population consists of young, fertile women rather than a mixed older population. These bleeds caused significant discomfort to the point of temporary discontinuation of the NOACs. This discontinuation could cause a recurrence of VTE. A study done in Sweden to assess the frequency of minor bleeding symptoms and menorrhagia amongst ninety fertile women between the age of 15–49 revealed that the mean duration of menses increased from 5.6 to 6.1 days (P < 0.01) and reported menorrhagia from 44.2 to 70.8% (P < 0.001). Eighteen percent were treated for menorrhagia before and 29.9% during oral anticoagulant treatment (P < 0.01)[18]. In a retrospective study to assess the management and outcomes of vaginal bleeding and heavy menstrual bleeding in women of reproductive age on NOACs, 32% of the patients had vaginal bleeding events [19].
Even if our study did not include the impact on the quality of life, it is still possible to infer that these bleeds impacted the patients' quality of life.

There were no reports of intracranial bleeding in this study. Intracranial bleeding was observed in 0.2% (6 out of 2619) of patients in a prospective study assessing the safety and effectiveness of rivaroxaban in DVT (XALIA) (4). In an observational study conducted to assess rivaroxaban's safety and efficacy for VTE in routine care, there were no intracranial bleeds in the rivaroxaban group (10). However, in the EINSTEIN-PE study, there were three cases of intracranial bleeds, of which two were fatal (15).

Female sex was associated with a higher risk of major and clinically relevant non-major bleeding. Gender differences have been reported in patients with acute VTE treated with antithrombotic drugs. A meta-analysis was done to assess the relationship between gender and NOACS related bleeding. A higher risk of bleeding was found in women than men[20]. In another meta-analysis, women bled more than men while on NOACs[21]. Several reasons account for this finding. Doses of drugs are frequently not well adapted to the smaller body size, higher body fat content, or hepatic metabolism in women, or lower kidney function in older women [22]. Risk factors for adverse drug events, such as polytherapy, aging, and depression, are also more frequent in women than men. It is also important to note that sixty percent of all patients admitted to the hospital for adverse drug events are women [23].

Pulmonary embolism (78.93%) was the most common indication for initiating NOAC therapy, with most of the patients started on rivaroxaban (91.4%). 95% of patients in a retrospective study in Canada were on rivaroxaban[24]. Many reasons could account for this; the major one is that rivaroxaban is often readily available and cheaper than dabigatran and apixaban. Rivaroxaban may have higher market penetration, has cheap generic formulations, and has a convenient once-a-day dosing. Apixaban was the latest to be introduced to the Kenyan market, which accounts for the low usage in the study cohort.

There appears to be an association between dyslipidemia and bleeding outcome (P < 0.01). A few studies done have reported an increased risk of bleeding with statin use. Statins are thought to possess potentially unique antithrombotic properties. Mazen et al. revealed that the concomitant use of statins with warfarin is associated with a higher risk of bleeding than warfarin alone[25]. In a large retrospective study in the USA, statin users had an elevated risk of gastrointestinal hemorrhage[26]. However, other studies have found no association between statin use and increased bleeding risk[27, 28]. There was no significant association between heart failure, hypertension, liver dysfunction, renal dysfunction, and bleeding. An observational study from France was comparing rivaroxaban and VKA for symptomatic venous thromboembolism (REMOTEV). In this study, fragile patients defined by age > 75 years, eGFR < 50 ml/min, or low body weight ≤ 50 kg did not have more bleeding events than non-fragile patients [10].

One of the major bleeding events was fatal (0.4%), similar to the EINSTEIN DVT and EINSTEIN PE studies where there was one case of fatal bleeding (< 0.1% in EINSTEIN-PE. study) [3, 29]. No fatal bleeding events occurred in patients receiving rivaroxaban in REMOTEV[10].
This study has several strengths. It included all patients irrespective of underlying risk factors attempting to confirm whether the phase 3 trials’ findings had external validity in daily patient care in an East African setting. The randomized control trials included strict inclusion criteria, specific and well-balanced patients. For instance, in the RECOVER 1 trial [7] of dabigatran use versus warfarin, exclusion criteria included liver disease with aminotransferase levels of > 2* the upper limit of normal, estimated GFR of < 30ml/min, the requirement for long term antiplatelet therapy, recent unstable cardiovascular disease and high risk of bleeding. In the AMPLIFY trial [9] of apixaban use versus warfarin, subjects with uncontrolled high blood pressure, known cancer subjects with planned long term use of low molecular weight heparin, low hemoglobin < 9, glomerular filtration rate of < 25 were excluded. In this trial, only 3% of the subjects had cancer. Our study included all patients with VTE and therefore was more inclusive. Moreover, to our knowledge, this is the first study on NOAC use in Eastern Africa.

One limitation of this study is the lack of a direct comparator group such as VKA treated patients. However, there being several large-scale VKA studies, a reliable indirect comparison can be made as in the DRESDEN NOAC study[17]. Moreover, this being a retrospective study, data such as INR values would be challenging to obtain, especially if the patients are on subsequent follow-up at a different facility. We also noted that the uptake of NOACs has increased over the past five years, with a subsequent decline in VKA use for VTE. Perhaps the numbers would be too few and patients put on VKA may differ in patient characteristics and socio-economic class.

There was an imbalance of patients between treatment groups. Our study population mostly included patients on rivaroxaban, and a few were on apixaban and dabigatran. As a retrospective review of the patients’ charts, it was subject to missing information. The type and degree of bleeding may have been insufficiently recorded.

In terms of the data collected by telephone interviews, a standardized telephone questionnaire was used. This information was subject to recall bias and subjective evaluation of factors such as bleeding severity. However, interviews were carried out by appropriately trained professionals with the appropriate medical knowledge, and further information was sought from the patient’s medical practitioners.

**Conclusion**

The incidence rate of bleeding was 22.1 per 100 patient-years, with major bleeding accounting for 18.8%. The most common bleeding site was the gastrointestinal system, while the most common type of minor bleeding was menorrhagia. Females had a higher incidence of major and CRNM bleeding. Future clinical trials should include outcomes stratified by sex, and further trials are needed to investigate the clinical impact of this sex-related safety difference. A more extensive study with an adequate number of patients on the different types of NOACs would compare bleeding outcomes.

**Declarations**
Funding

No grant was received to fund this study.

Conflicts of interest/Competing interests

The authors have no conflicts of interest to declare that are relevant to the content of this article

Availability of data and material

The clinical information data used to support the findings of this study are included within the article. The anonymised data can be requested from the corresponding author.

Code availability

Not applicable

Ethics approval

Ethical approval was sought from the Aga Khan University Research Ethics Committee before conducting the study.

Consent to participate

Verbal informed consent was obtained prior to the interview.

Consent to publish

Patients signed informed consent regarding publishing their data

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Tables

Table 1: BASELINE PATIENT CHARACTERISTICS
### Variables (N=243)

| Variables           | (N=243) |
|---------------------|---------|
| Age (Years)         | 57 (45.71) |
| Gender (Female)     | 123 (50.6%) |

### Comorbidities

| Comorbidity         | (N)     |
|---------------------|---------|
| Heart failure       | 12 (4.9%) |
| Liver dysfunction   | 15 (6.4%) |
| Renal dysfunction   | 25 (10.3%) |
| Hypertension        | 77 (32.0%) |
| Diabetes            | 36 (15.1%) |
| Dyslipidaemia       | 40 (17.0%) |
| Cancer              | 25 (10.5%) |
| Stroke              | 12 (5.0%) |

### Index diagnosis

| Diagnosis                       | (N)     |
|---------------------------------|---------|
| Pulmonary embolism              | 191 (78.9%) |
| Lower limb proximal DVT         | 106 (43.6%) |
| Lower limb distal DVT           | 6 (2.5%)  |
| Upper limb DVT                  | 3 (1.2%)  |

### NOAC

| NOAC       | (N)     |
|------------|---------|
| Apixaban   | 9 (3.7%) |
| Dabigatran | 12 (4.9%) |
| Rivaroxaban| 222 (91.4%) |

### Table 2: TREATMENT-EMERGENT CLINICAL OUTCOMES

| Major Bleeding       | (N)     |
|----------------------|---------|
| Muscle               | 3 (25%) |
| Gastrointestinal     | 5 (41.7%) |
| Haemoptysis          | 3 (25%) |
| Menorrhagia          | 1.00 (8.3%) |
| **Clinically Relevant Non-Major Bleeding (CRNM)** | 11 (17.2%) |
| Epistaxis            | 1 (9.1%) |
| Haematuria           | 2 (18.2%) |
| Menorrhagia          | 7 (63.6%) |
| Gastrointestinal     | 1 (9.1%) |

### Minor bleeding

| Minor bleeding        | (N)     |
|-----------------------|---------|
| Gastrointestinal      | 4 (9.8%) |
| Haemoptysis           | 1 (2.4%) |
| Menorrhagia           | 16 (39%) |
| Haematuria            | 1 (2.4%) |
| Mucocutaneous         | 9 (22%) |
| Gum bleeding          | 4 (9.8%) |
| Nose Bleeding         | 6 (14.6%) |

### Table 3: BLEEDING EVENT INCIDENCE RATES AMONG PATIENTS WITH VTE ACCORDING TO AGE, SEX, AND RISK FACTORS FOR BLEEDING
### Bleeding Event Rates per 100 Patient-years

| Characteristic                  | Number of patients | Patient years | Any severity | Major | CRNM | Minor |
|--------------------------------|--------------------|---------------|--------------|-------|------|-------|
| All                            | 243                | 290.1         | 22.1         | 4.1   | 3.8  | 14.1  |
| **Age, y**                      |                    |               |              |       |      |       |
| 15-30                           | 7                  | 4.6           | 152.9        | 21.9  | 21.9 | 110   |
| 30-45                           | 69                 | 48.6          | 51.4         | 10.3  | 8.2  | 30    |
| 45-60                           | 68                 | 80.5          | 27.3         | 1.2   | 3.7  | 20    |
| 60-85                           | 93                 | 150.4         | 5.98         | 2.7   | 1.99 | 1     |
| >85                             | 6                  | 5.95          | 16.8         | 16.8  | 0    | 0     |
| **Gender**                      |                    |               |              |       |      |       |
| Female                          | 123                | 142.3         | 31.61        | 4.21  | 5.62 | 21.78 |
| Male                            | 120                | 147.7         | 12.86        | 4.06  | 2.03 | 6.77  |
| Hypertension                    | 77                 | 108.9         | 17.4         | 5.5   | 3.7  | 8.3   |
| Renal Dysfunction               | 25                 | 42.4          | 14.2         | 11.8  | 0    | 2.4   |
| Liver Dysfunction               | 15                 | 14.3          | 21.0         | 14.0  | 0    | 7     |
| Stroke History                  | 12                 | 10.4          | 38.4         | 19.2  | 0    | 19.2  |
| Aspirin use and other antiplatelets | 13             | 6.1           | 130.4        | 32.6  | 32.6 | 65.2  |
| Heart failure                   | 12                 | 30.9          | 16.1         | 12.9  | 0    | 3.2   |

**Table 4: FACTORS ASSOCIATED WITH BLEEDING**
|                          | No Bleeding (n=202) | Bleeding Event(n=41) | P-Value |
|--------------------------|---------------------|----------------------|---------|
| Age, years               | 60(46,72)           | 47(39,54)            | <0.001  |
| **Gender**               |                     |                      |         |
| Female                   | 94(46.5%)           | 29(70.7%)            | 0.006   |
| Heart failure            | 8(4%)               | 4(9.8%)              | 0.124   |
| Liver dysfunction        | 13(6.7%)            | 2(5.1%)              | 1       |
| Renal dysfunction        | 21(10.4%)           | 4(9.8%)              | 1       |
| Hypertension             | 64(32%)             | 13(31.7%)            | 1       |
| Peripheral vascular disease /myocardial infarction | 3(1.6%) | 1(2.7%) | 0.515 |
| Diabetes                 | 32(16.2%)           | 4(10%)               | 0.468   |
| Dyslipidaemia            | 27(13.8%)           | 13(32.5%)            | 0.009   |
| Smoking                  | 11(5.9%)            | 2(5.1%)              | 1       |
| Aspirin use              | 5(2.6%)             | 2(4.9%)              | 0.348   |
| Other anti-platelets     | 4(2.00%)            | 2(4.9%)              | 0.269   |
| Cancer                   | 20(10.10%)          | 5(12.5%)             | 0.581   |
| Stroke                   | 11(5.5%)            | 1(2.4%)              | 0.697   |
| Excessive use of alcohol | 5(2.6%)             | 1(2.5%)              | 1       |
| **NOAC**                 |                     |                      | 0.803   |
| Apixaban                 | 7(3.5%)             | 2(4.9%)              |         |
| Dabigatran               | 10(5.0%)            | 2(4.9%)              |         |
| Rivaroxaban              | 185(91.6%)          | 37(90.2%)            |         |

**Table 5: LOGISTIC REGRESSION ANALYSIS**

|                          | Adjusted OR* | 95% CI       | P       |
|--------------------------|--------------|--------------|---------|
| Age                      | 0.93         | 0.90 – 0.96  | <0.001  |
| Female                   | 2.97         | 1.30 – 6.80  | 0.010   |
| Dyslipidemia             | 9.87         | 3.51 – 27.76 | <0.001  |

**Figures**
A total of 608 patients were assessed for eligibility; 288 did not meet the inclusion criteria. Three hundred twenty were enrolled, of whom 77 were excluded (unavailable or declined to participate). A total of 243 patients were included in the final analysis.

**Figure 1**

A total of 608 patients were assessed for eligibility; 288 did not meet the inclusion criteria. Three hundred twenty were enrolled, of whom 77 were excluded (unavailable or declined to participate). A total of 243 patients were included in the final analysis.
The median follow-up time was 213 (IQR: 119 - 477) days, and the total follow-up was 105,872 days. A total of 64 bleeding events were identified in 41 patients (16.9%) with a bleeding event rate of 22.1/100 patient-years. Of these, 18.8% were major, 17.2% were CRNM, and 64.1% were minor.

Figure 2

The median follow-up time was 213 (IQR: 119 - 477) days, and the total follow-up was 105,872 days. A total of 64 bleeding events were identified in 41 patients (16.9%) with a bleeding event rate of 22.1/100 patient-years. Of these, 18.8% were major, 17.2% were CRNM, and 64.1% were minor.