Introduction

Rivaroxaban and apixaban are Factor Xa (FXa) inhibitor oral anticoagulants that are used to treat and prevent stroke and systemic embolism in patients with non-valvular atrial fibrillation, deep vein thrombosis and pulmonary embolism. As with all anticoagulants, the use of rivaroxaban and apixaban carries an increased risk of bleeding events.

Only two FXa inhibitors (i.e. rivaroxaban and apixaban) are available in Malaysia, but their safety and effectiveness data in the local setting are still limited. Rivaroxaban and apixaban were initially registered in Malaysia in 2011 and 2013, respectively. Based on the preliminary data by the Malaysian National Pharmaceutical Regulatory Agency in 2014, the most reported adverse drug reaction (ADR) was bleeding related events; 59.3% for rivaroxaban, 5.3% for apixaban.

Bleeding and Thromboembolic Events in Patients with Non-Valvular Atrial Fibrillation Treated with Apixaban or Rivaroxaban

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Abstract

Rivaroxaban and apixaban are effective oral anticoagulants, but their usage has been associated with an increased risk of bleeding events. This study examined the bleeding and thromboembolic events of rivaroxaban and apixaban. Medical records from 114 patients (rivaroxaban n = 64, apixaban n = 80) treated for stroke prevention in atrial fibrillation at a tertiary hospital in Malaysia were retrospectively reviewed. Patients with bleeding or stroke/systemic embolism events were identified and the bleeding risk factors were investigated using logistic regression analysis. Stroke or systemic embolism after treatment with Factor Xa (FXa) inhibitor occurred in 12 (8.33%) of the patients, 5 (3.47%) were ischaemic stroke and 7 (4.86%) of them were presented with myocardial infarction. Bleeding occurred in 32 (22.20%) patients, where 7 (4.90%) were presented with major bleeding (rivaroxaban n = 3, apixaban n = 4), while another 25 (17.40%) experienced clinically relevant non-major bleeding. Furthermore, concomitant antiplatelet used and serum creatinine level were significant predictors of bleeding events ($P < 0.05$). In conclusion, stroke or systemic embolism events were low for both drugs, but this may be an underestimation of the true prevalence due to the small sample size in the present study.

Keywords: Factor Xa inhibitors, atrial fibrillation, thromboembolism, haemorrhage
while for apixaban only one report which was gastrointestinal bleeding (1).

Therefore, this study aimed to evaluate the safety and effectiveness of rivaroxaban and apixaban at Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia. In addition, risk factors associated with bleeding outcomes in patients receiving rivaroxaban or apixaban were investigated in the present study.

Statistical Analysis

Jamovi v1.6.15 (2) was used to conduct all statistical analyses. Descriptive statistic was used to analyse demographic data. Categorical data such as sex, race, comorbidities, concomitant medications and presence of bleeding or thromboembolic events were presented as frequency and percentage, while continuous variables were presented as mean and standard deviation or median and interquartile range (IQR) depending on normality distribution which was tested using the Kolmogorov-Smirnov equation. Univariate analysis logistic regression was used to screen covariates for significance at $P < 0.2$. Factors and covariates with $P < 0.2$ in the univariate analysis were used in a multivariate logistic regression analysis to identify predictors of bleeding events at the $P < 0.05$ level of significance using a stepwise approach. Factors with probability values of more than 0.20 but high possibility of association as shown by previous studies were also included in the multivariate analysis.

Methods

Study Design

This research was a retrospective observational study conducted at Universiti Kebangsaan Malaysia Medical Centre. The list of patients receiving rivaroxaban or apixaban were traced from the computerised pharmacy system. Patients treated for stroke prevention in atrial fibrillation (SPAF) were screened from the system and those who underwent treatment for deep vein thrombosis or pulmonary embolism were excluded. Then, eligible patients were conveniently sampled into the study by reviewing their medical records manually. Data collection was carried out over three and half months from mid-February 2019 until the end of May 2019.

Data Collection

The data collection form consisted of five parts: i) demographic data such as age, sex, race, weight, height, smoking status and alcohol intake status; ii) comorbidities and concomitant medications; iii) congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female) (CHA2DS2-VASc) score upon initiation and hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, elderly, drugs/alcohol concomitantly (HAS-BLED) score; iv) laboratory investigation data which include haemoglobin level, platelet level, renal profile, liver profile and coagulation profile; and v) thromboembolic and bleeding events that were documented after treatment with FXa inhibitor.

Results

The baseline demographic and clinical characteristics of the patients are summarised in Table 1. Majority of them were males (56.3%), Chinese (49.3%), with a median [IQR] age of 69.5 years old [63, 74]. Meanwhile, the most common comorbidities recorded were hypertension (90.3%) followed by diabetes mellitus (48.6%). The median congestive heart failure, hypertension, age ≥ 75 years old (doubled), diabetes, stroke/transient ischemic attack/thromboembolism (doubled), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age 65 years old–74 years old, sex category (female) (CHA2DS2-VASc) score for males was 3 and 4 for females, while the overall median CHA2DS2-VASc score was 3. On the other hand, the median for HASBLED score for all patients was 2. A total of 12 (8.33%) patients presented with thromboembolic events; five patients were presented with recurrent ischaemic stroke and another seven presented with myocardial infarction. There was no significant difference in thromboembolic events between rivaroxaban and apixaban.
Table 1. Demographic and clinical characteristics of patients

| Characteristics                        | All N = 144 (%) | Rivaroxaban n = 64 (%) | Apixaban n = 80 (%) |
|----------------------------------------|-----------------|------------------------|---------------------|
| Age (y), median (IQR)                 | 69.5 (63.74)    | 70 (63.75)             | 69.0 (63.74)        |
| ≤ 54 years old                        | 8 (5.60)        |                        |                     |
| 55 years old–64 years old             | 34 (23.60)      |                        |                     |
| 65 years old–74 years old             | 70 (48.60)      |                        |                     |
| ≥ 75 years old                        | 32 (22.20)      |                        |                     |
| Sex                                    |                 |                        |                     |
| Male                                   | 81 (56.30)      | 42 (65.60)             | 39 (48.80)          |
| Female                                 | 63 (43.80)      | 22 (34.40)             | 41 (51.20)          |
| Race                                   |                 |                        |                     |
| Malay                                  | 66 (45.80)      | 34 (53.10)             | 32 (40.00)          |
| Chinese                                | 71 (49.30)      | 27 (42.20)             | 44 (55.00)          |
| Indian                                 | 5 (3.50)        | 3 (4.70)               | 2 (2.50)            |
| Others                                 | 2 (1.40)        |                        | 2 (2.50)            |
| Medical history                        |                 |                        |                     |
| Diabetes mellitus                      | 70 (48.60)      | 29 (45.30)             | 41 (51.30)          |
| Hypertension                           | 130 (90.30)     | 57 (89.10)             | 73 (91.30)          |
| Congestive cardiac failure             | 12 (8.30)       | 2 (3.10)               | 10 (12.50)          |
| Ischaemic heart disease                | 59 (41.00)      | 29 (45.30)             | 30 (37.50)          |
| Stroke/Transient ischaemic attack      | 33 (22.90)      | 15 (23.40)             | 18 (22.50)          |
| Chronic kidney disease                 | 7 (4.90)        | 2 (3.10)               | 5 (6.30)            |
| Peptic ulcer disease                   | 3 (2.10)        |                        | 3 (3.80)            |
| Prior bleeding history                 | 2 (1.40)        |                        | 2 (2.50)            |
| Concomitant medication                 |                 |                        |                     |
| Antiplatelet                           | 43 (29.90)      | 17 (26.60)             | 26 (32.50)          |
| ACE-i/ARB                              | 89 (61.80)      | 38 (59.40)             | 51 (63.80)          |
| Beta-blockers                          | 108 (75.00)     | 49 (76.60)             | 59 (73.80)          |
| Calcium channel blocker                | 57 (39.60)      | 28 (43.80)             | 29 (36.30)          |
| NSAIDs                                 | 3 (2.10)        | 2 (3.10)               | 1 (1.30)            |
| Statin                                 | 116 (80.60)     | 53 (82.80)             | 63 (78.80)          |
| CHA₂DS₂-L-VAsc score, median (IQR)     | 3.00 (1.00)     | 3.00 (2.00)            | 4.00 (1.00)         |
| HAS-BLED score, median (IQR)           | 2.00 (1.00)     | 2.00 (1.00)            | 2.00 (1.00)         |

A total of 32 bleeding events (14 rivaroxaban and 18 apixaban) were recorded in this study, consisting of seven major bleeding cases, while 25 were clinically relevant non-major (CRNM) bleeding. Three of the major bleeding occurred in rivaroxaban-treated patients while four occurred in apixaban-treated patients. Furthermore, two patients presented with CRNM were categorised as major bleeding because they required blood transfusion due to bleeding and low haemoglobin level. The summary of thromboembolic and bleeding events is summarised in Table 2. The detail characteristic for each patient with thromboembolic events and major bleeding are presented in Supplementary Tables S1 and S2, respectively.
Brief Communication | Factor Xa inhibitor bleeding and thromboembolism

Table 2. Thromboembolic and bleeding events after treatment with FXa inhibitor

| Outcome | All N = 144 (%) | Rivaroxaban n = 64 (%) | Apixaban n = 80 (%) |
|---------|----------------|------------------------|---------------------|
| Thromboembolic events after treatment with FXa inhibitor | | | |
| Yes | 12 (8.33) | 6 (9.38) | 6 (7.50) |
| No | 132 (91.70) | 58 (90.62) | 74 (92.50) |
| Type of thromboembolic events | | | |
| Ischaemic stroke | 5 (3.47) | 2 (3.13) | 3 (3.75) |
| Myocardial infarction | 7 (4.80) | 4 (6.25) | 3 (3.75) |
| Bleeding | | | |
| Yes | 32 (22.20) | 14 (21.90) | 18 (22.50) |
| No | 112 (77.80) | 50 (78.10) | 62 (77.50) |
| Severity of bleeding | | | |
| Major | 7 (4.90) | 3 (4.70) | 4 (5.00) |
| Clinically relevant non-major bleeding | 25 (17.40) | 11 (17.20) | 14 (17.50) |
| Major bleeding | | | |
| Intracerebral haemorrhage | 1 (0.70) | 0 | 1 (1.30) |
| Melena | 4 (2.80) | 2 (3.10) | 2 (2.50) |
| CRNM required blood transfusion | 2 (1.40) | 1 (1.60) | 1 (1.30) |
| Clinically relevant non-major bleeding | | | |
| Haematuria | 9 (6.30) | 6 (9.40) | 3 (3.80) |
| Gum bleeding | 5 (3.50) | 1 (1.60) | 4 (5.00) |
| Haematoma | 5 (3.50) | 2 (3.10) | 3 (3.80) |
| Bleeding from anus/rectum | 1 (0.70) | 0 | 1 (1.30) |
| Haemoptysis | 2 (1.40) | 1 (1.60) | 1 (1.30) |
| Acute gastritis with bleeding | 1 (0.70) | 1 (1.60) | 0 |
| Epistaxis | 1 (0.70) | 0 | 1 (1.30) |
| Conjunctival haemorrhage | 1 (0.70) | 0 | 1 (1.30) |

In the univariate analysis, the occurrence of bleeding events was significantly associated with congestive heart failure, chronic kidney disease, concomitant antiplatelet (aspirin or clopidogrel), history of bleeding, baseline haemoglobin level, history of peptic ulcer disease and serum creatinine at the time of bleeding (Table 3). On the other hand, only antiplatelet use and serum creatinine level during the event were significant risk factors for bleeding events in the multiple regression analysis. The use of an antiplatelet was associated with a 4.17 times higher risk of bleeding (adjusted OR: 4.171; 95% CI: 1.18, 14.714; \( P = 0.03 \)). In addition, the serum creatinine level (\( \mu \text{mol/L} \)) during the event (indicating possible poor renal function during the event) will increase the risk of bleeding (OR: 1.03; 95% CI: 1.01, 1.05; \( P = 0.003 \)).
Table 3. Multiple logistic regression regarding predictors of bleeding outcome in patient on FXa inhibitor

| Variables                      | B    | Adjusted OR | 95% CI          | χ² (df) | P-value |
|-------------------------------|------|-------------|-----------------|--------|---------|
| Comorbidities                 |      |             |                 | a      |         |
| Congestive cardiac failure    | 0.62 | 1.86        | 0.26, 13.14     | 0.39 (1)| 0.53    |
| Chronic kidney disease        | −0.27| 0.766       | 0.04, 13.81     | 0.03 (1)| 0.86    |
| Peptic ulcer disease          | 1.70 | 5.495       | 0.22, 137.0     | 0.31 (1)| 0.31    |
| Prior bleeding event          | −0.72| 0.485       | 0.00, 383.8     | 0.05 (1)| 0.83    |
| Concomitant medications       |      |             |                 | a      |         |
| Antiplatelet                  | 1.43 | 4.17        | 1.18, 14.7      | 5.11 (1)| 0.02    |
| Baseline haemoglobin level    | −0.21| 0.81        | 0.59, 1.11      | 1.87 (1)| 0.17    |
| Serum creatinine during event | 0.03 | 1.03        | 1.01, 1.05      | 12.88 (1)| < 0.001|

Notes: df-degree of freedom; *Omnibus likelihood ratio test; *P-value < 0.05 denotes significance

Discussion

Medical records from 144 patients taking rivotaroxaban or apixaban for SPAF were reviewed in the present study. When each patient was analysed individually, the majority of those who presented with ischaemic stroke were > 60 years old with more than three comorbidities. Moreover, most of them have CHA²DS₂-VASc score of more than 3, which translates to more than 3.2% increase in strokes each year (3). On the other hand, patients presented with acute myocardial infarction aged between 64 years old and 79 years old with more than two comorbidities, with one patient recording a CHA²DS₂-VASc score of 7.

Bleeding events in the rivotaroxaban group were 21.90% and 22.50% in the apixaban group. In the rivotaroxaban ROCKET-AF trial, the reported percentage of bleeding was 20.7% (4), whereas the proportion of any bleeding is 25.6% (5) in the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial; both were comparable with the present study. Besides major bleeding, 17.40% of the patients experienced CRNM bleeding or minor bleeding. In this study, the most frequently documented minor bleeding was haematuria followed by gum bleeding and haematoma. In cases where Xa was administered on patients, no prominent minor bleeding is not expected to occur; nonetheless, the frequency of minor bleeding varies between studies (6–7). It should be noted that documentation of minor bleeding largely depends on patients’ reports.

Visually obvious bleeding such as haematuria, haematoma, epistaxis and gum bleeding might be reported more than non-obvious bleeding that is non-clinically apparent such as acute gastritis with bleeding and changes in menstruation frequency or volume.

Antiplatelet use and higher serum creatinine level are associated with increased bleeding risk, thus useful predictors in some studies (8). However, the diagnosis of renal impairment was not reported in this study; instead, it is based on the single value of recorded serum creatinine during patient presentation with the bleeding events. Upon further investigation of these patients, their serum creatinine level exceeded 150 µmol/L. Thus, although the FXa inhibitor is partially cleared by the kidney, there is a possibility of accumulation due to decreased clearance (9). Moreover, antiplatelet usage (aspirin or clopidogrel) was associated with an increased risk of bleeding (10). Other known factors from prior studies that were associated with increased risk of bleeding are increased age, sex (male), diastolic blood pressure ≥ 90 mmHg, history of chronic obstructive pulmonary disease or gastrointestinal bleeding, prior aspirin use and anaemia (10).

Currently, there is a lack of studies on the safety and efficacy of FXa in the Malaysian population, but several clinical studies have been reported on dabigatran. Yap et al. (11) described the clinical experience from a single centre (National Heart Institute of Malaysia) on the reported adverse and bleeding events and
Brief Communication | Factor Xa inhibitor bleeding and thromboembolism

reasons for switching anticoagulants. Dabigatran and warfarin usage were compared and it was found that the overall bleeding events were lower in the dabigatran group (12). Furthermore, no thromboembolic events were detected in the cohort within their 340.7 ± 322 day follow up for dabigatran and 410.5 ± 321 day follow up for the warfarin group. However, another study by Yap et al. (13) with a larger sample size found no significant differences in the efficacy and safety of dabigatran and warfarin. In contrast, another study conducted in Malaysia found that the predicted rate for dabigatran-induced major bleeding was low, however, the fatality risk was high (14). As aforementioned, no studies on FXa have been conducted in Malaysia. The first published study on a pair-wise comparison between FXa, dabigatran and warfarin suggested the efficacy of dabigatran and FXa were parallel (15). Nevertheless, apixaban bleeding rates were lower than warfarin, but rivaroxaban bleeding rates were higher than warfarin (15).

There are several limitations in the present study. Firstly, this retrospective study manually screened patients’ medical records; thus, the outcome depended heavily on the physicians’ documentation and patient reporting. Some information such as minor bleeding or if the patient sees a different physician in-between visits might not be documented in the medical records, hence the possibility of underrepresentation in clinical events. Secondly, the small sample size was inadequate for a robust multivariate analysis. Furthermore, the medical records were sampled randomly, which resulted in the possibility of selection bias. Nevertheless, medical records selection was not based on any pre-set criteria, but rather retrieval was of medical records done upon their availability within the study period. In addition, the safety and efficacy between apixaban and rivaroxaban were not compared in this study. A proper comparison between these anticoagulants would require propensity matched-scoring to balance the baseline characteristics and reduce bias due to confounding variables. Unfortunately, this was not possible with a relatively small dataset, and time and resource constraints hampered further data collection. Lastly, the follow up duration varied between patients; thus, some clinical events might not be recorded within a short follow up.

Conclusion

Thromboembolic events after treatment with rivaroxaban or apixaban were low (8.33%). Bleeding events occurred in ~22% of patients on either rivaroxaban or apixaban and was associated with antiplatelet use and higher serum creatinine during the bleeding event. Most importantly, this study provides valuable data for planning future research on oral anticoagulants, particularly in Malaysia.

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Ethics of Study

Ethics approval was obtained from the Universiti Kebangsaan Malaysia Research Ethics Committee prior to the commencement of the study (UKM PPI/111/8/JEP-2019-068).

Conflict of Interest

None.

Funds

None.

Authors' Contributions

Conception and design: ASA, HPT, SMS
Analysis and interpretation of the data: ASA, SMS
Drafting of the article: ASA, SMS
Critical revision of the article for important intellectual content: HPT, SMS
Final approval of the article: ASA, HPT, SMS
Administrative, technical, or logistic support: HPT
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### Supplementary Tables

#### Table S1. Characteristic of patients with thromboembolic events

| No | Sex, age (years old) | Factor Xa inhibitor | Dosage | Time to event | CHA2DS2-VASc | HAS-BLED | SCr, µmol/L | Thromboembolic event |
|----|----------------------|----------------------|--------|---------------|--------------|-----------|-------------|---------------------|
| 1  | Male, 66             | Apixaban             | 5mg BD | 6 months      | 4            | 3         | 83          | MI                  |
| 2  | Male, 65             | Apixaban             | 5mg BD | 1 month       | 3            | 1         | 74          | MI                  |
| 3  | Male, 79             | Apixaban             | 5mg BD | > 1 year      | 7            | 2         | 119         | Ischaemic stroke    |
| 4  | Female, 62           | Apixaban             | 5mg BD | 2 years       | 4            | 1         | 112         | Ischaemic stroke    |
| 5  | Male, 74             | Apixaban             | 5mg BD | 3 years       | 4            | 1         | 120         | Ischaemic stroke    |
| 6  | Male, 63             | Apixaban             | 5mg BD | 3 months      | 3            | 2         | 130         | MI                  |
| 7  | Male, 75             | Apixaban             | 5mg BD | > 1 year      | 3            | 2         | 100         | MI                  |
| 8  | Female, 77           | Apixaban             | 20mg OD| < 6 months    | 5            | 2         | 108         | MI                  |
| 9  | Male, 60             | Apixaban             | 20mg OD| 11 months     | 3            | 1         | 85          | MI                  |
| 10 | Female, 71           | Apixaban             | 20mg OD| 1 year        | 4            | 2         | 114         | MI                  |
| 11 | Male, 60             | Rivaroxaban          | 20mg OD| 9 months      | 3            | 1         | 98          | Ischaemic stroke    |
| 12 | Female, 71           | Rivaroxaban          | 20mg OD| 4 years       | 4            | 2         | 92          | Ischaemic stroke    |

#### Table S2. Characteristic of patients with major bleeding events

| Sex, age (years old) | Concomitant antiplatelet | CHA2DS2-VASc | HAS-BLED | Drug and dosage | SCr (µmol/L) | Bleed type                  | Time to bleed (month) |
|----------------------|--------------------------|--------------|----------|-----------------|--------------|----------------------------|-----------------------|
| Male, 52             | none                     | 2            | 1        | Apixaban 5mg BD  | 170          | Bleeding from anus and rectum | 1.5                   |
| Female, 70           | aspirin                  | 6            | 3        | Apixaban 5mg BD  | 188          | Intracerebral hemorrhage     | 11                    |
| Male, 72             | clopidogrel              | 3            | 3        | Apixaban 5mg BD  | 224          | Melena                      | 2                     |
| Male, 84             | none                     | 5            | 3        | Apixaban 5mg BD  | 154          | Melena                      | 11                    |
| Male, 63             | aspirin plus clopidogrel| 3            | 2        | Rivaroxaban 20mg OD | 511         | Bleeding from anus and rectum | 7                     |
| Female, 77           | aspirin                  | 5            | 2        | Rivaroxaban 20mg OD | 194         | Melena                      | 10                    |
| Male, 73             | none                     | 3            | 2        | Rivaroxaban 20mg OD | 169         | Melena                      | 21                    |

(continued on next page)
Table S2. (continued)

| Sex, age (years old) | Concomitant antplatelet | CHA₂DS₂-VASc | HAS-BLED | Drug and dosage | SCr (µmol/L) | Bleed type | Time to bleed (month) |
|----------------------|-------------------------|--------------|-----------|-----------------|--------------|------------|----------------------|
| Minor bleed          |                         |              |           |                 |              |            |                      |
| Male, 66             | aspirin and clopidogrel | 2            | 3         | Apixaban 5mg BD | 76           | Bleeding from anus and rectum | 5         |
| Female, 61           | aspirin                 | 3            | 2         | Apixaban 5mg BD | 62           | Conjunctival haemorrhage | 17        |
| Female, 61           | aspirin                 | 3            | 1         | Apixaban 5mg BD | -            | Epistaxis   | 10        |
| Male, 68             | aspirin                 | 4            | 3         | Apixaban 5mg BD | 138          | Gum bleeding | 7         |
| Female, 70           | none                    | 3            | 2         | Apixaban 5mg BD | 73           | Gum bleeding | 48        |
| Male, 63             | aspirin and clopidogrel | 3            | 2         | Apixaban 5mg BD | 145          | Gum bleeding | 6         |
| Male, 73             | none                    | 3            | 2         | Apixaban 5mg BD | 144          | Gum bleeding | 19        |
| Male, 63             | none                    | 4            | 1         | Apixaban 5mg BD | 151          | Hematoma    | 13        |
| Female, 67           | none                    | 4            | 2         | Apixaban 5mg BD | 70           | Hematoma    | 12        |
| Female, 66           | aspirin                 | 3            | 2         | Apixaban 5mg BD | -            | Hematoma    | 2         |
| Male, 68             | none                    | 4            | 3         | Apixaban 5mg BD | 88           | Hematuria   | 7         |
| Female, 62           | none                    | 4            | 1         | Apixaban 5mg BD | -            | Hematuria   | 2.2       |
| Male, 67             | aspirin                 | 2            | 2         | Apixaban 5mg BD | 88           | Hematuria   | 2.1       |
| Male, 76             | none                    | 4            | 2         | Apixaban 5mg BD | -            | Hemothysis  | 19        |
| Male, 60             | clopidogrel             | 2            | 1         | Rivaroxaban 20mg OD | 167      | Acute gastritis with bleeding | 5         |
| Female, 77           | none                    | 3            | 1         | Rivaroxaban 20mg OD | 65       | Gum bleeding | 3         |
| Female, 77           | aspirin                 | 5            | 2         | Rivaroxaban 20mg OD | 86       | Hematoma    | 26        |
| Female, 66           | none                    | 4            | 2         | Rivaroxaban 20mg OD | 88       | Hematoma    | 6         |
| Female, 70           | none                    | 5            | 3         | Rivaroxaban 20mg OD | 73       | Hematuria   | 13        |
| Male, 81             | aspirin                 | 4            | 3         | Rivaroxaban 20mg OD | 468      | Hematuria   | 0.10      |
| Male, 88             | none                    | 5            | 3         | Rivaroxaban 20mg OD | 94       | Hematuria   | 1.5       |
| Male, 60             | none                    | 3            | 1         | Rivaroxaban 20mg OD | 178      | Hematuria   | 14        |
| Female, 70           | aspirin                 | 6            | 3         | Rivaroxaban 20mg OD | 60       | Hematuria   | 1.3       |
| Male, 88             | none                    | 5            | 3         | Rivaroxaban 20mg OD | 1623     | Hematuria   | 2         |
| Female, 78           | aspirin                 | 7            | 5         | Rivaroxaban 20mg OD | 158      | Hemothysis  | 41        |