Factor Xa inhibitor-related major bleeding events in the Netherlands

Elisabeth Smits[1], Jordy Gaspersz[1], Eline Houben[1], Fernie Penning-van Beest[1], Alexander T. Cohen[2], Jil Billy Mamza[3], Wendy Beekman[4], Noortje Houthuizen[4], Jenneke Leentjens[5]

[1]PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands; [2]Department of Haematological Medicine, Guys and St. Thomas' Hospitals NHS Foundation Trust, King's College, London, UK; [3]AstraZeneca, London, UK; [4]AstraZeneca, The Hague, The Netherlands; [5]Radboud UMC, Nijmegen, The Netherlands

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Background

Despite the lower bleeding risk of oral factor Xa inhibitors (FXai) compared to vitamin K antagonists, the risk of major bleeding complications of FXai is still very substantial and associated with significant morbidity and mortality. National bleeding incidence rates based on real-world data could contribute to creating better guidelines for the management of FXai-related major bleeding (MB) by showing the timing of bleeds, and the differences by FXai type.

Objective

To explore the incidence of MB following initial FXai use by bleeding type, FXai type and rates over time

Methods

- A retrospective cohort study was performed using the PHARMO Data Network in the Netherlands.
- The study population consisted of adult new FXai users (apixaban, edoxaban or rivaroxaban) between 2008 and 2021 with a therapeutic indication (e.g., venous thromboembolism, atrial fibrillation, non-mechanical cardiac valve replacement, adult congenital heart disease). Start date of FXai treatment was defined as index date.
- FXai users were excluded if they had a record of a MB (hospital admission) in the last 60 days before their index date.
- Follow-up ended on the first of any of the following events: FXai therapy discontinuation, switching to or concomitant use of a non-FXai anticoagulants, MB event, pregnancy, end of the study period, end of data availability or death.
- Incidence rates (IRs) for MB were calculated over different time intervals and stratified by FXai type.

Table 1: Baseline characteristics of new FXai users stratified by FXai type

	Overall	Apixaban	Rivaroxaban	Edoxaban
	N = 17,356	N = 6,821	N = 8,627	N = 1,908
Age (years)				
Mean (SD)	71 (12)	72 (12)	70 (13)	72 (11)
Sex				
Male	9,783 (56)	3,817 (56)	4,906 (57)	1,060 (56)
Female	7,573 (44)	3,004 (44)	3,721 (43)	848 (44)
Follow-up time (days)				
Median (IQR)	293 (78-760)	327 (91-766)	266 (70-763)	296 (88-742)
FXai indications				
VTE	3,649 (21)	1,091 (16)	2,346 (27)	212 (11)
AF	13,560 (78)	5,668 (83)	6,217 (72)	1,675 (88)
CVR	185 (1)	86 (1)	73 (1)	26 (1)
ACHD	50 (<0.5)	20 (<0.5)	25 (<0.5)	5 (<0.5)
Comorbidities				
Diabetes type 2	3,417 (20)	1,469 (22)	1,562 (18)	386 (20)
Chronic kidney kisease	2,555 (15)	1,145 (17)	1,108 (13)	302 (16)
Hypertension	9,533 (55)	3,972 (58)	4,422 (51)	1,139 (60)
Ischemic stroke	2,110 (12)	953 (14)	885 (10)	272 (14)
Hemorrhagic stroke	74 (<0.5)	40 (1)	25 (<0.5)	9 (<0.5)
Comedication				
Non-FXai AC	4,047 (23)	1,569 (23)	1,950 (23)	528 (28)
Lipid lowering drugs	7,298 (42)	3,123 (46)	3,292 (38)	883 (46)
NSAIDs	2,923 (17)	1,133 (17)	1,523 (18)	267 (14)
Antiplatelet drugs	5,044 (29)	2,157 (32)	2,308 (27)	579 (30)
Antihypertensive drugs	13,717 (79)	5,614 (82)	6,496 (75)	1,607 (84)

VTE = venous thromboembolism, AF = atrial fibrillation, CVR = non-mechanical cardiac valve replacement, ACHD = adult congenital heart disease.
NOTE: Patients were allowed to have multiple therapeutic indications if the most recent indication could not be determined.

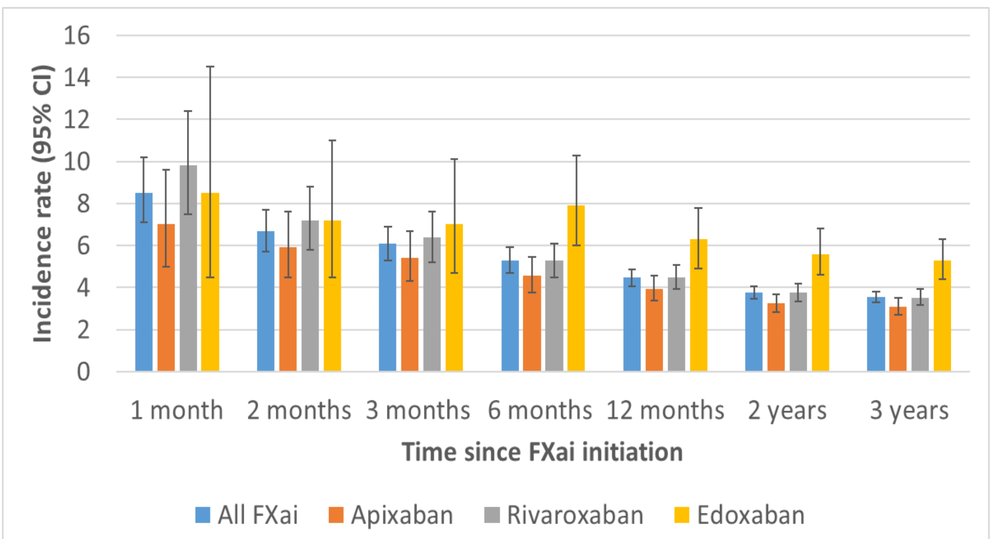

Figure 1: Major bleeding IRs per 100 person-years stratified by FXai type

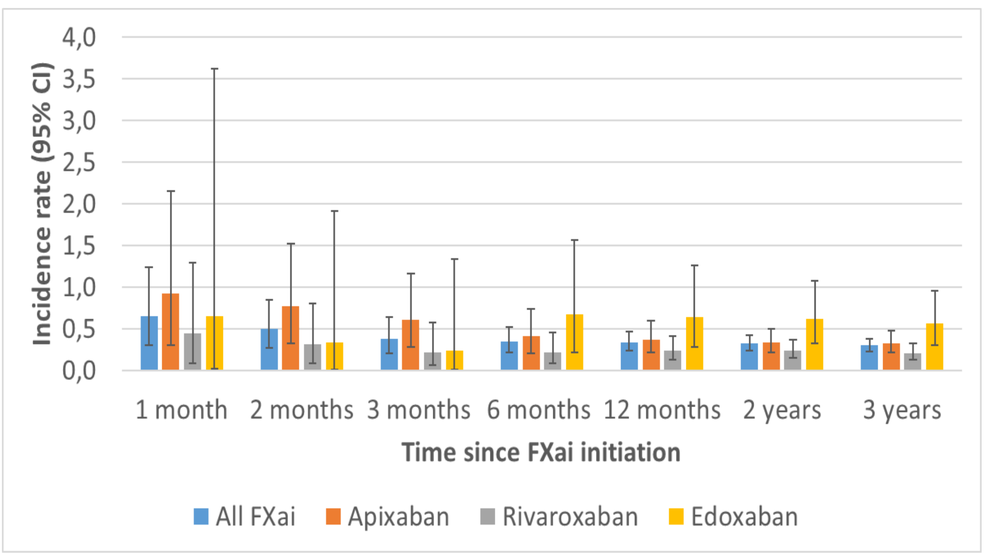

Figure 2: Fatal major bleeding IRs per 100 person-years stratified by FXai type

Results

- A cohort of 17,356 new FXai users was identified with a median follow-up of 293 days (Table 1).
- The most common therapeutic indication was atrial fibrillation followed by venous thromboembolism.
- Comorbidities and comedication were similar for all FXai types.
- There were 162 FXai users who had a gastrointestinal MB as their first MB after FXai initiation, 49 had an intracranial MB, 18 had a trauma MB, and 552 had other/unspecified types of MB.
- MB IR within one month after starting FXai use was 8.5 [7.1 – 10.2] per 100 PY. Fatal MB IR within one month after starting FXai use was 0.65 [0.30 – 1.24] per 100 PY. Both decreased with longer time intervals (Figure 1 and 2).
- One month after FXai initiation, MB IR was 9.8 [7.5 - 12.4] per 100 PY for rivaroxaban, 8.5 [4.5 – 14.5] for edoxaban and 7.0 [5.0 – 9.6] for apixaban. One month after FXai initiation, the fatal MB IR was 0.92 [0.30 – 2.15] per 100 PY for apixaban, 0.65 [0.02 – 3.62] for edoxaban and 0.44 [0.09 – 1.29] for rivaroxaban.

Conclusions

The MB IRs were highest in the first month after initiating FXai and decreased over time. Gastrointestinal MBs were more common than intracranial and trauma MBs. MB events seemed higher in edoxaban users. However, no adjustments or formal comparisons were made across the different FXai types.

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