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Appendix

Summary of Disproportionality Analysis Using VigiBase

November 26, 2025

Purpose of investigation	In Canada, a policy to update the product monographs (package inserts) of all oral anticoagulants marketed in Canada to additionally include the contents regarding the risk of splenic rupture was announced as a result of the safety review in February 2025. Therefore, the necessity of providing precautions concerning splenic rupture was evaluated for oral anticoagulants (apixaban, edoxaban tosilate hydrate, dabigatran etexilate methanesulfonate, rivaroxaban, warfarin potassium) marketed in Japan.
Scope of investigation	Target drugs • "Apixaban (active ingredient)", "Edoxaban (active ingredient)", "Dabigatran (active ingredient)", "Rivaroxaban (active ingredient)", "Warfarin (active ingredient)" Target events • MedDRA v28.0 PT "Splenic rupture", "Spontaneous splenic rupture", "Splenic haemorrhage", and "Splenic haematoma"
Outline of method	A disproportionality analysis[*2] for reports of splenic rupture associated with oral anticoagulants was performed using the dataset of the World Health Organization (WHO) Individual Case Safety Reports (ICSRs) Global Database (VigiBase)[*1] as of October 5, 2025. Information Component (IC) was calculated as signal indices, and when the lower limit of the 95% confidence interval (IC_{025}) was greater than 0, it was considered that a signal was detected (Eur J Clin Pharmacol. 1998; 54: 315–21, Pharmacoepidemiol Drug Saf. 2009; 18: 427-36). VigiLyze, a signal detection/management tool of the WHO, was used for the data analysis.
Outline of results	Results The results of the disproportionality analysis for the reports of splenic rupture associated with oral anticoagulants using VigiBase are shown in the table. The numbers of adverse reactions of "splenic rupture" reported for all the five ingredients of oral anticoagulants were shown to be statistically significantly higher than would be expected based on the entire database.

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In addition, as an event related to splenic rupture, “Splenic haemorrhage” and “Splenic haematoma” showed a similar trend to that of "Splenic rupture”. As for "Spontaneous splenic rupture", the number of reports was as small as 15 for all drugs included in the database, suggesting that there is a limitation to evaluation with this event term.

Table: Signal detection using VigiBase datasets

Ingredients	Number of adverse reaction reports (observed)	Number of reports (observed)	Number of reports (expected)	IC value	Lower limit of the 95% confidence interval of IC value
"Splenic rupture" (Number of reports in the entire DB: 1253)					
Apixaban	175253	56	5	3.3	2.9
Edoxaban	21435	4	1	2.0	0.2
Dabigatran	82935	74	2	4.6	4.3
Rivaroxaban	179029	124	5	4.4	4.1
Warfarin	135718	30	4	2.7	2.2
"Spontaneous splenic rupture" (Number of reports in the entire DB: 15)					
Apixaban	175253	5	0	3.3	1.8
Edoxaban	21435	-	-	-	-
Dabigatran	82935	-	-	-	-
Rivaroxaban	179029	-	-	-	-
Warfarin	135718	-	-	-	-
"Splenic haemorrhage" (Number of reports in the entire DB: 404)					
Apixaban	175253	29	2	3.8	3.2
Edoxaban	21435	1	0	1.1	-2.7
Dabigatran	82935	26	1	4.4	3.7
Rivaroxaban	179029	78	2	5.1	4.8
Warfarin	135718	24	1	3.8	3.1
"Splenic haematoma" (Number of reports in the entire DB: 251)					
Apixaban	175253	19	1	3.7	2.9
Edoxaban	21435	1	0	1.3	-2.5
Dabigatran	82935	17	0	4.1	3.4
Rivaroxaban	179029	50	1	5.0	4.6
Warfarin	135718	15	1	3.6	2.7

Discussion based on the results

The disproportionality analysis using VigiBase suggested an association between all oral anticoagulants and splenic rupture[*3]. It was determined that the results of the disproportionality analysis be regarded as one of the bases for the revisions to additionally include precautions concerning splenic rupture in the electronic package insert of oral anticoagulants.

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*1: VigiBase is the WHO global database of reported potential adverse reactions of medicinal products, developed and maintained by Uppsala Monitoring Center (UMC). The information comes from a variety of sources, and the probability that the suspected adverse reaction is drug-related is not the same in all cases.

*2: Disproportionality analysis is a hypothesis-generating or refinement approach.

*3: The information, results, and conclusions drawn do not represent the opinions of the Uppsala Monitoring Centre, the WHO Collaborating Centre for International Drug Monitoring, or of the World Health Organization.