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Direct oral anticoagulants and oesophageal disorders: A pharmacovigilance analysis

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Case reports have linked dabigatran[1, 2] and rivaroxaban[3] to oesophageal inflammation. Dabigatran has also been linked to oesophageal ulcers[4, 5], and dabigatran-related exfoliative oesophagitis was found to harbour an oesophageal carcinoma[6]. To date, no trials or observational studies have assessed the risk of oesophageal disorders associated with direct oral anticoagulants (DOACs). Thus, we conducted a pharmacovigilance analysis using spontaneous reports as a first step to address this important safety issue.

For this hypothesis-generating study, we queried the US Food and Drug Administration Adverse Event Reporting System (FAERS) from January 2011 to December 2017 for reports including dabigatran, rivaroxaban, and apixaban. We used Medical Dictionary for Regulatory Activities terms to define the study outcomes: oesophageal inflammation, ulcer, and carcinoma. For risk quantification, we used the Bayesian Confidence Propagation Neural Network (BCPNN) data mining method[7]. BCPNN incorporates prior information 'shrinking' the variability towards the null hypothesis of independence in the reporting of drugs and adverse events and is well-suited for the investigation of safety signals involving newly-marketed medications and rare events[7]. BCPNN compares observed and expected reporting rates using the information component (IC) with 95% credible intervals (CrIs) as disproportionality measure. In sensitivity analyses, we calculated proportional reporting ratios (PRR) and 95% confidence intervals (CIs) and age- and sex-adjusted odds ratios and 95% CIs using logistic regression[7]. Positive IC/PRR/OR values (on the log scale) indicate that the specific drug-adverse event-pairing was reported more often than expected, with 95% CrIs/CIs >0 suggesting a potential signal. Between 2011 and 2017, 6,445,532 spontaneous reports were submitted to FAERS (51,951 reports involved dabigatran, 84,435 rivaroxaban, and 31,863 apixaban). **Table 1** shows that dabigatran was reported at disproportionately high rate with oesophageal inflammation (IC, 0.60;

95% CrI, 0.41-0.79), ulcer (IC, 1.46; 95% CrI, 1.24-1.69), and carcinoma (IC, 2.12; 95% CrI, 1.74-2.50). Rivaroxaban was reported at disproportionately high rate with oesophageal ulcer (IC, 1.24; 95% CrI, 1.06-1.42), but there was no significant effect for inflammation or carcinoma. Apixaban was reported at disproportionately high rate with oesophageal ulcer (IC, 0.67; 95% CrI, 0.25-1.10) and carcinoma (IC, 1.05; 95% CrI, 0.25-1.85) without a significant effect for inflammation. The sensitivity analyses yielded lower estimates, but the dabigatran and rivaroxaban signals retained statistical significance.

Our hypothesis-generating study identified novel safety signals linking DOACs to oesophageal disorders. However, the apixaban signals were based on few events and were not robust across sensitivity analyses; they should thus be interpreted with caution. While the potential mechanism for FXa inhibitors is unclear[3], there is a biologic rationale for dabigatran-related oesophageal toxicity. Specifically, dabigatran capsules contain tartaric acid lowering the pH in the upper gastrointestinal tract to enhance drug absorption: this acidity may lead to local tissue inflammation and oesophageal damage[5]. Of note, in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, an imbalance in the incidence of oesophageal cancer was observed with 7 and 5 events in the dabigatran arms (150 mg and 110 mg bid) versus 3 events in the warfarin arm[8].

The main study limitation includes under-reporting and other potential reporting biases inherent to spontaneous reports databases[7]. Moreover, dabigatran-related dyspepsia and DOAC-related gastrointestinal bleeding may have led to increased diagnostic work-up and enhanced detection of oesophageal adverse events. However, gastroscopy rates in dabigatran patients are not necessarily higher than in warfarin patients[9], and bleeding-related detection of oesophageal disorders would be expected to affect apixaban rather than dabigatran or

rivaroxaban, since apixaban is the DOAC associated with the highest bleeding rates in the upper gastrointestinal tract[10]. Overall, our findings demonstrate a need for large observational studies assessing the potential association between DOACs and particularly dabigatran and rivaroxaban and risk of oesophageal disorders.

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Authors contributions

A.D. drafted the manuscript. D.M., C.G., D.K., L.A., B.H., and A.D. conceived and designed the study. D.M., C.G., D.K., L.A., B.H., and A.D. analysed and interpreted data. D.M., C.G., D.K., L.A., B.H., and A.D. critically revised the manuscript for important intellectual content. D.M., C.G., and A.D. performed the statistical analysis. A.D. supervised the study. A.D. is the guarantor of this work.

Conflict of interest

The authors have no conflicts of interest to declare.

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Table 1. Disproportionality analysis using different data mining methods to identify potential links between the use of direct oral anticoagulants and the risk of oesophageal inflammation, ulcer, or carcinoma.

	Reports of drug and AE	Expected reports with drug and AE	IC (95% CrI)	PRR (95% CI)	Adjusted OR* (95% CI)
Inflammation					
Dabigatran¥	223	148	0.60 (0.41 to 0.79)	0.41 (0.28 to 0.54)	0.28 (0.14 to 0.43)
Rivaroxaban	253	277	-0.13 (-0.30 to 0.05)	-0.09 (-0.21 to 0.03)	-0.19 (-0.33 to -0.06)
Apixaban	77	73	0.08 (-0.24 to 0.41)	0.05 (-0.17 to 0.28)	-0.02 (-0.29 to 0.25)
Ulcer					
Dabigatran¥¥	165	60	1.46 (1.24 to 1.69)	1.02 (0.87 to 1.17)	0.87 (0.70 to 1.04)
Rivaroxaban	263	111	1.24 (1.06 to 1.42)	0.87 (0.75 to 0.99)	0.73 (0.59 to 0.87)
Apixaban	44	28	0.67 (0.25 to 1.10)	0.46 (0.16 to 0.75)	0.36 (0.00 to 0.73)
Carcinoma					
Dabigatran¥¥¥	56	13	2.12 (1.74 to 2.50)	1.47 (1.21 to 1.74)	0.76 (0.45 to 1.07)
Rivaroxaban	27	23	0.24 (-0.30 to 0.78)	0.15 (-0.23 to 0.53)	-0.39 (-0.81 to 0.03)
Apixaban	12	6	1.05 (0.25 to 1.85)	0.69 (0.12 to 1.26)	0.40 (-0.20 to 0.99)

Abbreviations: AE, adverse event, IC, information component; CrI, credible interval; PRR, proportional reporting ratio; CI, confidence interval; OR, odds ratio.

* Adjusted for age and sex. These analyses were based on fewer events since reports with missing information on age and sex were not included.

¥ Restricting to reports with one suspected drug and one AE yielded the following results: 14 observed reports versus 6 expected reports; IC, 1.23; 95% CrI, 0.48-1.98. Respective analyses with rivaroxaban and apixaban were not feasible due to low numbers of events (<10).

¥¥ Restricting to reports with one suspected drug and one AE yielded the following results: 22 observed reports versus 6 expected reports; IC, 1.87; 95% CrI, 1.27-2.48. Respective analyses with rivaroxaban and apixaban were not feasible due to low numbers of events (<10).

¥¥¥ Restricting to reports with one suspected drug and one AE yielded the following results: 10 observed reports versus 4 expected reports; IC, 1.23; 95% CrI, 0.35-2.12. Respective analyses with rivaroxaban and apixaban were not feasible due to low numbers of events (<10).