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Original Research

Oral anticoagulant-proton pump inhibitor interactions: A pharmacovigilance assessment using disproportionality and interaction analyses

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Abstract

Objective: Oral anticoagulants operate within a narrow therapeutic window, with upper gastrointestinal bleeding representing a significant safety concern. While proton pump inhibitors (PPIs) have demonstrated gastroprotective properties, existing literature presents conflicting evidence regarding their interactions with oral anticoagulants. **Methods:** A detailed analysis was conducted using the United States Food and Drug Administration Adverse Event Reporting System (USFDA AERS) database. The study examined interactions between five oral anticoagulants (warfarin, apixaban, dabigatran, edoxaban, and rivaroxaban) and six PPIs (lansoprazole, dexlansoprazole, omeprazole, esomeprazole, pantoprazole, and rabeprazole). A case-non-case disproportionality analysis was employed, utilizing both frequentist and Bayesian data mining algorithms. Interaction Signal Scores were calculated to evaluate interaction strengths. **Results:** Of 29,163,222 initial reports, 5,222 met inclusion criteria. Significant interactions were identified across multiple anticoagulant-PPI combinations. Notably, dabigatran combined with omeprazole or pantoprazole, and apixaban with most PPIs, demonstrated increased hemorrhagic event risks. Gastrointestinal hemorrhage interactions were most extensive, with significant signals across multiple drug combinations. Certain combinations, like rivaroxaban-esomeprazole, showed protective effects, while others, such as rivaroxaban-rabeprazole, exhibited increased venous thromboembolic event risks. **Conclusion:** This pharmacovigilance analysis reveals complex interactions between oral anticoagulants and PPIs, highlighting the need for individualized risk assessment. Healthcare providers should carefully monitor patients receiving these combinations, considering potential hemorrhagic complications and patient-specific risk factors.

Keywords: Warfarin, Dabigatran, Rivaroxaban, Apixaban, Omeprazole, Esomeprazole

INTRODUCTION

Oral anticoagulants, particularly vitamin K antagonists, operate within a narrow therapeutic window, making any drug interactions potentially hazardous to patient safety. Among the various safety concerns, upper gastrointestinal bleeding remains a significant risk. Recent nationwide surveillance data has revealed an alarming major bleeding incidence rate of 27.9 per 1000 person-years (95% CI: 24.6–31.5) in patients using oral anticoagulants, with gastrointestinal bleeding being predominant at 12.6 per 1000 person-years (95% CI: 10.4–15.1)[1].

Proton pump inhibitors (PPIs) have demonstrated gastroprotective properties, effectively reducing gastrointestinal bleeding risk in patients receiving both warfarin and novel oral anticoagulants, including dabigatran[2-4]. Clinical evidence suggests that PPI co-administration in warfarin-treated patients reduces upper gastrointestinal bleeding by 24% compared to warfarin monotherapy[5]. Moreover, the combination of novel oral anticoagulants with PPIs has shown superior safety profiles compared to warfarin-PPI combinations, with an adjusted hazard ratio of 0.78 (95% confidence interval 0.65-0.94) for upper gastrointestinal bleeding[6].

However, the literature presents conflicting evidence regarding the clinical implications of oral anticoagulant-PPI interactions. While a Northern European study found no clinically significant interactions between PPIs and warfarin, its conclusions were limited by small sample sizes ranging from 24 to 106 patients per PPI group, covering only omeprazole, pantoprazole, lansoprazole, and esomeprazole[7]. Contrarily, a study of patients undergoing open heart surgery identified increased bleeding risk with warfarin-lansoprazole but not with warfarin-rabeprazole combinations[8]. These contradictions have led to careful monitoring recommendations, with the National Institute of Clinical Health Excellence advocating INR monitoring when initiating PPIs in warfarin-treated patients, particularly in elderly populations[9].

The interaction concerns extend beyond vitamin K antagonists to direct-acting anticoagulants. Pharmacokinetic studies have revealed that pantoprazole reduces dabigatran's average area under the curve and maximal concentration by 22% and 33%, respectively[10]. Additional research has documented a 15% reduction in dabigatran exposure, potentially elevating thromboembolic risk[11]. This interaction was further confirmed in a withdrawal study where cessation of PPI therapy led to significant increases in both trough (97.2±79.7 to 163.8±105.5

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ng/mL) and peak (142.4±102.8 to 255±129.5 ng/mL) dabigatran levels[12].

The underlying mechanisms potentially involve varying degrees of Cytochrome P450 enzyme inhibition by different PPIs[13]. While omeprazole primarily undergoes CYP2C19-mediated metabolism and vitamin K antagonists through CYP2C9[14], evidence suggests that at higher concentrations, omeprazole may utilize CYP2C9, potentially interfering with oral anticoagulant metabolism[15].

The United States Food and Drug Administration's Adverse Event Reporting System (USFDA AERS) serves as a vital pharmacovigilance tool, providing valuable insights into potential drug safety signals through both mandatory manufacturer reports and voluntary healthcare professional submissions[16]. Disproportionality analysis has emerged as a robust statistical approach for detecting safety signals within this database, particularly for identifying adverse events arising from drug interactions, as demonstrated in previous studies of DPP-4is and RAAS-modulating agents[17,18].

Given the conflicting evidence and potential clinical significance of oral anticoagulant-PPI interactions, we conducted a comprehensive pharmacovigilance investigation utilizing the USFDA AERS database. Through detailed disproportionality and interaction analyses, this study aims to provide healthcare providers with critical evidence-based insights for optimal therapeutic decision-making in patients requiring concurrent oral anticoagulant and PPI therapy.

METHODS

Data source

Data for this study were retrieved from the USFDA AERS, using three Standardised MedDRA (Medical Dictionary for Regulatory Activities) Query (SMQ) (Narrow) "Haemorrhage terms (excl laboratory terms)" (MedDRA code: 20000039), "Gastrointestinal haemorrhage" (MedDRA code: 20000108) and "Embolic and thrombotic events, venous" (MedDRA code: 20000084) [19]. The Preferred Terms included in these SMQs are listed in the Electronic Supplementary Tables 1-3. Data encompassed adverse event reports submitted to AERS from the first quarter of 2004 through the third quarter of 2024, covering a span of 82 quarterly reports.

Data processing

The USFDA AERS was systematically searched for reports involving oral anticoagulants with their combinations with PPIs to ensure comprehensive retrieval of Individual Case Safety Reports (ICSRs) [20]. The following oral anticoagulants were included: warfarin, dabigatran, rivaroxaban, apixaban and edoxaban. Their interactions were studies with the following PPIs: lansoprazole, dexlansoprazole, omeprazole, esomeprazole, pantoprazole and rabeprazole. We excluded cases receiving concomitant acetylsalicylic acid/aspirin, clopidogrel and heparin that were reported either as suspect or concomitantly. Similarly, while search for the reports related to monotherapy (for interaction analyses) with oral anticoagulants and PPIs, we excluded reports containing the above antiplatelet drugs as the anticoagulants (including heparin) for PPIs and vice versa. To avoid duplication, we followed the USFDA's deduplication guidelines, sorting reports in ascending order by Case_IDs and retaining only those with the latest FDA_DT or Individual Safety Report number, representing the most recent entry. Reports were included in the final analysis only if they identified oral anticoagulants as the "primary suspect" drug. We restricted our search to non-proprietary drug names for oral anticoagulants and their combination with PPIs. The following variables were collected from deduplicated reports: age, gender, report year, and reporting country.

Data mining algorithms

A "case-non-case" disproportionality analysis method was employed to evaluate the association of combined oral anticoagulants with various PPIs for the risk of hemorrhage, gastrointestinal hemorrhage and venous thrombo-embolic events[21]. Data retrieval and analysis were conducted using the OpenVigil 2.1 platform for oral anticoagulant-PPI-adverse event pairs. We used two frequentists and two Bayesian data mining algorithms to detect potential safety signals for the adverse events of interest.

In the frequentist approach, we calculated the Reporting Odds Ratio (ROR) and the Proportional Reporting Ratio (PRR). Signal detection criteria adhered to Evans' standards, which include a minimum of three reports, a PRR >2, and a chi-square (χ^2) statistic >4 for each oral anticoagulant-PPI-adverse event pair[22]. A 95% confidence interval (CI) was calculated for both ROR and PRR, with a signal identified if the lower limit of the ROR CI exceeded 1.

Bayesian analyses were conducted using the Bayesian Confidence Propagation Neural Network (BCPNN) and the Multi-Item Gamma Poisson Shrinker (MGPS). For BCPNN, signal detection was determined by the Information Component (IC), defined as the logarithmic ratio of the observed co-occurrence of DPP-4i and angioedema relative to the expected frequencies in the database. An IC-based signal was detected if the lower bound of the 95% CI (IC025) exceeded zero. MGPS used the Empirical Bayes Geometric Mean (EBGM), with a signal detected if the lower bound of the EBGM's 95% CI (EBGM05) exceeded 2[23].

Interaction Signal Scores

The interaction strength between oral anticoagulants and PPIs for the risk of hemorrhage, gastrointestinal hemorrhage and venous thrombo-embolic events as evaluated using Interaction Signal Scores (INTSS). These scores were based on the EBGM scores of observed-to-expected reports and calculated using 90% confidence intervals (EB05 and EB95). EB05 and EB95 values were determined for oral anticoagulants and PPIs alone, as well as in combination for each adverse event of interest [24]. INTSS was calculated as follows:

An INTSS >1 indicated a statistically significant interaction between oral anticoagulant and co-administered PPI for the concerned adverse event of interest[24].

Outcomes Assessed

For the oral anticoagulant-PPI-adverse event pairs, the primary outcomes evaluated included death and life-threatening events.

Compliance with Reporting Standards

This study adheres to the guidelines outlined in the Reporting of a Disproportionality Analysis for drUg Safety signal detection using spontaneously reported adverse events in Pharmacovigilance (READUS-PV)[25].

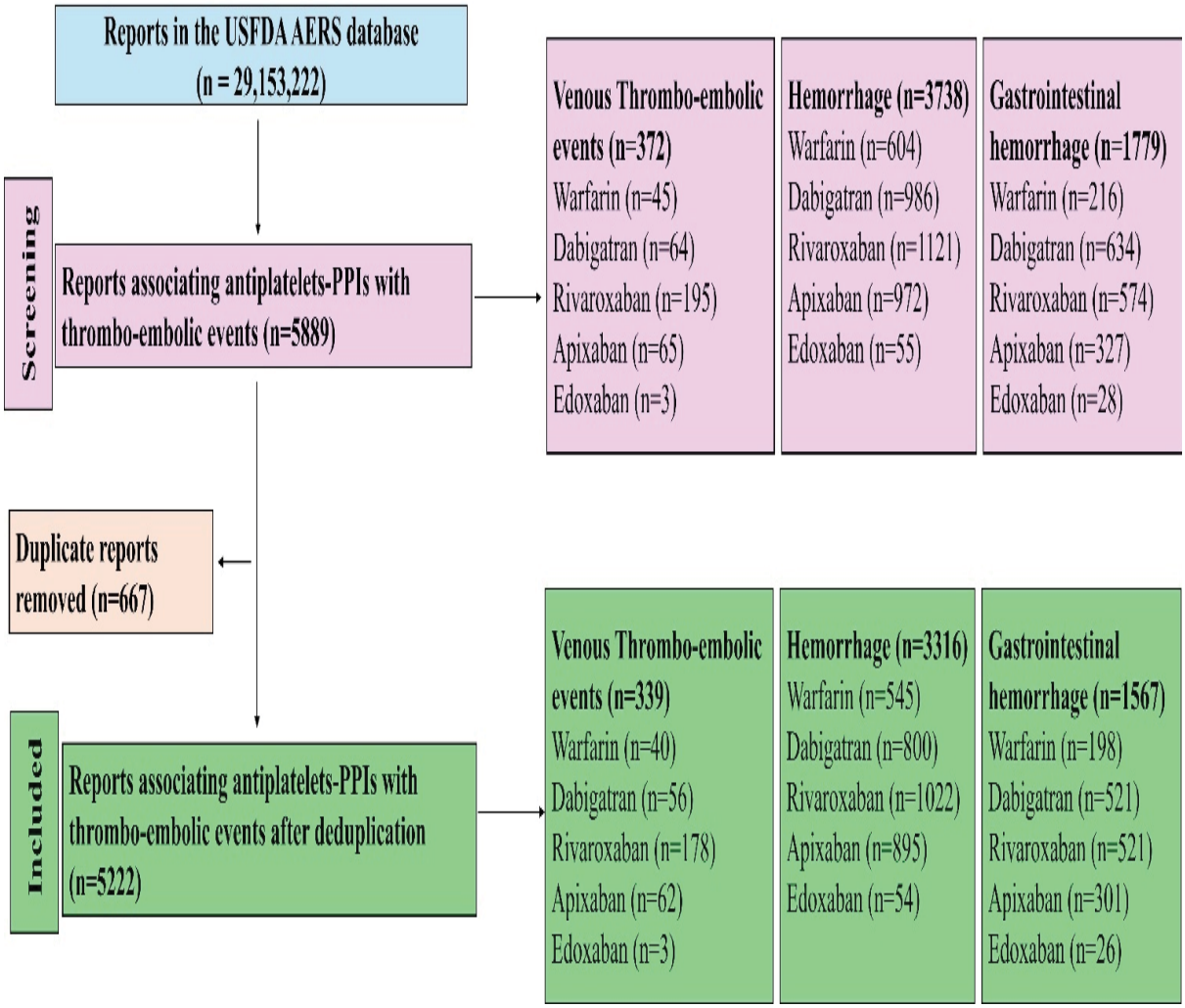
Statistical Analysis

Descriptive statistics were used to summarize demographic variables, presenting numerical variables as means (SD) and categorical variables as proportions (%) from the AERS ICSRs. All statistical analyses were performed in SPSS© (IBM SPSS Statistics for Windows, Version 27.0; IBM Corp., Armonk, NY).

RESULTS

Search results

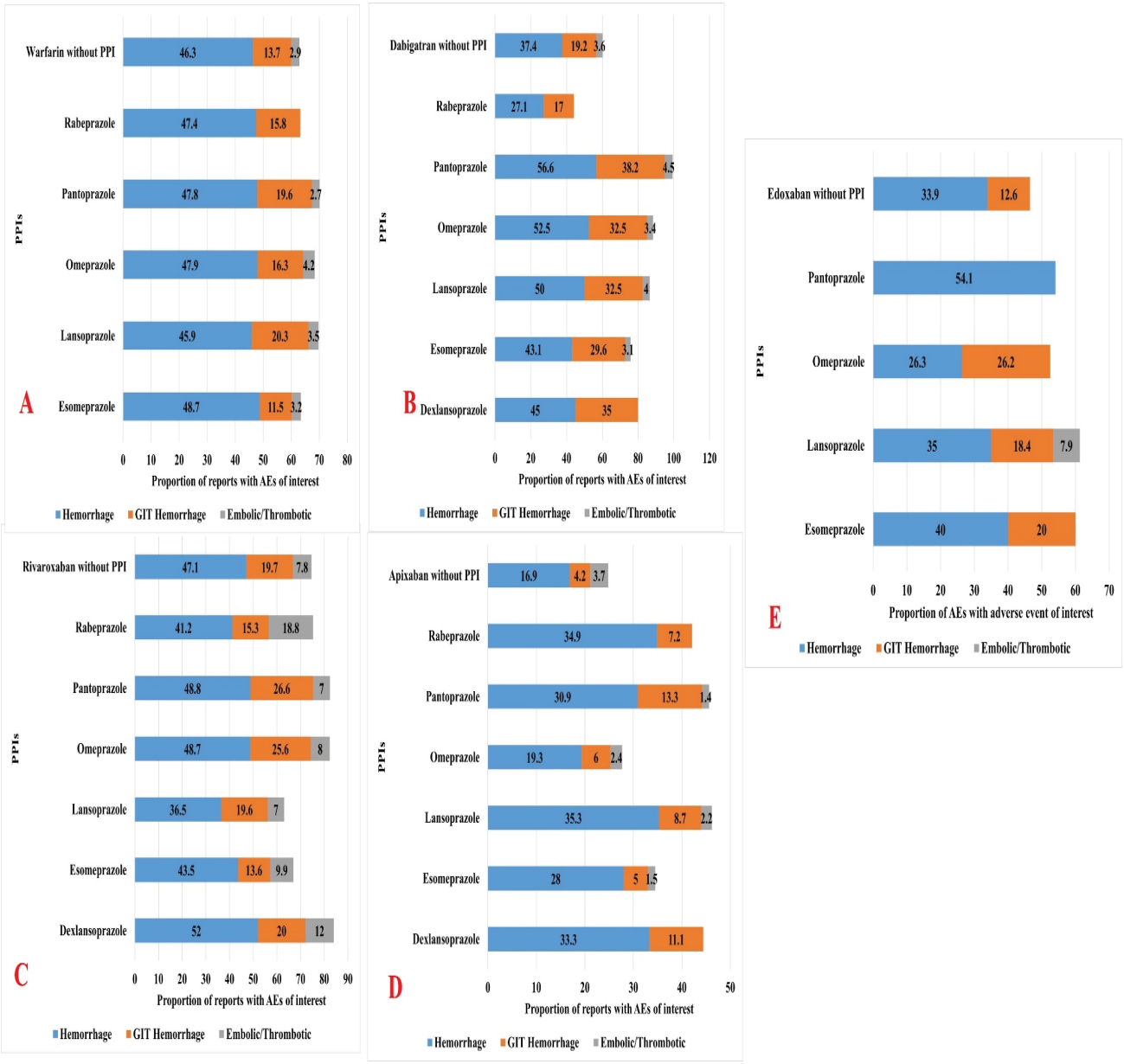
A comprehensive review of the USFDA AERS database yielded 29,163,222 reports, of which 5222 met the predefined inclusion criteria and underwent detailed analysis (Figure 1). Among the total reports, 3316 were included for hemorrhage, 1567 for gastrointestinal hemorrhage, and 339 for venous thrombo-embolic events. Amongst the oral anticoagulants, rivaroxaban had the maximum number of reports for all adverse events of interests, followed by dabiga



A total of 5222 unique reports were included in the final analysis for assessing the clinical impact of oral anticoagulant-PPI interactions.

Figure 1. Study flow diagram.

tran. Amongst the concomitant PPIs with oral anticoagulants, pantoprazole (n=2029), followed by omeprazole (n=1839) had the maximum number of reports, followed by others (lansoprazole: 662; esomeprazole: 491; rabeprazole: 149; and dexlansoprazole: 69) (Electronic Supplementary Table 4). The following combinations were not included in the final analysis as there were <3 reports as per the standard signal detection criteria: warfarin dabigatran and apixaban with dexlansoprazole and rabeprazole for venous thrombo-embolic



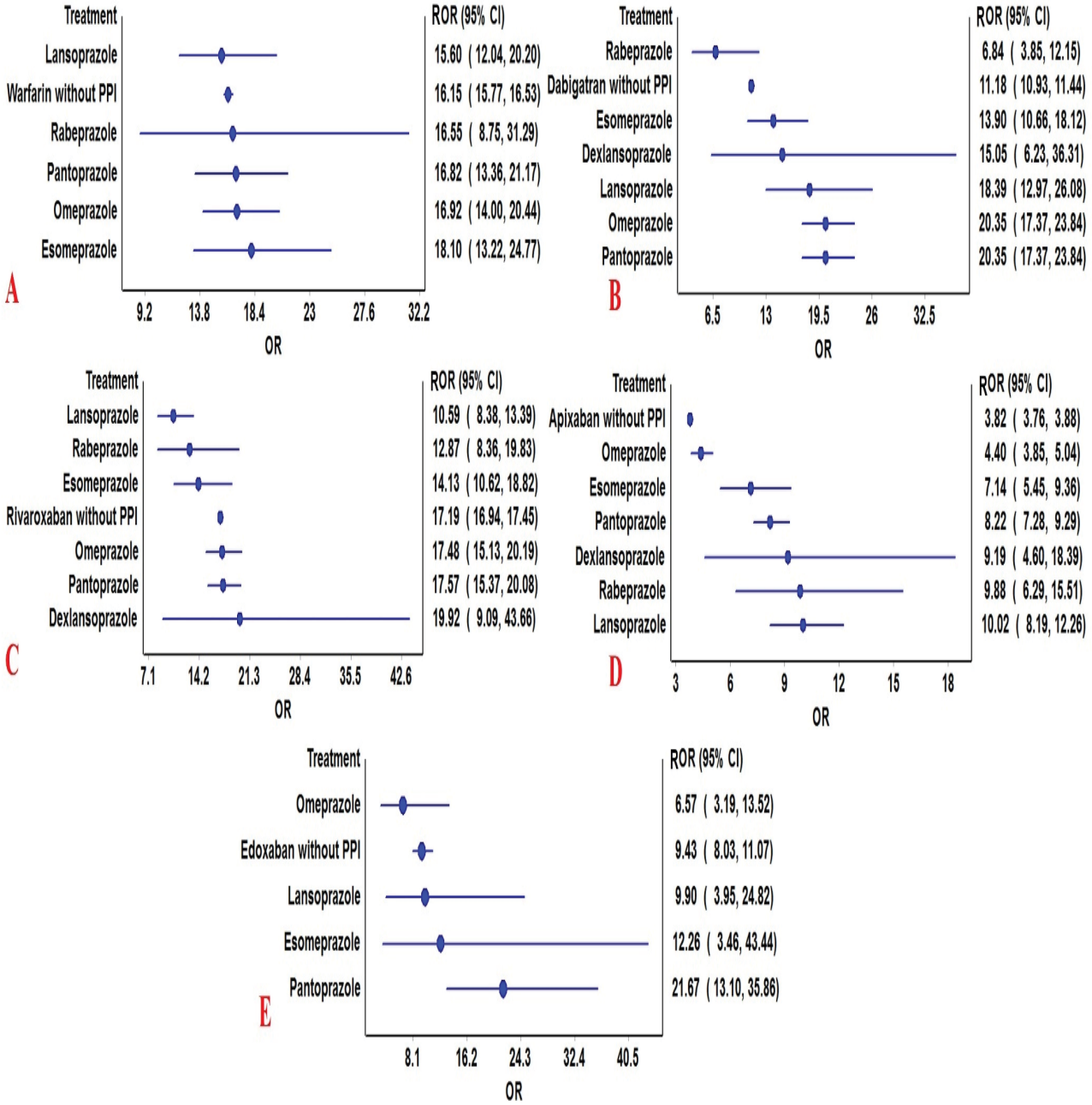
A: Warfarin; B: Dabigatran; C: Rivaroxaban; D: Apixaban and E: Edoxaban. The horizontal bars represent the rates of reporting of hemorrhage, gastrointestinal hemorrhage and venous thrombo-embolic events amongst various combinations of oral anticoagulants with PPIs.

Figure 2. Rate of reporting of adverse events of interest with oral anticoagulant-PPI combinations.

events, and edoxaban with esomeprazole (for hemorrhage and venous thrombo-embolic events), with lansoprazole and pantoprazole (for venous thrombo-embolic events) and with dexlansoprazole and rabeprazole for all adverse events of interest. Demographic analysis (Electronic Supplementary Tables 5-19) revealed that many patients were in the elderly age category with no clear gender predilection.

Signal Detection Analysis

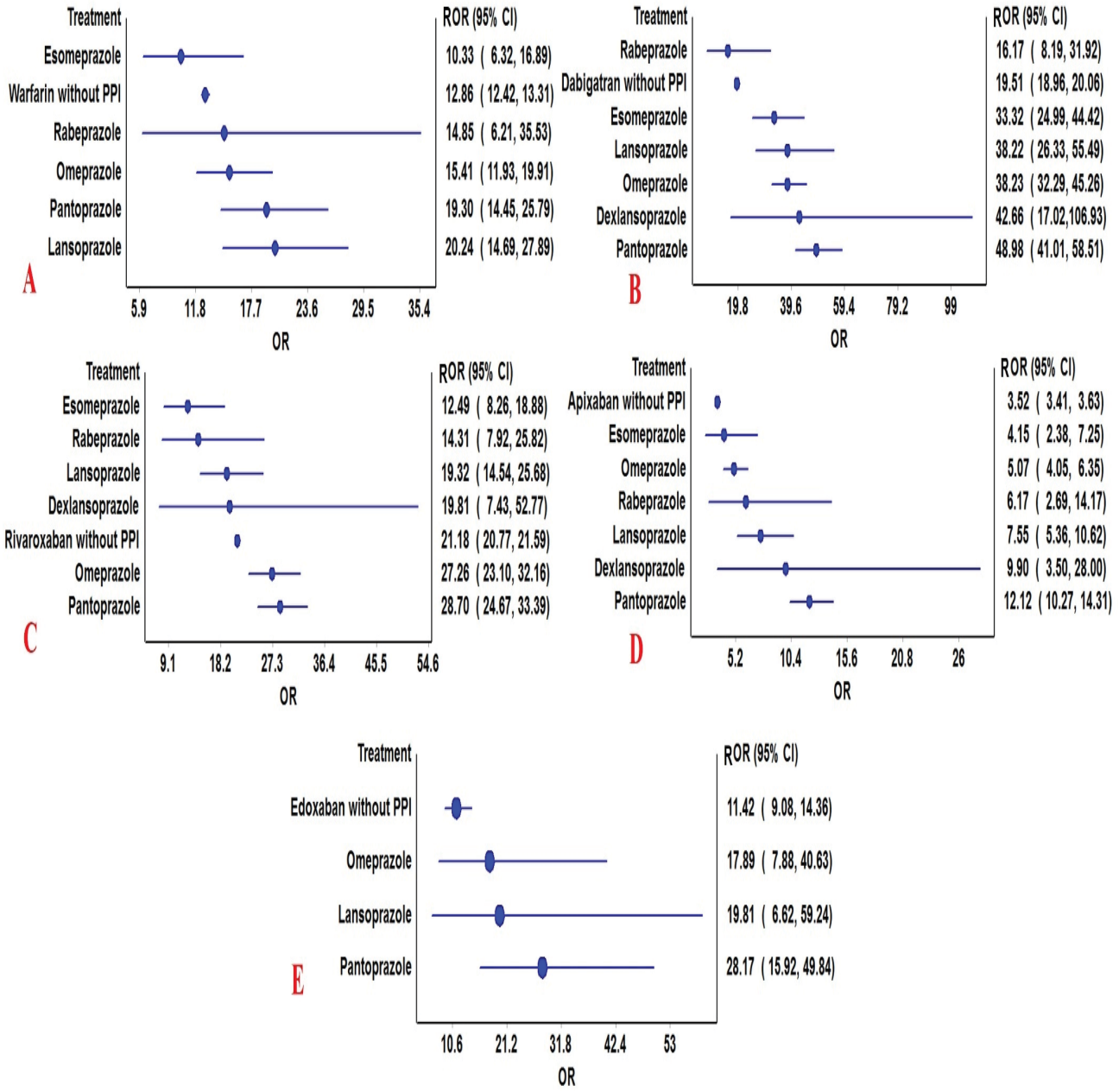
Analysis of reporting rates (Figure 2) revealed specific safety patterns among oral anticoagulant-PPI combinations. For general hemorrhage, most combinations showed similar rates, with the notable exceptions of rabeprazole-dabigatran demonstrating lower rates and PPI combinations with apixaban observed with higher rates compared to the respective



A: Warfarin; B: Dabigatran; C: Rivaroxaban; D: Apixaban and E: Edoxaban.

The blue circles represent the point estimates, and the horizontal lines represent the 95% CI of RORs.

Figure 3. Reporting odds ratios for the risk of hemorrhage with oral anticoagulant combinations with PPIs.



A: Warfarin; B: Dabigatran; C: Rivaroxaban; D: Apixaban and E: Edoxaban.

The blue circles represent the point estimates, and the horizontal lines represent the 95% CI of RORs.

Figure 4. Reporting odds ratios for the risk of gastrointestinal hemorrhage with oral anticoagulant combinations with PPIs.

anticoagulants without PPIs. Gastrointestinal hemorrhage rates were notably lower in with rivaroxaban-esomeprazole combination. In contrast, the combination of rivaroxaban and rabeprazole showed an increased rate of venous thrombo-embolic events.

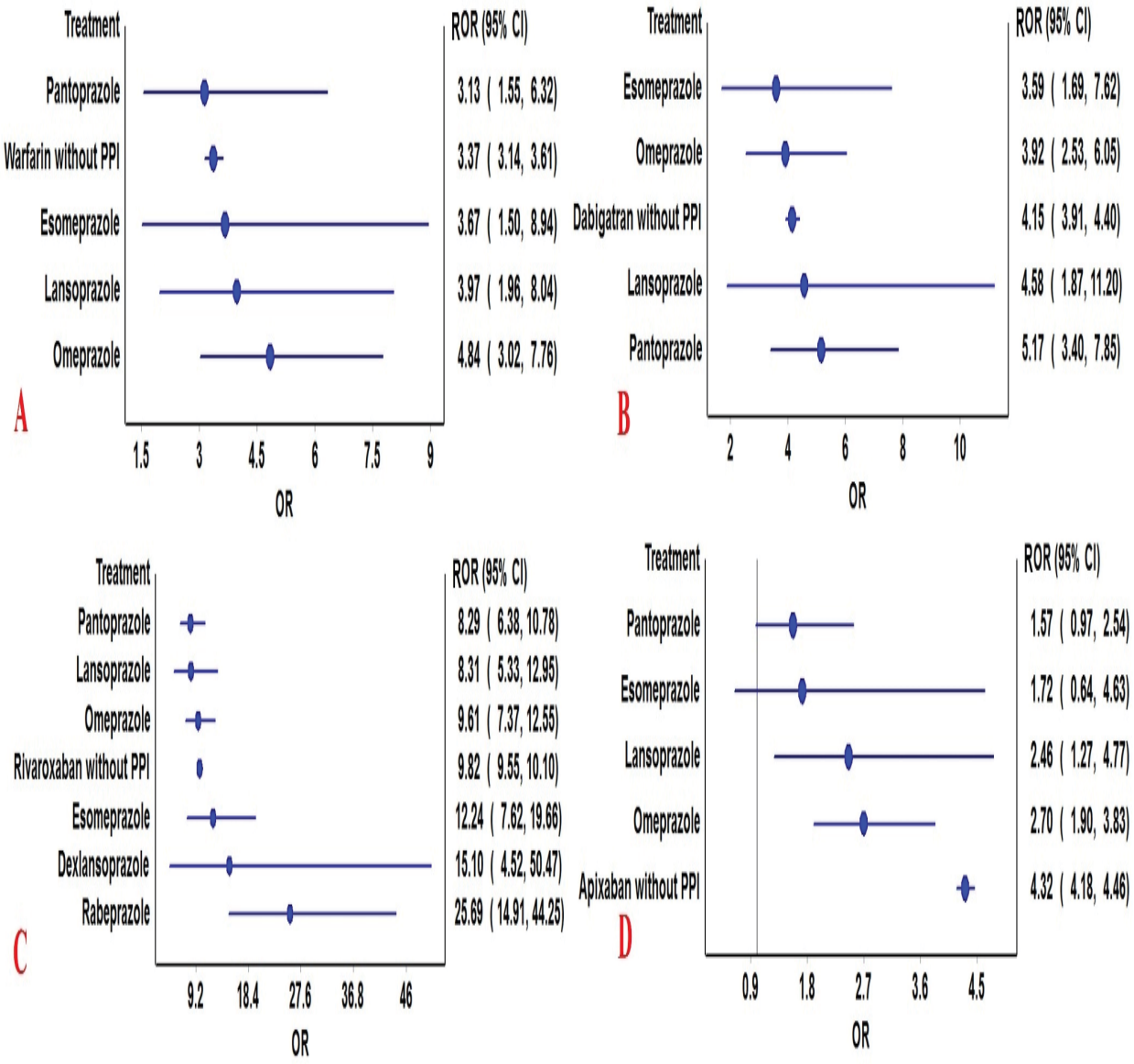
Analysis of adverse events revealed specific risk patterns among oral anticoagulant-PPI combinations. For hemorrhagic events (Figure 3), the rivaroxaban-lansoprazole combination showed a distinct non-overlapping increased ROR compared to rivaroxaban monotherapy. Similarly, apixaban combined with any PPI (except omeprazole) demonstrated higher RORs than apixaban alone, a pattern also observed with dabigatran when combined with lansoprazole, omeprazole, or pantoprazole.

For gastrointestinal hemorrhage (Figure 4), increased RORs were

observed in several combinations: warfarin with pantoprazole or lansoprazole; dabigatran and rivaroxaban with omeprazole or pantoprazole; apixaban with omeprazole, lansoprazole, or pantoprazole; and edoxaban with pantoprazole. Notably, esomeprazole showed a protective effect when combined with rivaroxaban.

Regarding venous thrombo-embolic events (Figure 5), while warfarin and dabigatran showed no significant interactions with PPIs, the rivaroxaban-rabeprazole combination demonstrated increased risk. Conversely, apixaban combinations with pantoprazole, esomeprazole, or omeprazole were associated with lower RORs.

While frequentist signal measures were consistently positive across all combinations (Table 1), the Bayesian analysis



A: Warfarin; B: Dabigatran; C: Rivaroxaban; and D: Apixaban.

The blue circles represent the point estimates, and the horizontal lines represent the 95% CI of RORs. The vertical black line in Figure 5D represents the line of no difference in the risk of venous thrombo-embolic events between the drug combinations.

Figure 5. Reporting odds ratios for the risk of venous thrombo-embolic events with oral anticoagulant combinations with PPIs.

Table 1. Frequentist signal detection measures for oral anticoagulant-PPI combinations for adverse events of interest.

Drugs	Hemorrhage						Gastrointestinal hemorrhage						Venous thrombo-embolism							
	PRR	Lower limit 95% CI of PRR	Upper limit 95% CI of PRR	RRR	χ2	No.	PRR	Lower limit 95% CI of PRR	Upper limit 95% CI of PRR	RRR	χ2	No.	PRR	Lower limit 95% CI of PRR	Upper limit 95% CI of PRR	RRR	χ2	No.		
Warfarin with PPI																				
Esomeprazole	9.4	8	11.1	9.4	596	76	9.3	6	14.3	6	126	18	3.6	1.5	8.5	3.6	7	5		
Lansoprazole	8.9	7.7	10.2	8.9	775	106	16.3	12.7	21.1	16	669	47	3.9	2	7.6	3.9	14	8		
Omeprazole	9.3	8.4	10.3	9.3	###	206	13.1	10.5	16.2	13	777	70	4.7	3	7.4	4.7	49	18		
Pantoprazole	9.3	8.2	10.4	9.3	###	139	15.7	12.5	19.8	16	780	57	3.1	1.6	6.1	3.1	9.3	8		
Rabeprazole	9.2	6.6	12.8	9.2	130	18	12.7	6.1	26.4	13	54	6	Not estimable							
Dabigatran with PPI																				
Dexlansoprazole	8.7	5.4	14.2	8.7	57	9	28.1	15.4	51	28	159	7	Not estimable							
Esomeprazole	8.3	7.2	9.7	8.3	647	96	23.8	19.4	29.1	24	1433	66	3.5	1.7	7.3	3.5	10	7		
Lansoprazole	9.7	8.1	11.5	9.7	509	63	26.1	20.3	33.6	26	977	41	4.4	1.9	10.5	4.4	10	5		
Omeprazole	10.2	9.5	11	10	###	323	26.1	23.3	29.3	26	4861	200	3.8	2.5	5.8	3.8	41	21		
Pantoprazole	11	10.2	11.8	11	###	292	30.7	27.4	34.2	27	5688	197	5	3.3	7.4	5	70	23		
Rabeprazole	5.3	3.5	8	5.3	54	16	13.6	7.7	23.9	14	106	10	Not estimable							
Rivaroxaban with PPI																				
Dexlansoprazole	10.1	6.9	14.7	10	102.8	13	16.1	7.3	35.1	16	57	5	13	4.6	38.8	13	23	3		
Esomeprazole	8.4	7.2	9.9	8.4	564.9	83	10.9	7.6	15.6	11	227	26	11	7.3	17	11	##	19		
Lansoprazole	7.1	6.1	8.2	7.1	599.8	##	15.7	12.5	19.8	16	809	59	7.8	5.2	11.8	7.8	##	21		
Omeprazole	9.5	8.8	10.2	9.4	2857	##	20.5	18.2	23.2	21	3534	189	8.9	7	11.4	8.9	##	59		
Pantoprazole	9.5	8.8	10.1	9.5	3354	##	21.3	19.1	23.9	21	4469	229	7.8	6.1	9.9	7.8	##	60		
Rabeprazole	8	6.2	10.3	8	218.1	35	12.3	7.4	20.2	12	125	13	21	13.5	32.7	21	##	16		
Apixaban with PPI																				
Dexlansoprazole	6.5	7.1	10.3	6.5	52.8	12	8.9	3.5	22.5	8.9	21	4	Not estimable							
Esomeprazole	5.4	4.5	6.6	5.4	273	73	4	2.4	6.8	4	26.6	13	1.7	0.6	4.5	1.7	1	4		
Lansoprazole	6.8	6	7.8	6.8	761.1	##	7	5.1	9.5	7	181	36	2.4	1.3	4.6	2.4	6	9		
Omeprazole	3.7	3.4	4.2	3.7	548.8	##	4.8	3.9	6	4.8	245	81	2.7	1.9	3.7	2.7	32	32		
Pantoprazole	6	5.5	6.5	6	1638	##	10.6	9.2	12.3	11	1414	161	1.6	1	2.5	1.6	3	17		
Rabeprazole	6.8	5.1	9.1	6.8	144.5	29	5.8	2.7	12.5	5.8	19.5	6	Not estimable							
Edoxaban with PPI																				
Esomeprazole	7.8	3.6	16.6	7.8	18.2	4	16.1	6.7	38.6	16	42.9	4	Not estimable							

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Lansoprazole	6.8	3.7	12.3	6.8	30.6	7	14.8	7.6	28.9	15	77.6	7	8.8	3	26.1	8.8	13.8	3
Omeprazole	5.1	3	8.7	5.1	30.6	10	21	13.8	32.1	21	289	16	Not estimable					
Pantoprazole	10.5	8.3	13.2	11	288.8	33	Not estimable											

No.: Total number of reports; RRR: Relative reporting ratio; PRR: Proportional reporting ratio; and χ2: Chi-square test statistics.

Table 2. Bayesian signal detection measures for oral anticoagulant-PPI combinations for adverse events of interest.

Drugs	Hemorrhage		Gastrointestinal hemorrhage		Venous thrombo-embolism	
	IC025	EBGM05	IC025	EBGM05	IC025	EBGM05
Warfarin with PPI						
Esomeprazole	2.4	7.1	2	5.7	0.8	1.5
Lansoprazole	2.4	6.8	2.9	11.8	2	1.9
Omeprazole	2.7	7.7	2.9	10.1	1.4	2.9
Pantoprazole	2.6	7.4	3	11.8	0.8	1.5
Rabeprazole	1.7	4.9	1.5	5.3	Not estimable	
Dabigatran with PPI						
Dexlansoprazole	1.3	3.6	1.9	11.2	Not estimable	
Esomeprazole	2.3	6.4	3.4	17.8	0.9	1.7
Lansoprazole	2.3	6.8	3.2	18	0.9	1.8
Omeprazole	2.9	8.7	4	22	1.3	2.5
Pantoprazole	2.9	9.2	4.1	25.6	3.3	1.5
Rabeprazole	1.3	3	1.9	6.9	Not estimable	
Rivaroxaban with PPI						
Dexlansoprazole	1.5	4.6	1.5	6	1.1	4
Esomeprazole	2.3	6.3	2.3	7.2	2.2	6.9
Lansoprazole	2.2	5.6	3	11.8	1.9	5
Omeprazole	2.8	8.2	3.7	17.4	2.4	6.8
Pantoprazole	2.8	8.3	3.8	18.3	2.3	6
Rabeprazole	1.9	5.2	2	6.8	2.6	12.2
Apixaban with PPI						
Dexlansoprazole	1.3	3.2	1.1	3.2	Not estimable	
Esomeprazole	1.9	4.1	1.1	2.3	0.3	0.6
Lansoprazole	2.3	5.6	2	5	0.7	1.3
Omeprazole	1.7	3.3	1.8	3.9	1	1.9
Pantoprazole	2.3	5.3	2.9	9	0.4	1
Rabeprazole	1.8	4.3	1.1	2.5	Not estimable	
Edoxaban with PPI						
Esomeprazole	0.8	2.2	1.3	5.4	Not estimable	
Lansoprazole	1.1	2.7	1.7	6.5	1	2.7
Omeprazole	1.1	2.5	2.5	11.9	Not estimable	
Pantoprazole	2	6.3	Not estimable			

PPI: Proton pump inhibitor; IC: Information component; and EBGM: Empirical Bayes geometric mean.

Table 3. Interaction signal scores with oral anticoagulant-PPI combinations for the adverse events of interest.

Drugs	Hemorrhage				Gastrointestinal hemorrhage				Venous thrombo-embolism			
	EBGM	EB05	EB95	INTSS	EBGM	EB05	EB95	INTSS	EBGM	EB05	EB95	INTSS
Warfarin with PPI												
Esomeprazole	9.8	7.5	12.7	0.8	9.3	6.1	14	0.5	3.6	1.7	8	1
Lansoprazole	8.9	7.2	11.1	0.8	16.3	12.5	21.4	1.1*	3.9	2.1	7	1
Omeprazole	9.3	7.9	10.9	0.9	13.1	10.5	16.2	0.9	4.7	3.1	7	1
Pantoprazole	9.3	7.6	11.2	0.8	15.7	12.3	20	1.1*	3.1	1.7	6	1
Rabeprazole	9.2	5.4	15.7	0.6	12.7	6.1	26.3	0.5	Not estimable			
Dabigatran with PPI												
Dexlansoprazole	9	4.2	18.3	0.6	28.1	13	60.7	0.8	Not estimable			
Esomeprazole	8	6.7	10.4	0.9	23.7	18.7	30.2	1.2*	3.5	2	7	1
Lansoprazole	10	7.2	13	1	26.1	19.1	35.7	1.2*	4.4	2	9	1
Omeprazole	10	8.9	11.6	1.2*	26.1	22.6	30.1	1.4*	3.8	3	6	1
Pantoprazole	11	9.5	12.7	1.3*	30.6	26.4	35.6	1.7*	5	4	7	1
Rabeprazole	5	3.2	8.5	0.4	13.6	7.7	24.1	0.5	Not estimable			
Rivaroxaban with PPI												
Dexlansoprazole	10	5.2	19.5	0.6	16	7	36.5	0.4	13.4	5	37	1
Esomeprazole	8	6.6	10.7	0.7	10.9	7.7	15.5	0.5	11.1	8	17	1
Lansoprazole	7	5.8	8.3	0.6	15.7	12.4	20	0.8	7.8	5	11	1
Omeprazole	9	8.4	10.7	0.9	20.6	17.9	23.6	1.1*	8.9	7	11	1
Pantoprazole	10	8.5	10.6	0.9	21.3	18.8	24.2	1.2*	7.8	6	10	1
Rabeprazole	8	5.6	11.5	0.6	12.3	7.5	20.1	0.5	21	#	33	1.5*
Apixaban with PPI												
Dexlansoprazole	7	3.6	11.6	1.1*	8.9	3.7	21.3	1.1*	Not estimable			
Esomeprazole	5	4.3	6.8	1.3*	4	2.5	6.4	0.7	1.7	1	4	0
Lansoprazole	7	5.8	8.1	1.8*	7	5.2	9.3	1.5*	2.4	1	4	0
Omeprazole	4	3.3	4.2	1	4.8	4	5.8	1.2*	2.7	2	4	1
Pantoprazole	6	5.4	6.6	1.6*	10.6	9.3	12.2	2.7*	1.6	1	2	0
Rabeprazole	2	4.6	9.9	1.4*	5.8	2.9	11.6	0.9	Not estimable			
Edoxaban with PPI												
Esomeprazole	8	2.7	22.4	0.4	Not estimable				Not estimable			
Lansoprazole	7	3.1	14.7	0.4	16	6.4	40.2	0.5				
Omeprazole	5	2.8	9.4	0.4	14.8	7.4	29.4	0.6	8.8	3	24	1
Pantoprazole	11	6.9	16	0.9	21	13	34	1.1*	Not estimable			
Oral anticoagulant/PPI monotherapy												
Warfarin	9	8.8	9.2	NA	11	10.7	11.3	NA	3.3	3	4	NA
Dabigatran	7	7.1	7.4	NA	15.4	15	15.7	NA	4	4	4	NA
Rivaroxaban	9	9	9.2	NA	15.8	15.5	16	NA	8.7	9	9	NA
Apixaban	3	3.2	3.3	NA	3.3	3.2	3.4	NA	4.1	4	4	NA
Edoxaban	7	5.7	7.5	NA	10.1	8.3	12.2	NA	5.2	4	7	NA
Lansoprazole	1	0.5	0.7	NA	0.6	0.5	0.7	NA	0.2	0	0	NA
Dexlansoprazole	0	0.2	0.3	NA	0.6	0.5	0.8	NA	0.2	0	0	NA
Pantoprazole	1	0.5	0.6	NA	1.1	1	1.2	NA	0.4	0	0	NA
Omeprazole	1	0.7	0.8	NA	1.3	1.2	1.4	NA	0.4	0	1	NA

Rabeprazole	1	0.7	1	NA	2	1.7	2.5	NA	0.3	0	1	NA
Esomeprazole	1	0.6	0.6	NA	1.4	1.3	1.5	NA	0.2	0	0	NA

PPI: Proton pump inhibitor; EBGM: Empirical Bayes geometric mean; EB05: Lower limit of 90% CI of EBGM; EB95: Upper limit of 90% CI of EBGM; INTSS: Interaction signal score; *: Statistically significant; and NA: Not applicable.

supported these findings (Table 2), with some exceptions in venous thrombo-embolic events.

Interaction Signal Analysis

The interaction signal score (INTSS) analysis (Table 3) identified several significant drug-drug interactions between oral anticoagulants and PPIs. For hemorrhagic events, significant interactions were found when dabigatran was combined with omeprazole or pantoprazole, and when apixaban was paired with all PPIs except omeprazole. Gastrointestinal hemorrhage showed the most widespread interactions: warfarin interacted significantly with lansoprazole and pantoprazole; dabigatran showed interactions with four PPIs (esomeprazole, lansoprazole, omeprazole, and pantoprazole); rivaroxaban interacted with omeprazole and pantoprazole; apixaban demonstrated significant interactions with all PPIs except esomeprazole and rabeprazole; and edoxaban showed interaction with pantoprazole. For venous thrombo-embolic

Table 4. Comparison of outcomes reported with oral anticoagulants for the adverse events of interest.

Oral anticoagulants-PPI combinations	Hemorrhage			GIT hemorrhage			Venous thrombo-embolic events		
	Death	Life-threatening events	Chi-square value; df; p-value	Death	Life-threatening events	Chi-square value; df; p-value	Death	Life-threatening events	Chi-square value; df; p-value
Warfarin PPI combinations									
Esomeprazole	11	10	6.8; 5; 0.2	0	3	18.6; 5; 0.002*	1	1	Not estimable
Lansoprazole	14	6		10	1		0	0	
Omeprazole	24	33		5	12		4	7	
Pantoprazole	9	13		5	3		0	0	
Rabeprazole	1	4		1	1		Not available		
Without PPI	1303	1420		232	413		49	51	
Dabigatran PPI combinations									
Dexlansoprazole	3	4	4.5; 6; 0.6	3	4	6.5; 6; 0.4	Not available		Not estimable
Esomeprazole	32	9		23	9		0	0	
Lansoprazole	12	4		7	2		0	1	
Omeprazole	82	26		48	14		0	5	
Pantoprazole	69	27		38	17		5	3	
Rabeprazole	5	2		3	0		Not available		
Without PPI	3510	1201		1385	446		100	108	
Rivaroxaban PPI combinations									
Dexlansoprazole	5	1	124.3; 6; 0.005*	1	0	65.6; 6; 0.00001*	0	1	17.6; 6; 0.007*
Esomeprazole	22	12		9	1		1	0	
Lansoprazole	14	23		5	11		0	6	
Omeprazole	87	36		53	10		6	16	
Pantoprazole	86	50		49	23		8	14	
Rabeprazole	5	3		2	1		0	1	
Without PPI	6355	1189		2995	441		341	297	
Apixaban PPI combinations									

Dexlansoprazole	1	2	9.3; 6; 0.2	0	0	Not estimable	Not available		Not estimable
Esomeprazole	15	18		3	6		0	0	
Lansoprazole	28	35		3	10		2	0	
Omeprazole	19	29		6	5		0	5	
Pantoprazole	53	55		18	25		1	2	
Rabeprazole	5	3		2	0		Not available		
Without PPI	1769	1482		384	400		143	164	
Edoxaban PPI combinations									
Esomeprazole	1	0	Not estimable	Not available		Not estimable	Not available		1.1; 1; 0.3
Lansoprazole	0	0		0	0				
Omeprazole	4	0		2	0		0	1	
Pantoprazole	3	3		0	1		Not available		
Without PPI	30	23		13	8		4	3	

GIT: Gastrointestinal tract; PPI: Proton pump inhibitors; *-Statistically significant ($p \leq 0.05$).

events, only the rivaroxaban-rabeprazole combination showed significant interaction.

Clinical Outcome Analysis

The distributions of key outcomes between various anticoagulant-PPI combinations are summarized in Table 4. Differential mortality patterns were observed across various oral anticoagulant-PPI combinations. The lansoprazole-warfarin combination was significantly associated with increased mortality specifically in cases of gastrointestinal hemorrhage. In contrast, when lansoprazole was combined with rivaroxaban, it demonstrated a protective effect, showing a significantly reduced mortality in both overall hemorrhagic events and gastrointestinal hemorrhage. For venous thrombo-embolic events, multiple PPIs (lansoprazole, omeprazole, and pantoprazole) were significantly associated with reduced mortality outcomes with rivaroxaban.

DISCUSSION

Key findings

For hemorrhagic events, the analysis revealed significant interactions when dabigatran was combined with omeprazole or pantoprazole, and when apixaban was combined with most PPIs (except omeprazole). This was further supported by higher RORs observed with dabigatran-PPI combinations (specifically with lansoprazole, omeprazole, and pantoprazole) and apixaban-PPI combinations (except with omeprazole). The rivaroxaban-lansoprazole combination distinctly showed a non-overlapping increased ROR. For gastrointestinal hemorrhage, the interactions were more extensive, with significant signals observed across multiple combinations: warfarin with lansoprazole and pantoprazole (showing higher RORs); dabigatran with four PPIs (esomeprazole, lansoprazole, omeprazole, and pantoprazole); rivaroxaban with omeprazole and pantoprazole; and apixaban with all PPIs except esomeprazole and rabeprazole. Notably, esomeprazole demonstrated a protective effect when combined with rivaroxaban. Regarding venous thrombo-embolic events, the findings were more limited, with the rivaroxaban-rabeprazole combination showing both significant interaction signals and higher RORs. Conversely, apixaban combinations with pantoprazole, esomeprazole, or omeprazole showed lower RORs, while warfarin and dabigatran showed no significant interactions with any PPIs for this outcome.

Comparison with existing literature

Our analysis revealed an increased incidence of hemorrhagic events, including gastrointestinal hemorrhage, when dabigatran and apixaban were co-administered with most PPIs. This interaction pattern can be explained through multiple pharmacological mechanisms. For dabigatran, PPIs create a less favorable absorption environment by elevating gastrointestinal pH through proton pump inhibition[26]. Paradoxically, this pH-dependent effect shows opposite results with warfarin, where increased gastric pH enhances its absorption[27]. This phenomenon is primarily attributed to improved dissolution rates of warfarin tablets in a less acidic environment[28], potentially explaining the elevated hemorrhage risk observed with certain warfarin-PPI combinations. The complexity of these interactions extends beyond pH-dependent effects to metabolic pathways.

While warfarin predominantly undergoes CYP2C9 metabolism, apixaban and rivaroxaban exhibit distinct metabolic profiles. Apixaban is partially metabolized (approximately 25%) by CYP3A4/5, whereas rivaroxaban utilizes multiple cytochrome P450 pathways. This metabolic diversity was demonstrated in a study where ritonavir, a broad-spectrum CYP inhibitor, resulted in a 13% reduction in apixaban metabolism compared to a dramatic 90% reduction for rivaroxaban[29]. Further evidence of these complex interactions comes from preclinical rodent studies, where co-administration of apixaban and esomeprazole led to increased maximum plasma concentration and area-under-the-concentration curve for

apixaban, while simultaneously reducing these parameters for esomeprazole and shortening apixaban's time to peak concentration[30]. These metabolic interactions may explain our observation of reduced venous thrombo-embolic events with apixaban-PPI combinations. The interaction landscape is further complicated by transport protein involvement. Both dabigatran and edoxaban are substrates of the P-glycoprotein efflux transporter[31], while several PPIs, notably omeprazole, lansoprazole, and pantoprazole, function as both substrates and inhibitors of this transport system[32]. This dual interaction at the transport protein level adds another layer of complexity to the clinical outcomes observed. Previous research has suggested that the protective effect of PPIs against gastrointestinal hemorrhage in dabigatran-treated patients may be limited to those with a history of peptic ulcer or gastrointestinal bleeding[33]. However, a limitation of our current study is the inability to analyze this risk factor due to the absence of historical acid peptic disorder data in the FAERS database. Based on these findings, we recommend an enhanced clinical monitoring for patients receiving combinations of dabigatran or apixaban with PPIs, particularly for signs of hemorrhagic complications; individual risk-benefit assessment before initiating PPI therapy in patients on oral anticoagulants, considering patient-specific factors such as bleeding history; regular review of the necessity for continued PPI therapy in anticoagulated patients; and conducting prospective studies to better characterize these interactions, particularly focusing on specific patient subgroups and risk factors for optimizing the safety profile of oral anticoagulant-PPI combinations while maintaining their therapeutic benefits.

Strengths and limitations

This study offers several notable strengths. First, it leverages the extensive FAERS database, providing a large-scale, real-world assessment of oral anticoagulant-PPI interactions across diverse patient populations and clinical settings. The application of both disproportionality and interaction signal analyses enhances the robustness of our findings and provides complementary perspectives on safety signals. Additionally, our investigation encompasses all commercially available PPIs and oral anticoagulants, offering a comprehensive evaluation of class-wide and agent-specific interactions. Also, we excluded patients receiving aspirin, acetylsalicylic acid, clopidogrel and heparin as these are the major confounders. However, several limitations warrant consideration. As with all spontaneous reporting systems, FAERS data is subject to reporting bias, underreporting, and variable quality of submitted information. The database lacks important clinical details such as drug dosages, duration of therapy, timing of adverse events, concomitant medications beyond the studied combinations, and patient comorbidities, particularly the history of acid peptic disorders or previous bleeding events. The absence of a true denominator of patients using these drug combinations prevents the calculation of true incidence rates. The analysis was limited by missing demographic data, making it impossible to assess how age and gender influenced the results. Furthermore, the database cannot establish definitive causal relationships between drug combinations and adverse events, and confounding by indication cannot be ruled out, particularly since PPIs might have been prescribed to high-risk patients more prone to bleeding events. The analysis also cannot account for over-the-counter PPI use or patient compliance with prescribed medications. Therefore, while our findings provide important signals regarding oral anticoagulant-PPI interactions, they should be interpreted as hypothesis-generating and validated through prospective clinical studies with more rigorous designs.

CONCLUSION

Our pharmacovigilance analysis of the FAERS database reveals significant safety signals regarding oral anticoagulant-PPI interactions, particularly concerning hemorrhagic complications. The findings demonstrate that specific combinations, notably dabigatran and apixaban with various PPIs, warrant careful clinical consideration due to increased hemorrhagic event signals, including gastrointestinal bleeding. Conversely, certain combinations showed protective effects against venous thromboembolic events, highlighting the complex nature of these drug interactions. These interactions appear to be mediated through multiple mechanisms, including pH-dependent absorption changes, metabolic enzyme interactions, and transport protein modifications. The observed safety signals underscore the importance of individualized risk assessment when prescribing PPIs to patients on oral anticoagulation therapy. Healthcare providers should carefully weigh the potential benefits of gastroprotection against the risks of bleeding complications, particularly in high-risk patients. Regular monitoring of patients on these combinations, periodic reassessment of PPI necessity, and consideration of patient-specific risk factors are essential for optimal therapeutic management. Future prospective studies are needed to further characterize these interactions, establish definitive causal relationships, and develop evidence-based guidelines for managing patients requiring both medication classes. Until then, our findings serve as an important reference point for healthcare providers in making informed decisions about the concurrent use of oral anticoagulants and PPIs.

AUTHORS' CONTRIBUTIONS

KS: Conceived the idea; KS and GS: Data curation, analysis and interpretation; KS: Wrote the first draft of the manuscript; and KS and GS: Involved in critical revisions and final acceptance of the manuscript.

CONFLICT OF INTEREST

KS and GS declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

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