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Adverse Reactions With VEGF Inhibitors in Combination With NSAIDs: Disproportionality Analysis Using JADRE and FAERS

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Abstract

Background/Aim: The concurrent use of vascular endothelial growth factor (VEGF) inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs) raises concerns regarding the increased risk of adverse drug reactions (ADRs) due to potential pharmacodynamic interactions. However, no studies have specifically addressed this issue. The objective of this study was to investigate whether the combination of these drugs increased the risk of ADRs.

Patients and Methods: Disproportionality analysis was conducted on ADR reports from the Japanese Adverse Drug Event Report (JADER) and FDA Adverse Event Reporting System (FAERS) databases. The concomitant signal score and Ω shrinkage measure were used to identify safety signals associated with the drug combination. Additionally, logistic regression analysis focused on reports of ADRs related to cancer treatment and assessed the significance of the adjusted reporting odds ratio (aROR) for the interaction between these drugs.

Results: Disproportionality analysis included ADR data from the JADER (n=1,509,399) and FAERS (n=38,610,433) databases. The concomitant signal score and Ω shrinkage measure identified a signal for gastrointestinal perforation in both databases. Logistic regression on cancer treatment-related ADRs (JADER: n=255,177; FAERS: n=1,167,941) showed a synergistic increase in gastrointestinal perforation risk with the drug combination [aROR for interaction term: JADER: 1.74 (95% confidence interval (CI)=1.45-2.07); FAERS: 1.49 (95% CI=1.29-1.72)].

Conclusion: The combination of VEGF inhibitors and NSAIDs is associated with an increased risk of gastrointestinal perforation, a serious and potentially fatal ADR. Therefore, caution is warranted when prescribing a combination of these drugs.

Keywords: Vascular endothelial growth factor inhibitor, non-steroidal anti-inflammatory drug, spontaneous reporting databases, disproportionality analysis.

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Introduction

Inhibiting angiogenesis is a key strategy in cancer therapy, with vascular endothelial growth factor (VEGF) as the primary target (1). VEGF inhibitors block VEGF activity, suppressing tumour angiogenesis, which reduces tumour size and provides clinical benefits, including prolonged overall survival (2). Monoclonal antibodies, including bevacizumab, and tyrosine kinase inhibitors (TKIs), including axitinib, have been approved for the treatment of various solid tumours. However, these therapies are associated with various adverse drug reactions (ADRs). Healthcare providers must carefully manage ADRs, focusing on their prevention and early detection in patients receiving VEGF inhibitors.

Meta-analyses of clinical trials have identified significant associations between VEGF inhibitors and ADRs, including gastrointestinal perforation (3-5), cardiovascular toxicity (*e.g.* heart failure, thromboembolism, and hypertension) (6, 7), and proteinuria (8). These ADRs commonly occur regardless of whether the VEGF inhibitors are TKIs or non-TKIs (7). These reactions interrupt treatment and can be severe or even fatal (9, 10). Several risk factors are associated with ADRs. The cancer type (3), history of coronary artery disease (11), and poorly controlled hypertension (12) are risk factors for gastrointestinal perforation, cardiovascular toxicity, and proteinuria, respectively.

Pain is a common symptom among patients with cancer, with 50-70% of patients undergoing aggressive treatment (13). Mild cancer pain is often managed with analgesics, such as acetaminophen (AAP) and non-steroidal anti-inflammatory drugs (NSAIDs), while moderate to severe pain typically requires opioids. Patients receiving chemotherapy along with pain relief have complex pharmacological profiles. Although VEGF inhibitors and NSAIDs have distinct mechanisms of action, their overlapping ADR profiles raise concerns about potential pharmacodynamic interactions (14). However, evidence on the impact of the concomitant use of VEGF inhibitors and NSAIDs on adverse events remains limited.

Spontaneous reporting databases, which collect real-world reports of ADRs, are valuable tools for examining the correlations between drugs (or drug combinations) and ADRs. These large datasets also allow the analysis of rare ADRs. This study aimed to evaluate the association between concomitant NSAID use and the risk of ADRs associated with VEGF inhibitors in a real-world setting. Using two major spontaneous reporting databases, the Japanese Adverse Drug Event Report (JADER) and FDA Adverse Event Reporting System (FAERS), we conducted disproportionality and logistic regression analyses to detect safety signals associated with the combined use of VEGF inhibitors and NSAIDs.

Patients and Methods

Study design. The workflow is illustrated in Figure 1. Disproportionality analysis was conducted to individually calculate the ADR signals for VEGF inhibitors and NSAIDs, followed by an assessment of the increased ADR risk associated with their combination. Data from the JADER and FAERS databases encompassing all reported ADRs were used. Logistic regression analysis was performed to calculate the adjusted reporting odds ratios (aROR) for the combined use of VEGF inhibitors and NSAIDs. This analysis only included cancer treatment-related ADR reports from the JADER and FAERS databases. AAP, which has a nonoverlapping side effect profile, was used as the reference drug in all analyses.

Disproportionality analysis results were reported according to the READUS-PV statement (15), whereas logistic regression results adhered to the STROBE statement checklist (16) (Table SI and Table SII). All data analyses and processing were conducted using purpose-written R language (version 4.3.1) scripts managed using R AnalyticFlow (version 3.2.3, Ef-prime, Inc., Tokyo, Japan).

Data acquisition and pre-processing. The JADER database contains adverse event reports, primarily from Japan. This was downloaded from the PMDA website

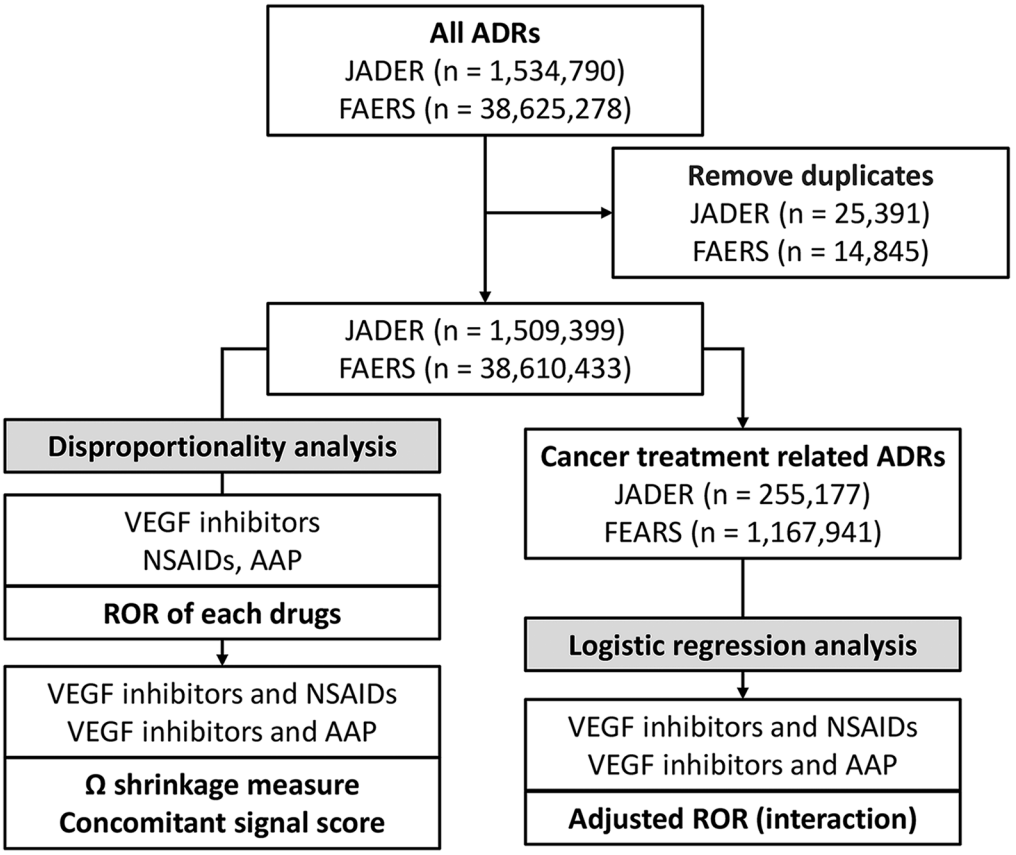

Figure 1. *Flowchart of data analysis in this study. The study first conducted a disproportionality analysis on all ADR reports, excluding duplicates (left). In this analysis, the RORs for VEGF inhibitors, NSAIDs, and AAP were calculated, followed by an assessment of the safety signal for their combination. Logistic regression analyses were then performed on cancer treatment-related ADR reports (right). ADR: Adverse drug reactions; VEGF: vascular endothelial growth factor; NSAID: non-steroidal anti-inflammatory drug; AAP: acetaminophen; ROR: reporting odds ratio.*

(https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0004.html). The version used in this study was JADER ver. 202410, comprising reports from April 2004 to October 2024. The FAERS database primarily includes adverse event reports from the United States, with additional reports from other countries. In this study, we used a standardised version of the FAERS database developed by Khaleel *et al.* (17). This version includes all reports from the original FAERS database spanning January 2004 to September 2021 and features drug names normalised using RxNorm. Both databases allow the linkage of data on drugs, patient backgrounds, and outcomes using unique ID numbers. Reports with duplicate ID numbers and ADRs were removed during pre-processing, ensuring unique ADR reports reports were analysed. The final dataset included JADER (*n*=1,509,399) and FAERS (*n*=38,610,433) reports. Patient demographics and clinical characteristics are summarised in Table SIII.

Definition of drugs and ADRs. The VEGF TKI inhibitors included in this study were axitinib, sunitinib, sorafenib, nindetanib, pazopanib, vandetanib, regorafenib, lenvatinib, and cabozantinib. The VEGF non-TKI inhibitors were bevacizumab, ramucirumab, and aflibercept. NSAIDs include six commonly used drugs, diclofenac, etodolac, ibuprofen, naproxen, celecoxib, and loxoprofen (18), selected for their widespread use in clinical practice and

systemic effects relevant to this study. Combination products were excluded to eliminate the potential confounding effects of other drugs. Drugs were identified by their generic names, with hydrates and salts included in the analysis. ADRs were defined using the preferred terms in the standardised medical dictionary for regulatory activity (MedDRA) queries (SMQs; MedDRA version 27.1). The SMQs analysed in this study included gastrointestinal perforation (SMQ: 20000107), gastrointestinal haemorrhage (SMQ: 20000108), haemorrhagic central nervous system (CNS) vascular conditions (SMQ: 20000064), embolic and thrombotic events (SMQ: 20000081), cardiac failure (SMQ: 20000004), hypertension (SMQ: 20000147), and proteinuria (SMQ: 20000220).

Disproportionality analysis. The reporting odds ratio (ROR) and 95% confidence interval (CI) of the target ADR for each drug alone were calculated using the following formula and Table I. If the lower limit of the 95% CI was >1, it was considered a signal.

$$ROR=(N_{11}/N_{10})/(N_{01}/N_{01})$$

$$95\%\ CI = exp\left(lnROR \pm 1.96\sqrt{\frac{1}{N_{11}}+\frac{1}{N_{10}}+\frac{1}{N_{01}}+\frac{1}{N_{01}}}\right)$$

The ADR signals of the VEGF inhibitors in combination with NSAIDs were also investigated. In this study, two indicators were employed to detect drug interactions in disproportionality analysis: the concomitant signal score (CSS), which is an extended model of the proportional reporting ratio (PRR), and the Ω shrinkage measure (19, 20). Each was obtained using the following equations:

$$CSS = \frac{PRR_{025\ D1\wedge D2}}{max(PRR_{975\ D1}, PRR_{975\ D2})}$$

$$\Omega = \log_2 \frac{n_{111}+0.5}{E_{111}+0.5}$$

$$\Omega_{025} = \Omega - \frac{\varphi(0.975)}{\log(2)\sqrt{n_{111}}}$$

$PRR_{025\ D1\wedge D2}$ indicates the lower 95% CI limit of the PRR when the two drugs are used in combination, and $PRR_{975\ D1}$ and $PRR_{975\ D2}$ indicate the upper limit of the 95% CI for the PRR when each drug is used individually. A signal was considered present if $PRR_{025D1\wedge D2}$ >1 and CSS >1. E_{111} refers to the expected ADR when the two drugs are used together. A signal is indicated if Ω_{025} >0. For ADRs in which a signal was detected with the combination of VEGF inhibitors and NSAIDs, individual combinations of VEGF inhibitors (all VEGF inhibitors, TKIs, and non-TKIs) with specific NSAIDs were further reviewed to assess the risk associated with each NSAID. This approach also served as a sensitivity analysis for disproportionality analysis.

Table I. *A 4×2 contingency table for signal detection of drug-drug interactions.*

	Target ADR	Other ADRs	Total
Concomitant use of D1 and D2	n_{111}	n_{110}	n_{11+}
Only D1	n_{101}	n_{100}	n_{10+}
Only D2	n_{011}	n_{010}	n_{01+}
Neither D1 or D2	n_{001}	n_{000}	n_{00+}

D1 is a VEGF inhibitor and D2 is a non-steroidal anti-inflammatory drug or acetaminophen. For the calculation of the reporting odds ratio, the following values are further calculated: $N_{11}=n_{111}+n_{101}$, $N_{10}=n_{110}+n_{100}$, $N_{01}=n_{011}+n_{001}$, $N_{00}=n_{010}+n_{000}$.

The JADER and FAERS databases record the contribution of each drug to ADRs. In this study, all ADRs were analysed without restricting the contribution of the drugs. This decision was based on the uncertainty that VEGF inhibitors, NSAIDs, or AAP would consistently be recognised as suspected drugs by reporters, and the notion that *a priori* restriction should not be performed in drug-drug interaction analysis (21). Thus, all contributions – whether classified as "suspected", "interaction", or "concomitant" – were included in the analysis.

Logistic regression analysis. In logistic regression analysis, the aROR for ADRs associated with VEGF inhibitors and NSAIDs (or control AAPs), either alone or in combination, were calculated. Only ADR reports related to cancer treatment were included from the JADER and FAERS databases. Cancer treatment-related ADRs were defined as reports from the JADER and FAERS databases that listed

Table II. *Disproportionality analysis of VEGF inhibitors, NSAIDs and AAP.*

	JADER			FAERS		
	ADR	Total	ROR (95% CI)	ADR	Total	ROR (95% CI)
Gastrointestinal perforation						
VEGFi	7,581	95,098	6.95 (6.69-7.22)	7,215	896,548	4.81 (4.69-4.93)
NSAID	1,713	112,439	2.00 (1.90-2.10)	5,539	2,332,986	1.32 (1.29-1.36)
AAP	302	46,095	0.79 (0.70-0.88)	5,504	3,094,474	0.97 (0.94-1.00)
Gastrointestinal haemorrhage						
VEGFi	2,397	95,098	1.75 (1.67-1.82)	8,241	896,548	1.51 (1.48-1.55)
NSAID	2,692	112,439	1.66 (1.59-1.73)	8,241	2,332,986	1.84 (1.81-1.86)
AAP	530	46,095	0.48 (0.43-0.52)	22,053	3,094,474	1.17 (1.16-1.19)
Haemorrhagic CNS vascular conditions						
VEGFi	1,032	95,098	0.89 (0.83-0.95)	4,374	896,548	1.00 (0.97-1.03)
NSAID	854	112,439	0.61 (0.57-0.65)	10,117	2,332,986	0.88 (0.86-0.90)
AAP	243	46,095	0.51 (0.44-0.59)	12,518	3,094,474	0.81 (0.80-0.83)
Embolic and thrombotic events						
VEGFi	4,932	95,098	1.63 (1.58-1.68)	21,580	896,548	1.33 (1.31-1.34)
NSAID	3,038	112,439	1.00 (0.97-1.03)	46,197	2,332,986	1.08 (1.07-1.09)
AAP	987	46,095	0.62 (0.58-0.66)	53,070	3,094,474	0.93 (0.92-0.93)
Cardiac failure						
VEGFi	1,316	95,098	1.27 (1.20-1.34)	4,713	896,548	1.07 (1.04-1.11)
NSAID	1,057	112,439	0.83 (0.78-0.89)	7,965	2,332,986	0.68 (0.67-0.70)
AAP	500	46,095	0.98 (0.89-1.07)	14,265	3,094,474	0.93 (0.92-0.95)
Hypertension						
VEGFi	2,577	95,098	5.62 (5.37-5.89)	20,326	896,548	3.27 (3.22-3.31)
NSAID	450	112,439	0.61 (0.56-0.67)	19,379	2,332,986	1.13 (1.11-1.15)
AAP	155	46,095	0.52 (0.45-0.61)	27,664	3,094,474	1.23 (1.21-1.24)
Proteinuria						
VEGFi	2,201	95,098	15.86 (14.94-16.85)	4,458	896,548	8.58 (8.31-8.86)
NSAID	317	112,439	0.99 (0.88-1.11)	1,631	2,332,986	1.02 (0.97-1.08)
AAP	65	46,095	0.49 (0.38-0.62)	2,187	3,094,474	1.04 (0.99-1.08)

ADR indicates the number of adverse event reports for the subject and Total indicates the total number of reports for the subject drug; a lower 95% CI of ROR >1 is considered as a signal. VEGFi: Vascular endothelial growth factor inhibitor; NSAID: non-steroidal anti-inflammatory drug; AAP: acetaminophen; CNS: central nervous system; CI: confidence interval.

terms, such as "cancer", "tumor", "neoplasm", "carcinoma", "leukemia", "lymphoma", or "myeloma" (or equivalent Japanese terms in JADER) as the reason for drug use. This analysis accounted for the potential influences of cancer type, age, and sex on ADR incidence. Therefore, these variables were included as covariates in the logistic regression analysis. The logistic regression model was structured as follows:

$$lp=\beta_0+\beta_1 Age+\beta_2 Sex+\beta_3 CancerType+\beta_4 D1+\beta_5 D2+\beta_6 D1\times D2$$

Sex and cancer type were treated as the categorical variables. Age was modelled as a categorical variable in 10-year increments for JADER and continuous variable for FAERS owing to differences in database structures. Variable D1 indicates the use of VEGF inhibitors, and D2 indicates the use of NSAIDs or AAPs, both as binary variables. The coefficient β_6 represents the interaction term. In a logistic regression, an interaction term reflects an effect that arises only when multiple factors coexist. If β_6 is significantly positive, the combination of two drugs is interpreted as conferring an additional risk compared with their individual use. Under the assumption that missing values are missing at random, missing values for categorical variables were treated as "unknown", while missing continuous variables were imputed with mean values.

Table III. *Disproportionality analysis of VEGF inhibitors plus NSAIDs or AAP.*

	JADER					FAERS				
	ADR	Total	PRR_{025}	CSS	Ω_{025}	ADR	Total	PRR_{025}	CSS	Ω_{025}
Gastrointestinal perforation										
VEGFi and NSAID	707	7,589	11.00	1.91	0.81	610	41,722	7.42	1.59	0.41
VEGFi and AAP	130	2,484	5.36	0.78	–0.19	554	88,445	3.16	0.40	–0.83
Gastrointestinal haemorrhage										
VEGFi and NSAID	337	7,589	2.63	1.58	0.01	500	41,722	1.78	0.97	–0.66
VEGFi and AAP	59	2,484	1.20	0.67	–0.75	712	88,445	1.21	0.78	–0.78
Haemorrhagic CNS vascular conditions										
VEGFi and NSAID	81	7,589	0.71	0.74	–0.85	170	41,722	0.72	0.69	–0.80
VEGFi and AAP	22	2,484	0.48	0.50	–1.36	329	88,445	0.68	0.65	–0.90
Embolic and thrombotic events										
VEGFi and NSAID	307	7,589	1.07	0.64	–0.86	817	41,722	0.99	0.74	–0.81
VEGFi and AAP	105	2,484	1.03	0.62	–0.88	1,731	88,445	1.01	0.86	–0.69
Cardiac failure										
VEGFi and NSAID	80	7,589	0.76	0.55	–1.04	196	41,722	0.83	0.75	–0.68
VEGFi and AAP	22	2,484	0.52	0.39	–1.53	361	88,445	0.75	0.74	–0.86
Hypertension										
VEGFi and NSAID	106	7,589	1.83	0.31	–1.59	750	41,722	2.26	0.69	–0.83
VEGFi and AAP	37	2,484	1.70	0.29	–1.62	1,598	88,445	2.33	0.66	–0.83
Proteinuria										
VEGFi and NSAID	53	7,589	1.88	0.11	–2.55	111	41,722	3.24	0.36	–1.53
VEGFi and AAP	28	2,484	2.73	0.17	–1.86	252	88,445	3.71	0.70	–1.38

ADR indicates the number of adverse event reports under combination of both drugs, and Total indicates the total number of reports for combination of both. CSS: PRR_{025}>1 and CSS>1, Ω shrinkage measure: Ω_{025}>0 are considered as a signal. VEGFi: Vascular endothelial growth factor inhibitor; NSAID: non-steroidal anti-inflammatory drug; AAP: acetaminophen; CNS: central nervous system.

Results

Signals associated with VEGF inhibitors were detected in all ADRs, except for CNS vascular haemorrhage, with consistent results across both JADER and FAERS (Table II). For NSAIDs, signals indicating gastrointestinal perforation and haemorrhage were identified in both databases. However, thromboembolism and hypertension signals were detected only in the FAERS group. Similarly, for AAP, a signal for hypertension was detected exclusively using FAERS.

A disproportionality analysis was performed to evaluate the concomitant use of VEGF inhibitors, NSAIDs (or AAPs) (Table III). For gastrointestinal perforation, signals were detected using both CSS and Ω shrinkage measure, with consistent results across the JADER and FAERS databases. For gastrointestinal haemorrhage, signals (both CSS and Ω shrinkage measure) were detected only in JADER, whereas no signals were identified in FAERS for either measure. No signals were detected for other ADRs associated with concomitant NSAID use and no ADR signals were observed for AAP.

Next, the analysis focused on the signals for gastrointestinal perforation or gastrointestinal haemorrhage with combinations of VEGF inhibitors and individual NSAIDs (Table IV). For gastrointestinal perforation, combination signals (CSS and Ω shrinkage measure) were detected in JADER for all NSAIDs except ibuprofen, which had insufficient reports to calculate an indicator. In FAERS, signals were detected for diclofenac and loxoprofen, whereas etodolac showed signals in CSS. For gastrointestinal haemorrhage, signals (both CSS and Ω shrinkage measure) were detected only for loxoprofen and naproxen in JADER, and loxoprofen in FAERS. These trends remained consistent

Table IV. *Disproportionality analysis using VEGF inhibitors paired with each NSAID.*

		JADER									
		Gastrointestinal perforation					Gastrointestinal haemorrhage				
		ADR	Total	PRR_{025}	CSS	Ω_{025}	ADR	Total	PRR_{025}	CSS	Ω_{025}
Any VEGFi and	Any NSAIDs	707	7,589	11.00	1.91	0.81	337	7,589	2.63	1.58	0.01
Any VEGFi and	Celecoxib	79	925	8.26	1.21	0.38	31	925	1.54	0.86	-0.83
Any VEGFi and	Diclofenac	140	1,089	13.19	1.97	0.80	51	1,089	2.32	1.11	-0.44
Any VEGFi and	Etodolac	40	510	6.90	1.00	0.10	27	510	2.36	1.24	-0.23
Any VEGFi and	Ibuprofen	0	31	-	-	-	0	31	-	-	-
Any VEGFi and	Loxoprofen	442	4,960	10.11	1.62	0.69	221	4,960	2.57	1.49	0.05
Any VEGFi and	Naproxen	50	678	6.72	0.98	0.06	35	678	2.41	1.35	0.26
		FAERS									
		Gastrointestinal perforation					Gastrointestinal haemorrhage				
		ADR	Total	PRR_{025}	CSS	Ω_{025}	ADR	Total	PRR_{025}	CSS	Ω_{025}
Any VEGFi and	Any NSAIDs	610	41,722	7.42	1.59	0.41	500	41,722	1.78	0.97	-0.66
Any VEGFi and	Celecoxib	69	6,658	4.47	0.91	-0.28	72	6,658	1.39	0.90	-0.65
Any VEGFi and	Diclofenac	144	6,684	9.99	2.07	0.58	108	6,684	2.17	1.23	-0.33
Any VEGFi and	Etodolac	16	982	5.43	1.11	-0.05	25	982	2.78	1.33	-0.08
Any VEGFi and	Ibuprofen	99	17,315	2.56	0.52	-1.16	114	17,315	0.89	0.50	-1.64
Any VEGFi and	Loxoprofen	251	5,599	21.64	4.56	1.47	132	5,599	3.22	1.58	0.13
Any VEGFi and	Naproxen	61	8,279	3.13	0.64	-0.79	90	8,279	1.43	0.71	-1.07

ADR indicates the number of adverse event reports under combination of both drugs, and Total indicates the total number of reports for combination of both. CSS: $PRR_{025}>1$ and CSS>1, Ω shrinkage measure: $\Omega_{025}>0$ are considered as a signal. VEGFi: Vascular endothelial growth factor inhibitor; NSAID: non-steroidal anti-inflammatory drug.

when VEGF inhibitors were analysed separately as TKIs or non-TKIs (Table SIV).

Logistic regression analysis was performed to calculate the aROR for the VEGF inhibitors, NSAIDs, and their combinations. Reports related to cancer treatment from the JADER (*n*=255,177) and FAERS (*n*=1,167,941) databases were analysed (Table SV). The logistic regression model incorporated age, sex, and cancer type as covariates, along with an interaction term for drug combinations (Figure 2; all results, including unadjusted RORs, are shown in Table SVI). The analysis revealed that concomitant NSAID use significantly increased the risk of gastrointestinal perforation with VEGF inhibitors [JADER-aROR: 1.74 (95% CI=1.45-2.07), FAERS-aROR: 1.49 (1.29-1.72)]. Conversely, NSAIDs were associated with a significantly reduced risk of hypertension [JADER-aROR: 0.54 (0.36-0.79), FAERS-aROR: 0.85 (0.76-0.95)] and proteinuria [JADER-aROR: 0.42 (0.24-0.74), FAERS-aROR: 0.51 (0.37-0.69)] in combination with VEGF inhibitors. The reference drug, AAP, did not increase the risk of ADRs with VEGF inhibitors. Instead, it reduced the risk of hypertension [JADER-aROR: 0.32 (0.19-0.55), FAERS-aROR: 0.76 (0.70-0.82)]. In FAERS, AAP use was also associated with a reduced risk of heart failure [FAERS-aROR: 0.87 (0.75-0.99)] and proteinuria [FAERS-aROR: 0.61 (0.49-0.76)].

Discussion

In this study, we used two large spontaneous reporting databases to investigate the association between ADRs, including gastrointestinal perforation, bleeding (gastrointestinal or CNS vascular), thromboembolism, heart

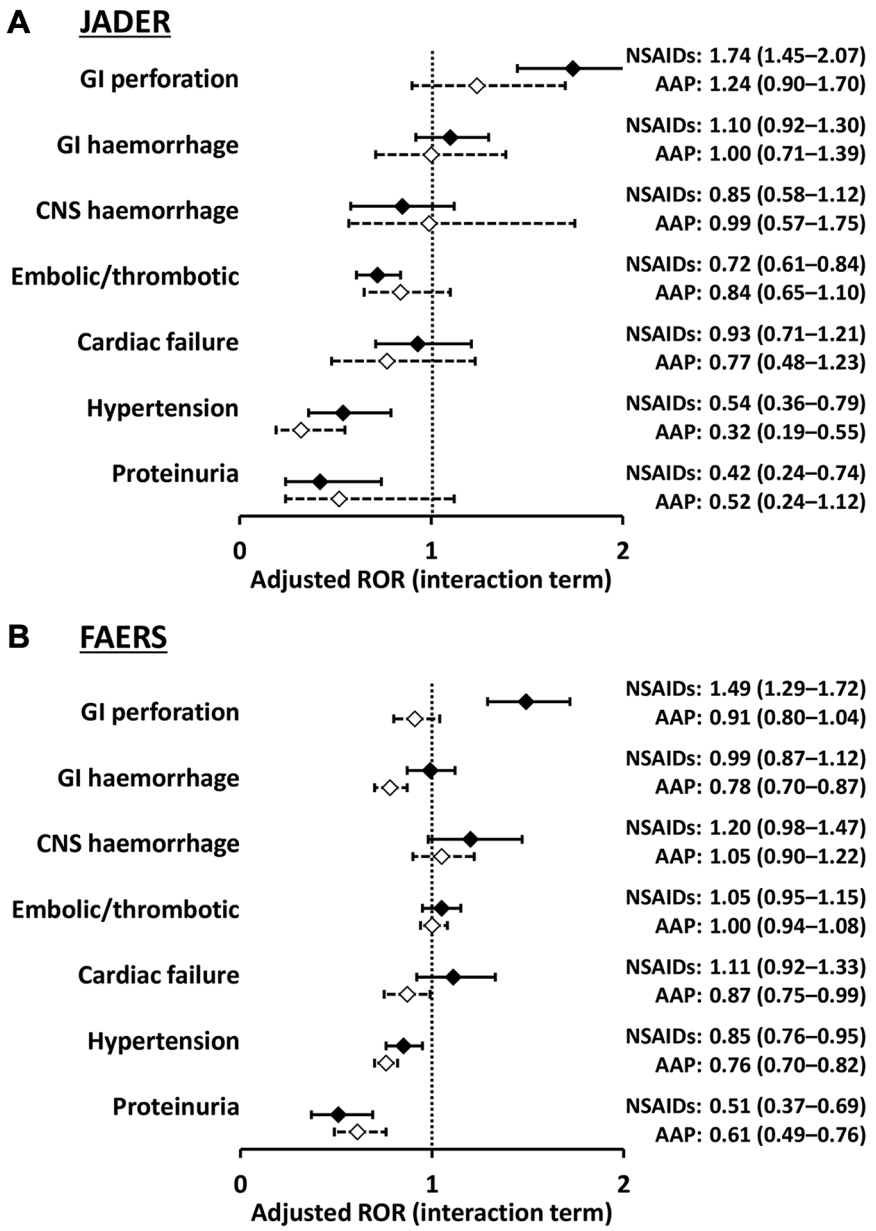

Figure 2. *Adjusted reporting odds ratio (ROR) of interaction terms in logistic regression analysis. This figure shows the adjusted ROR of the interaction term between VEGF inhibitors and NSAIDs (or AAP) for each ADR in the logistic regression model. (A) shows the results of JADER and (B) the results of the FAERS analysis. Diamonds (black: NSAIDs, white: AAP) indicate adjusted ROR point estimates for interaction terms; lines (solid: NSAIDs, dotted: AAP) indicate 95% confidence intervals. GI perforation: Gastrointestinal perforation; GI haemorrhage: gastrointestinal haemorrhage; CNS haemorrhage: haemorrhagic central nervous system vascular conditions; Embolic/thrombotic: embolic and thrombotic events; NSAID: non-steroidal anti-inflammatory drug; AAP: acetaminophen; ROR: reporting odds ratio.*

failure, hypertension, and proteinuria, and the concomitant use of VEGF inhibitors and NSAIDs. Our findings revealed a strong signal of gastrointestinal perforation associated with the combination of VEGF inhibitors and NSAIDs. This signal was identified using a conservative method for detecting drug interactions (19), and the results were

further supported by sensitivity analyses, including evaluation of individual NSAIDs and logistic regression analysis. These findings suggest that concomitant use of NSAIDs and VEGF inhibitors may significantly increase the risk of gastrointestinal perforation in a synergistic manner.

Gastrointestinal perforation signals were detected in both the JADER and FAERS databases. The potential risk of gastrointestinal perforation with the concomitant use of VEGF inhibitors and NSAIDs has been suggested (22, 23); however, conclusive data are lacking (24). Meta-analyses have estimated that gastrointestinal perforation occurs in 1-2% of patients treated with VEGF inhibitors (3-5). A meta-analysis of bevacizumab (3) reported that while the incidence of gastrointestinal perforation is rare, it is associated with a high fatality rate (21.7%). Gastrointestinal perforation associated with VEGF inhibitors has been reported to be more common in patients with colorectal cancer or renal cell carcinoma (3), as well as in those with a history of radiation therapy (25). The mechanism underlying VEGF inhibitor-induced gastrointestinal perforation remains unclear. However, it is thought to involve inflammation resulting from angiogenesis inhibition, leading to intestinal ischaemia, ulceration, and delayed ulcer repair (26, 27). In contrast, NSAIDs reduce prostaglandin levels in the gastrointestinal mucosa by inhibiting cyclooxygenase (COX), resulting in mucosal injury (28). Prolonged NSAID use is also associated with chronic intestinal tract inflammation (29). Additionally, animal models of peptic ulceration have shown that NSAIDs suppress VEGF production at ulceration sites (30, 31). These combined mechanisms could lead to a synergistic increase in the risk of gastrointestinal perforation when VEGF inhibitors and NSAIDs are used together.

In contrast, a gastrointestinal haemorrhage signal was detected only in the JADER database. Similar to gastrointestinal perforation, an increased risk of gastrointestinal haemorrhage with the concomitant use of VEGF inhibitors and NSAIDs is plausible because NSAIDs can cause gastrointestinal mucosal damage, whereas VEGF inhibitors impair mucosal healing. The discrepancy in signals between the JADER and FAERS may stem from differences in racial characteristics and healthcare practices. Randomised controlled trials of anticoagulants have suggested that Asians are more susceptible to gastrointestinal bleeding than other populations (32). Additionally, the high frequency of gastrointestinal endoscopy in Japan (33) may facilitate the detection of minor bleeding events. However, in logistic regression analysis restricted to cancer treatment-related ADRs, this increased risk of gastrointestinal haemorrhage was not observed. Further research is required to clarify the significance of these inconsistent signals.

Although NSAIDs were analysed as a group in this study, it is well known that gastrointestinal toxicity varies depending on the specific type of NSAID (34). NSAIDs with high COX-2 selectivity, such as celecoxib, have been associated with lower gastrointestinal toxicity (35). However, the JADER results indicated a gastrointestinal perforation signal with the combination of celecoxib and VEGF inhibitors (Table IV). This suggests that celecoxib in combination with VEGF inhibitors may not be safe. Ibuprofen is also associated with a relatively low risk of gastrointestinal toxicity (36). While underreported in the JADER database, no gastrointestinal perforation signal was detected for ibuprofen in the FAERS database. These results suggest that ibuprofen may be relatively safe in combination with VEGF inhibitors. However, the gastrointestinal toxicity of NSAIDs is influenced by their dosage and duration of use. Spontaneous reporting databases typically do not capture detailed information on exposure duration or dosing (37), which is one of the limitations of this study. Our findings do not support the conclusion that specific NSAID are completely safe when used in combination with VEGF inhibitors.

This study has several limitations. Firstly, using a spontaneous reporting database, which relies on ADRs observed in healthcare settings, introduces the possibility of reporting bias that could affect the results of the disproportionality analysis (38). Errors in the database processing and analysis may have also distorted the findings. To mitigate these issues, we employed the Ω shrinkage measure (19), a conservative detection method,

and conducted a multiple sensitivity analysis. Furthermore, errors in database processing were addressed by utilising the normalised FAERS database and adhering to standardized procedures (17). Another limitation of the spontaneous reporting databases is the lack of information on the total number of drug users, making it impossible to determine the frequency of ADRs. Moreover, this study was limited to six NSAIDs commonly used in clinical practice, meaning that the effects of other NSAIDs (*e.g.*, indomethacin and mefenamic acid) were not reflected in the results. Additionally, missing data in the logistic regression analysis were handled under the assumption of missing at random. However, if this assumption does not hold, it could lead to potential bias. Finally, this study was specifically designed to detect increased risk due to drug interactions. Therefore, the observed effect of NSAID combinations on reducing hypertension and proteinuria in logistic regression analysis cannot be directly interpreted as causal. Nevertheless, the findings are noteworthy. No agent has been shown to reduce urinary protein levels in patients receiving VEGF inhibitors, and NSAIDs have been reported to lower urinary protein levels (39, 40). Further studies are required to test this hypothesis.

Our findings suggest that a combination of VEGF inhibitors and NSAIDs may synergistically increase the risk of gastrointestinal perforation in a real-world setting. In addition, common signals between JADER and FAERS may suggest that this increased risk occurs in various racial and healthcare settings. However, owing to the limitations of the data source, our results indicate only a *potential* risk associated with their concomitant use. Despite this, our findings have important clinical significance because gastrointestinal perforation is a serious and life-threatening ADR. This study provides healthcare professionals with an overview of the emerging pharmacodynamic interactions in patients with cancer treated with both VEGF inhibitors and NSAIDs. Healthcare professionals should be vigilant about potential interactions when VEGF inhibitors and NSAIDs are used together. The risk of gastrointestinal perforation may be mitigated by opting for alternative medications, such as AAP, where appropriate, and ensuring careful patient monitoring. Our study provides a foundation for future research to test this hypothesis. Additional clinical and experimental studies are required to quantitatively assess the risks associated with this combination.

Supplementary Material

Supporting material (checklist of reporting guidelines, patient background and details of analysis results) is available at: https://doi.org/10.5281/zenodo.14871048

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Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

This study was designed by KS and SN. KS performed the statistical analysis and wrote the manuscript, which was reviewed by SN; JA and KK supervised the study.

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