

Haemorrhage-related adverse events associated with nintedanib: a pharmacovigilance study based on the FAERS database

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Abstract

Objective

We aimed to analyse the characteristics and positive signals of haemorrhage-related adverse event (HrAE) associated with nintedanib in the Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Methods

The reports of adverse events (AE) associated with nintedanib as the primary suspect (PS) drug were extracted from the FAERS database from the fourth quarter of 2014 to the third quarter of 2024. HrAE were identified using the Standardized Medical Dictionary for Regulatory Activities Queries (SMQs). The characteristics of AE reports were described and multivariate analysis was used to analyse the factors related to HrAE. Disproportionality analysis was performed to detect AE signals, and a multiplicative and additive model was applied to evaluate the association between drug-drug interaction (DDI) and HrAE. Sensitivity analysis was conducted on serious AE that life-threatening and death, as well as AE reported by physician and pharmacist.

Results

A total of 3,018 patients experienced HrAE associated with nintedanib were included. There was a total of 3,929 AE reports. Compared with non-HrAE, patients age ≥ 65 years ($p \leq 0.001$, OR=1.675, 95% CI 1.376-2.040) and the lower daily dose ($p=0.014$, OR=1.001, 95% CI 1.000-1.002) were associated with HrAE. The gastrointestinal system was the most frequently affected organ and/or system. Co-administration of antiplatelet agents (ROR=6.02, 95% CI 4.76-7.62), anticoagulants (ROR=4.57, 95% CI 3.85-5.42) or prednisone (ROR=1.63, 95% CI 1.15-2.31) was more common among HrAE patients than among non-HrAE patients. Patients age ≥ 65 years ($p=0.018$, OR=1.623, 95% CI 1.088-2.420) and the time-to-onset (TTO) from drug administration to AE onset >90 days ($p \leq 0.001$, OR=2.266, 95% CI 1.744-2.944) were associated HrAE when AE reports with life-threatening or fatal were included; male ($p=0.004$, OR=1.004, 95% CI 1.004-1.007) is associated with HrAE when AE reports by physician or pharmacist were included.

Conclusion

Gastrointestinal bleeding is the most commonly reported HrAE associated with nintedanib. Patients over 65 years were more likely to experience HrAE, especially in life-threatening and death AE reports.

Key words

pulmonary fibrosis, nintedanib, adverse events, haemorrhage, drug-drug interaction

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Received on October 29, 2025; accepted in revised form on January 19, 2026.

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EXPERIMENTAL RHEUMATOLOGY 2026.

Introduction

Nintedanib is a small-molecule tyrosine kinase inhibitor (TKIs) that targets platelet derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and vascular endothelial growth factor receptor (VEGFR) (1). Nintedanib has been approved for the treatment of idiopathic pulmonary fibrosis (IPF); furthermore, it was the first drug approved for the treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD) and chronic fibrotic interstitial lung disease with a progressive phenotype (PF-ILD) (2). The U.S. Food and Drug Administration (FDA) approved the marketing of nintedanib in 2014, and it was launched in China in 2017. In 2018, nintedanib was listed in the first batch of the National Rare Disease Catalogue. Additionally, the guidelines recommend the off-label use of nintedanib for managing interstitial lung damage (ILD) associated with various systemic autoimmune rheumatic diseases (3). Haemorrhagic events are common class-related adverse events (AE) related to vascular endothelial growth factor receptor (VEGFR) inhibitors. The incidence of bleeding events in clinical trials was slightly higher in the treatment group than in the placebo group, however, patients receiving oral anticoagulants or high-dose antiplatelet therapy were excluded from these trials (2). To date, the haemorrhagic risk profile of nintedanib has not been fully elucidated in the literature, and data on the influence of concomitant medications on nintedanib-associated bleeding events are scarce. Additionally, existing evidence is mainly based on clinical trials, while real-world safety data are lacking. Although spontaneous reporting systems for adverse reactions have limitations, they provide valuable insights into the real-world safety profile of drugs. These systems can capture rare or delayed-onset adverse events and highlight patterns not readily observable in clinical trial settings. Therefore, we performed this study to analyse the characteristics and positive signals of haemorrhage-related adverse associated with nintedanib and to provide evidence-based suggestions for patients with pulmonary fibrosis receiving antifibrotic medication.

Material and methods

Study design and data source

This retrospective pharmacovigilance study was conducted based on the FAERS database. FAERS is a publicly accessible spontaneous database that relies on voluntary reports and quarterly updates. AE reports were coded using terms in the Medical Dictionary for Regulatory Activities (MedDRA 27.0) terminology, including hierarchy of 5 categories that include broad (*e.g.* system organ class SOC) and specific categories (*e.g.* preferred term PT). SMQ is part of MedDRA (Medical Dictionary for Regulatory Activities) for standardising queries. The AE reports from the fourth quarter of 2014 to the third quarter of 2024 were extracted to obtain information on AE reports related to nintedanib. The cases of nintedanib were screened by generic names and trade names (BIBF 1120, CYENDIV, OFEV, VARGATEF) as the PS in FAERS.

Data collection

The duplicate reports were removed based on “primary id”, and the demographic and AE information from each report were extracted. Demographic information includes the gender, age, reporting year and country, reporter’s occupation and daily dose (DD), the AE information includes SMQ, SOC, PT and the time-to-onset (TTO) from drug administration to AE onset. The DD used the formula “DD=single dose×frequency”, missing or unreasonable data were deleted (unreasonable data is defined as a daily dose of nintedanib exceeding the range of 75–400 mg). The TTO from drug administration to AE onset used the formula “TTO=Event onset date–Therapy start date”. AE were standardised and categorised using the MedDRA 27.0.

HrAE were identified using SMQs column including “liver-related coagulation and bleeding disturbances” (code 20000015), “haemorrhage terms (excl laboratory terms)” (code 20000039), “haemorrhage laboratory terms” (code 20000040), “haemorrhagic central nervous system vascular conditions” (code 20000064), “gastrointestinal perforation, ulcer, haemorrhage, obstruction non-specific findings/proce-

Funding: this study was supported by the Noncommunicable Chronic Diseases - National Science and Technology Major Project 2023ZD0509500; National High Level Hospital Clinical Research Funding under Grant 2022-PUMCH-C-069; Peking Union Medical College Hospital Talent Cultivation Program (Category C) UBJ11756.

Competing interests: none declared.

dures” (code 20000104), “gastrointestinal haemorrhage” (code 20000108), and “conditions associated with central nervous system haemorrhages and cerebrovascular accidents” (code 20000166).

Statistical analysis

Demographic and AE characteristics of HrAE and non-HrAE associated with nintedanib were described. AE reports with complete information (gender, age, DD and TTO) were included in binary logistic regression for the analysis of relevant factors. Various measures could be used for disproportionality analysis, including Reporting Odds Ratio (ROR), proportional reporting ratio (PRR), which has been widely used and reported in the existing literature to determine the AE, the calculation method is detailed in Table I. There is currently no gold standard methodology for detecting safety signals, so we defined that a positive adverse event signal was simultaneously satisfied with number of reports (a) >3, the lower limit of ROR 95%CI >1, and the lower limit of PRR 95%CI >1, according to the existing research (4). A multiplicative and additive model was applied to evaluate the association between DDI and HrAE (5). The additive model assumes an additive increase in drug-related risk, while the multiplicative model assumes a synergistic increase (6, 7). The positive signal of HrAE related to (additive model) >0 and (multiplicative model) >1 and the number of reports (a) >3. In the sensitivity analysis, the analysis was conducted by only including the AE reported by physician and pharmacist and serious AE that led to life-threatening or fatal.

For categorical data, the frequency (proportion) was used for description. For numerical data, the normality of the measurement data was tested with Kolmogorov-Smirnov method. The mean±standard deviation was used for description of normal distribution parameters, and the median (25th percentile - Qi, 75th percentile - Q3) was used for description of non-normal distribution parameters. Binary logistic regression was used for the multi-factor analysis. SAS v. 9.4 (SAS Institute, Cary, NC,

Table I. The calculation method for disproportionality analysis.

Method	Formula
ROR	$ROR = \frac{a/c}{b/d}$ $SE(\ln ROR) = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$ $95\%CI = e^{\ln(ROR) \pm 1.96SE}$
PRR	$ROR = \frac{a/(a+b)}{c/(c+d)}$ $SE(\ln ROR) = \sqrt{\frac{1}{a} + \frac{1}{a+b} + \frac{1}{c} + \frac{1}{c+d}}$ $95\%CI = e^{\ln(PRR) \pm 1.96SE}$

(a) represents the number of specific AE reports of the target drug; (b) represents the number of other AE reports of the target drug; (c) represents the number of specific AE reports of other drugs; (d) represents the number of other AE reports of other drugs.

ROR: reporting odds ratio; PRR: proportional reporting ratio; CI: confidence interval.

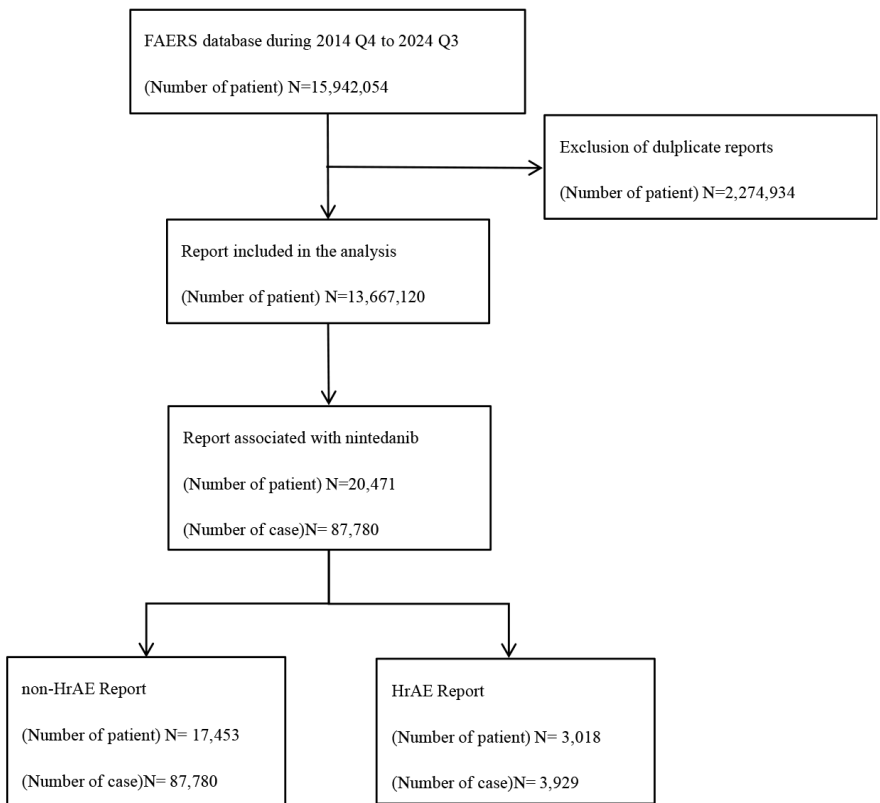


Fig. 1. Flowchart of data collection process.

USA), Microsoft EXCEL 2019, and the SPSS 22.0 were used to compile and process the data.

Results

Descriptive characteristics

The total number of patients with AE in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) from the fourth quarter of 2014 to the third quarter of 2024 was 15,942,054. After excluding duplicate reports, 13,667,120 patients (encompassing 39,583,574 AE reports) were included for analysis. A total of 20,471 patients with nintedanib related AE as the PS were included, resulting in 87,780 AE reports (the same patient

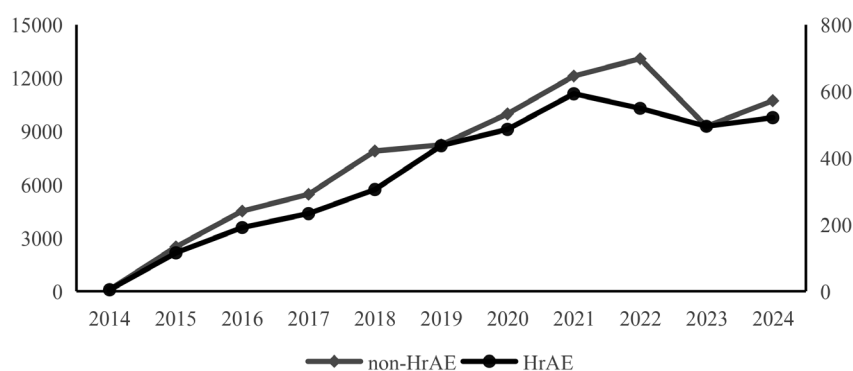
may have multiple reports of AE). A total of 3,018 patients reported HrAE, accounting for 14.7% of the patients. There were 3,929 reports of HrAE, accounting for 4.5% of all AE (Fig. 1). The number of AE reports associated with nintedanib increased from 2014 to 2022 and reached the highest point. In 2023-2024, the number decreased slightly. The trends of bleeding adverse events and non-bleeding adverse events were similar (Fig. 2). The proportion of male and age ≥65 years was higher in AE reports associated with nintedanib. USA, Canada, Japan, Germany and Spain were the top five countries of the number of reports. AE reported by patients had a higher

Table II. Demographic data of nintedanib HrAE.

	Total AE (n=87780)	HrAE (n=3929)	non-HrAE (n=83851)
Gender, n (%)			
Male	48184 (54.9)	2312 (58.8)	45872 (54.7)
Female	35482 (40.4)	1453 (37.0)	34029 (40.6)
Unknown	4114 (4.7)	164 (4.2)	3951 (4.7)
Age group, n (%)			
≥65 y	57315 (65.3)	2733 (69.6)	54582 (65.1)
<65 y	13297 (15.1)	478 (12.2)	12819 (15.3)
unknown	17168 (19.6)	718 (18.3)	16450 (19.6)
Report year, n (%)			
2014-2016	7397 (8.4)	310 (7.9)	7087 (8.5)
2017-2024	80383 (91.6)	3619 (92.1)	76764 (91.5)
Report country (top 5), n (%)			
United States (1)	56710 (64.6)	2735 (69.6)	53975 (64.4)
Canada (2)	9644 (11.0)	379 (9.6)	9265 (11.0)
Japan (3)	5573 (6.3)	161 (4.1)	5412 (6.5)
Germany (4)	2860 (3.3)	114 (2.9)	2746 (3.5)
Spain (5)	1804 (2.1)	61 (1.6)	1743 (2.1)
Reporter's occupation			
Medical doctor	17830 (20.3)	816 (20.8)	17014 (20.3)
Pharmacist	6495 (7.4)	222 (5.7)	6273 (7.5)
Patient	60094 (68.5)	2715 (69.1)	57379 (68.4)
Other	1492 (1.7)	75 (1.9)	1417 (1.7)
Unknown	1869 (2.1)	101 (2.6)	1768 (2.1)
DD, (mg)			
Median (Q1, Q3)	300 (200, 300)	300 (200, 300)	300 (200, 300)
TTO, (days)			
Median (Q1, Q3)	27 (3, 133)	37 (5, 189)	16 (2, 68)
TTO group, n (%)			
0-90 days	24213 (27.6)	1011 (25.7)	23202 (27.7)
>90 days	10898 (12.4)	577 (14.7)	10321 (12.3)
unknown	52669 (60.0)	2341 (59.6)	50328 (60.0)
Severity, n (%)			
Serious	70468 (80.3)	3440 (87.6)	67028 (79.9)
Non-serious	17312 (19.7)	489 (12.4)	16823 (20.1)
Outcome, n (%)			
Hospitalisation	45057 (51.3)	2522 (64.2)	42535 (50.7)
Other	43185 (49.2)	2030 (51.7)	41155 (49.1)
Death	13994 (15.9)	473 (12.0)	13521 (16.1)
Life-threatening	3056 (3.5)	175 (4.5)	2881 (3.4)
Disability	3048 (3.5)	119 (3.0)	2929 (3.5)
Congenital anomaly	77 (0.1)	2 (0.1)	75 (0.1)
Required intervention	44 (0.1)	1 (0)	43 (0.1)

The gender, age group, report year and country, reporter occupation, TTO group, severity and outcome were described with frequency (proportion, %). The DD and TTO did not follow a normal distribution, the median (Q1, Q3) is used for description.

AE: adverse event; HrAE: haemorrhage-related adverse event; DD: daily dose; TTO: time-to-onset.

**Fig. 2.** The time distribution of AE reports.

proportion than physician and pharmacist. The median DD for HrAE and non-HrAE were 300 mg; the median TTO from drug administration to AE onset was 37 days and 16 days respectively. The proportion of AE reports that $TTO \leq 90$ days and serious AE was higher (Table II). In the multivariate analysis, age ≥ 65 years ($p \leq 0.001$, $OR = 1.675$, 95%CI 1.376–2.040) and the lower DD ($p = 0.015$, $OR = 1.001$, 95%CI 1.000–1.002) were associated with HrAE, and there was a significant trend for $TTO > 90$ days $p = 0.082$, $OR = 1.520$, 95% CI 0.983–1.322) associated with HrAE.

Signals of preferred terms

Table III presents the nintedanib related HrAE positive signals (PTs), which were statistically significant were presented in Table III. 12 system organ classifications (SOCs) and 46 PTs were included. The number of PTs associated with gastrointestinal system diseases was the greatest, with 20 AE signals. The five most frequently reported AE were epistaxis, haematochezia, cerebrovascular accidents, gastrointestinal bleeding and rectal bleeding.

Table IV presents the SOC of positive signals for nintedanib-related HrAE. Gastrointestinal disorders were the most commonly reported AE ($a = 1324$, 41.1%). Respiratory, thoracic and mediastinal disorders ($a = 789$, 24.5%) and nervous system disorders ($a = 413$, 12.8%) were also common in other organ systems.

Signals of DDI

The consensus of nintedanib co-administration with other drugs reached 258 positive signals (PTs) of HrAE, involving 90 drugs. Table V shows the top 20 drugs with statistically significant positive signals. In the HrAE group, co-administration with antiplatelets (acetylsalicylic acid, clopidogrel, and ticagrelor; $ROR = 6.02$, 95% CI 4.76–7.62), anticoagulant drugs (apixaban, warfarin, rivaroxaban, edoxaban and dabigatran; $ROR = 4.57$, 95% CI 3.85–5.42), and prednisone ($ROR = 1.63$, 95% CI 1.15–2.31) were associated with a greater proportion of combinations with nintedanib.

Table III. Positive signals (PTs) of nintedanib HrAE.

SOCs	PTs	n. of reports (a)	ROR (95% CI)
Blood and lymphatic system disorders	Increased tendency to bruise	46	3.56 (2.66-4.76)
	Haemorrhagic diathesis	28	5.65 (3.89-8.21)
Gastrointestinal disorders	Haematochezia	362	4.51 (4.06-5.00)
	Gastrointestinal haemorrhage	254	2.12 (1.87-2.39)
	Rectal haemorrhage	244	4.25 (3.75-4.82)
	Diarrhoea haemorrhagic	88	6.88 (5.58-8.50)
	Gastric haemorrhage	78	5.18 (4.14-6.48)
	Haematemesis	67	2.09 (1.64-2.65)
	Haemorrhoidal haemorrhage	54	7.56 (5.78-9.90)
	Intestinal haemorrhage	48	6.53 (4.91-8.68)
	Large intestinal haemorrhage	23	7.35 (4.87-11.09)
	Gastric ulcer haemorrhage	19	2.72 (1.73-4.27)
	Lower gastrointestinal haemorrhage	19	1.64 (1.04-2.57)
	Diverticulum intestinal haemorrhagic	15	3.94 (2.37-6.55)
	Anal haemorrhage	12	3.18 (1.80-5.61)
	Duodenal ulcer haemorrhage	8	2.17 (1.08-4.35)
	Small intestinal haemorrhage	8	2.90 (1.45-5.81)
	Oesophageal haemorrhage	8	4.54 (2.26-9.11)
	Gastrointestinal ulcer haemorrhage	5	3.62 (1.50-8.74)
	Enterocolitis haemorrhagic	5	2.82 (1.17-6.79)
	Gastric antral vascular ectasia	4	5.88 (2.19-15.77)
	Large intestinal ulcer haemorrhage	3	7.14 (2.28-22.34)
General disorders and administration site conditions	Ulcer haemorrhage	52	6.22 (4.73-8.18)
Infections and infestations	Diverticulitis intestinal haemorrhagic	14	33.16 (19.27-57.06)
Injury, poisoning and procedural complications	Contusion	213	1.57 (1.37-1.80)
	Post procedural haemorrhage	30	2.08 (1.45-2.98)
	Bone contusion	8	5.29 (2.64-10.63)
Investigations	Blood urine present	78	2.91 (2.33-3.64)
Nervous system disorders	Cerebrovascular accident	301	1.51 (1.35-1.69)
	Cerebral haemorrhage	101	2.07 (1.70-2.52)
	Intracranial aneurysm	11	2.16 (1.19-3.90)
Renal and urinary disorders	Haematuria	71	1.51 (1.19-1.90)
	Urinary bladder haemorrhage	17	5.76 (3.57-9.30)
Reproductive system and breast disorders	Prostatic haemorrhage	3	6.43 (2.06-20.09)
Respiratory, thoracic and mediastinal disorders	Epistaxis	504	4.70 (4.31-5.14)
	Haemoptysis	219	5.79 (5.07-6.62)
	Pulmonary haemorrhage	42	4.38 (3.23-5.94)
	Pulmonary alveolar haemorrhage	19	2.53 (1.61-3.97)
	Respiratory tract haemorrhage	5	5.53 (2.29-13.35)
Skin and subcutaneous tissue disorders	Blood blister	9	2.02 (1.05-3.89)
Vascular disorders	Internal haemorrhage	101	4.46 (3.67-5.43)
	Vein rupture	7	2.26 (1.07-4.74)
	Vascular rupture	7	3.34 (1.59-7.03)
	Arterial rupture	3	3.13 (1.01-9.75)
	Aortic rupture	3	6.19 (1.98-19.35)

Sensitivity analysis

In the multivariate analysis, when only reports of life-threatening or fatal HrAE were included, age ≥ 65 years ($P=0.018$, OR=1.623, 95% CI 1.088–2.420) and TTO >90 days ($p<0.001$, OR=2.266, 95% CI 1.744–2.944) were associated with HrAE. When only reports by physician or pharmacist were included, male ($p=0.004$, OR=1.004,

95% CI 1.004–1.007) was associated with HrAE, and there was a significant trend for age ≥ 65 years ($p=0.007$, OR=1.520, 95% CI 0.967–2.390) associated with HrAE.

In the descriptive analysis, among the AE reports by physician or pharmacist, 22 out of 46 PT signals remained positive; among the AE reports with complete information (gender, age,

DD and TTO), 32 out of 46 positive signals still existed; and among the AE reports of life-threatening or deaths outcome, 32 out of 46 signals still existed (Fig. 3). We observed that in life-threatening or fatal HrAE reports, the positive signals of respiratory, thoracic and mediastinal disorders had a very high signal intensity, including haemoptysis (ROR=213.54, 95% CI=160.23–284.59), pulmonary haemorrhage (ROR=185.47, 95% CI=104.65–328.72) and pulmonary alveolar haemorrhage (ROR=176.63, 95% CI=91.37–341.44).

Discussion

VEGFR tyrosine kinase inhibitors are associated with an increased incidence of full-grade bleeding events, which has been reported in previous studies (8). The probable mechanisms include a reduction in endothelial cell proliferation and survival and the modulation of factors involved in platelet aggregation (9). Nintedanib is also a VEGFR inhibitor, several studies have reported that nintedanib is associated with an increased risk of bleeding (10). Lung cancer is a common comorbidity among ILD patients (11), other VEGFR inhibitors, such as anlotinib or bevacizumab, might be used in combination with nintedanib, thereby increasing the risk of bleeding.

The incidence of bleeding associated with nintedanib in the INPULSIS trial was similar to that associated with the placebo; however, patients receiving anticoagulants and high-dose antiplatelet drugs were not included during enrollment. However, in real-world studies, the incidence of bleeding was 36.8 cases per 1,000 patient-years on the basis of the global pharmacovigilance database (12) and was 24.2 cases per 1,000 patient-years in a study of post-marketing data (13). In the INPULSIS trial, severe bleeding accounted for only 1.3% of all adverse events, whereas in two real-world studies, serious events accounted for 19% and 19.7% of the bleeding events (12, 13). The constituent ratio of patients with HrAE was 14.5% in this study; 85.6% of HrAE were categorised as serious adverse events, while non-HrAE accounted for 66.9% of AE. The

Table IV. Positive signals (SOCs) of nintedanib HrAE.

SOCs	n. of reports (a)	ROR (95%CI)
Gastrointestinal disorders	1324	3.57 (3.38-3.77)
Respiratory, thoracic and mediastinal disorders	789	4.86 (4.53-5.21)
Nervous system disorders	413	1.63 (1.48-1.80)
Injury, poisoning and procedural complications	251	1.66 (1.46-1.88)
Vascular disorders	195	4.14 (3.60-4.77)
Renal and urinary disorders	88	1.76 (1.42-2.16)
Investigations	78	2.91 (2.33-3.64)
General disorders and administration site conditions	52	6.22 (4.73-8.18)
Infections and infestations	14	33.16 (19.27-57.06)
Skin and subcutaneous tissue disorders	9	2.02 (1.05-3.89)
Reproductive system and breast disorders	3	6.43 (2.06-20.09)

Table V. Positive signals of nintedanib drug interactions HrAE.

Drug	n. of positive signals	n. of cases in HrAE	n. of cases in non-HrAE	ROR (95%CI)
Amlodipine	16	25	537	1.52 (1.05-2.20)
Acetylsalicylic acid	15	27	243	5.87 (4.31-7.99)
Prednisone	15	34	566	1.63 (1.15-2.31)
Apixaban	11	27	748	3.91 (3.14-4.87)
Warfarin	10	31	313	3.80 (2.75-5.26)
Loperamide	10	14	1221	1.34 (1.03-1.75)
Pirfenidone	9	14	1220	0.47 (0.31-0.72)
Docetaxel	9	62	4041	0.43 (0.34-0.54)
Clopidogrel	9	10	195	5.12 (3.57-5.32)
Treprostinil	7	16	2854	0.41 (0.31-0.55)
Metformin	6	6	255	0.81 (0.40-1.65)
Prednisolone	6	7	167	1.25 (0.61-2.54)
Rivaroxaban	5	5	279	3.76 (2.67-5.30)
Ticagrelor	5	10	11	11.87 (4.11-34.24)
Esomeprazole	4	4	53	2.95 (1.27-6.89)
Omeprazole	4	7	201	1.03 (0.51-2.10)
Tadalafil	4	5	57	2.29 (0.91-5.72)
Alendronic acid	4	7	57	0.76 (0.28-2.05)
Edoxaban	4	6	137	26.08 (6.51-104.49)
Ibuprofen	3	3	4	2.89 (0.88-9.55)
Dabigatran	3	7	27	17.39 (4.90-61.74)

differences between clinical research and real-world research on nintedanib should be considered.

In real-world studies, the median TTO of bleeding events was 68 days (12), and 53% of the events occurred within 3 months of nintedanib administration (13). We found that TTO >90 days was associated with HrAE when only reports of life-threatening or fatal HrAE were included. Patients older than 65 years was associated with HrAE, as well in life-threatening or fatal HrAE reports. While age was not reported to be a high-risk factor for bleeding in patients treated with VEGFR inhibitors, it has been reported in patients treated with oral anticoagulants (14). The DD of nintedanib in HrAE was lower, suggesting that haemorrhage events may not be dose-dependent. For elder, and long-term use nintedanib, greater at-

tention should be required to the severe bleeding events. The proportion of death events in HrAE is lower, this might be attributed to a large amount of patient reports in the HrAE.

Gastrointestinal disorders were the most common AE (41.1%), and it was also associated with the highest number of positive signals. HrAE have also been reported in other organ systems, such as the respiratory system (24.5%), which was similar with the findings of real-world studies (31.7%) (12). When a sensitivity analysis was conducted on fatal or life-threatening HrAE, the positive signals of respiratory, thoracic and mediastinal disorders had a very high signal intensity. Previous studies have shown that fatal bleeding events caused by nintedanib include intestinal haemorrhage, cerebral haemorrhage, haemoptysis, and alveolar bleeding

(13, 15), and acute aortic syndrome combined with intramural haematoma has also been reported (16). Clinical decisions should be made based on the site and severity of the event, other bleeding risk and co-administration medications. Although the slight bleeding, such as haematuria and bruise, was identified as a positive signal, it is unlikely to affect the decision-making regarding the clinical use of drugs.

We found a higher proportion in HrAE patients treated with a combination of nintedanib and antiplatelets, oral anticoagulants or glucocorticoids. Existing studies have not reported that the combination of anticoagulants or antiplatelets with nintedanib increases the risk of bleeding (17), possibly because of the small number of patients included. A study based on the Japanese JADER database revealed that the combination of glucocorticoids might be associated with gastrointestinal bleeding (18), nintedanib and glucocorticoids are often combination used for patients with connective tissue disease-ILD, attention should be paid to the haemorrhagic risk. An unexpected discovery was that the combination of amlodipine and nintedanib had the greatest number of AE signals, which has not been reported in previous studies. Amlodipine has a mild inhibitory effect on platelet function and CYP3A4 (19), which may account for the increased risk of bleeding. We also found that in the non-HrAE group, the proportion of combination with pirfenidone, docetaxel, or treprostinil was lower. Treprostinil and pirfenidone, as a concomitant and an alternative medication to nintedanib, rarely caused haemorrhagic adverse reactions. However, there have been reports of bleeding events associated with docetaxel, the bleeding risk also requires attention combination with nintedanib.

Limitations

The spontaneous reports in the FAERS database have data gaps, the results derived from reports with incomplete information do not have good extrapolation capabilities. Additionally, the proportion of patient-reported was the high in nintedanib associated AE, which is problematic for haemorrhagic events

SOC	PT	ROR		
		Report by physician or pharmacist	Report with complete information	Report of life-threatening or fatal
Blood and lymphatic system disorders	Increased tendency to bruise		2.75	
	Haemorrhagic diathesis		5.63	
Gastrointestinal disorders	Haematochezia	2.65	4.10	75.10
	Gastrointestinal haemorrhage	2.95	2.11	65.83
	Rectal haemorrhage	4.34	4.68	57.66
	Diarrhoea haemorrhagic	6.49	6.34	92.09
	Gastric haemorrhage		5.05	98.08
	Haematemesis	2.92	2.53	41.33
	Haemorrhoidal haemorrhage	2.53	8.16	123.29
	Intestinal haemorrhage	5.40	7.23	139.90
	Large intestinal haemorrhage	5.76	8.90	
	Gastric ulcer haemorrhage		4.35	
	Lower gastrointestinal haemorrhage	4.35	1.96	88.64
	Diverticulum intestinal haemorrhagic	8.53	3.99	
	Anal haemorrhage		5.37	
	Duodenal ulcer haemorrhage	5.88		
	Small intestinal haemorrhage	5.23		
General disorders and administration site conditions	Ulcer haemorrhage		6.06	140.87
Infections and infestations	Diverticulitis intestinal haemorrhagic		42.00	
Injury, poisoning and procedural complications	Contusion		1.51	22.13
	Post procedural haemorrhage	2.50	2.63	50.76
Investigations	Blood urine present		2.46	32.86
Nervous system disorders	Cerebrovascular accident	1.79	1.26	55.68
	Cerebral haemorrhage	2.59	1.77	74.38
	Intracranial aneurysm	2.83		
Renal and urinary disorders	Haematuria	2.22	1.72	47.35
	Urinary bladder haemorrhage		8.58	
Respiratory, thoracic and mediastinal disorders	Epistaxis	3.19	4.94	83.23
	Haemoptysis	6.40	6.63	213.54
	Pulmonary haemorrhage	4.52	5.28	185.47
	Pulmonary alveolar haemorrhage	8.17	3.37	176.63
	Respiratory tract haemorrhage		11.20	
Skin and subcutaneous tissue disorders	Blood blister		2.84	
Vascular disorders	Internal haemorrhage	1.91	4.03	78.56

Fig. 3. Sensitivity analysis of HrAE associated with nintedanib.

requiring medical diagnosis, may over-report subjective symptoms while ignoring objective events. We conducted a sensitivity analysis on reports with complete information and on reports by physician and pharmacist, and we also selected life-threatening and fa-

tal reports for sensitivity analysis. The analysis based on the FAERS database also has the following limitations, we were unable to obtain the incidence rate of adverse reactions of nintedanib and we could not distinguish between true drug interactions and bleeding risks.

Conclusion

Gastrointestinal bleeding was the most commonly HrAE associated with nintedanib. Patients older than 65 years were more likely to experience HrAE, especially in life-threatening and fatal AE reports.

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