


ORIGINAL ARTICLE

Comparison of the incidence of bleeding between baloxavir marboxil and other anti-influenza drugs among outpatients with influenza virus infection: A retrospective cohort study using an employment-based health insurance claims database in Japan

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Abstract

Purpose: Alerts for bleeding events are included in the Japanese package inserts of some anti-influenza drugs, including baloxavir marboxil and oseltamivir. However, there are few reports on the incidence of bleeding events during treatment with anti-influenza drugs. This large-scale quantitative assessment compared the incidence of bleeding events in influenza patients treated with baloxavir and other anti-influenza drugs and in untreated patients.

Methods: This retrospective cohort study used a large-scale Japanese employment-based health insurance claims database provided by JMDC Inc. and included outpatients diagnosed with influenza between October 1, 2018 and April 11, 2019. Bleeding events were identified by International Classification of Diseases 10th revision codes. Incidences were compared between patients treated with baloxavir or neuraminidase inhibitors and untreated patients. Odds ratios were calculated after exact matching to adjust for potential confounders.

Results: Among 529 201 influenza episodes, 30 964 were untreated and 498 237 were treated with anti-influenza drugs: baloxavir, 207 630; oseltamivir, 143 722; zanamivir, 28 208; peramivir, 5304; laninamivir, 113 373. Crude incidence proportions for total bleeding up to 20 days after influenza diagnosis were similar among treated groups, with a slightly higher value for peramivir (0.21% vs. 0.19% for baloxavir, oseltamivir, zanamivir, and laninamivir), and 0.30% in untreated patients. After exact matching, the incidence of bleeding for baloxavir was similar to that for other anti-influenza treatments (odds ratios for baloxavir were 0.90–0.99 compared to other therapies).

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Conclusions: Based on real-world observation using a large-scale claims database, a similar incidence of bleeding events was observed in recipients of the different anti-influenza drugs.

KEYWORDS

baloxavir marboxil, bleeding, influenza, neuraminidase inhibitors

Key Points

- Bleeding events are included in the Japanese package inserts of some anti-influenza drugs.
- This retrospective cohort study compared the incidences of bleeding events in patients treated with baloxavir or neuraminidase inhibitors and untreated patients.
- The incidence of bleeding events with baloxavir was not higher than that for patients who received neuraminidase inhibitors and patients who did not receive any anti-influenza drugs.

Plain Language Summary

Based on real-world observation using a large-scale claim database, a similar incidence of bleeding was observed across recipients of different anti-influenza drugs. Bleeding events were also observed at a similar frequency in patients who did not receive anti-influenza drugs. These results didn't suggest that anti-influenza drugs, including baloxavir and neuraminidase inhibitors, are associated with an increased incidence of bleeding in influenza patients.

1 | INTRODUCTION

Neuraminidase inhibitors such as laninamivir, oseltamivir, peramivir, and zanamivir have been available for the treatment of influenza over the last two decades, and are widely prescribed to patients with influenza in Japan.^{1,2} One of the most recent drugs to become available for the treatment of influenza is the cap-dependent endonuclease inhibitor baloxavir marboxil (hereafter referred to as baloxavir), which was approved in Japan in February 2018.

There have been occasional reports of an increased incidence of bleeding events after influenza infection.³⁻⁷ Furthermore, there have been several reports of bleeding events in patients taking anti-influenza drugs.⁸⁻¹⁴ Various bleeding events, such as hemorrhagic colitis, nasal bleeding, subcutaneous bleeding, irregular uterine bleeding, bloody stool, melena, hematemesis, and hematuria are listed as adverse reactions in the Japanese package inserts for baloxavir and neuraminidase inhibitors, except laninamivir.¹⁵⁻¹⁸ In particular, the package inserts for baloxavir and oseltamivir contain alerts for general bleeding risk based on multiple spontaneous reports.^{15,16} The US prescribing information for baloxavir and oseltamivir also mention bleeding events.^{19,20} However, as far as we know, quantitative assessments of the risk of bleeding events after treatment with anti-influenza drugs have not been reported.

In the current study, the incidence of bleeding events was compared in influenza outpatients treated with baloxavir and other anti-influenza drugs, as well as in untreated patients, using a large-scale employment-based claims database.

2 | METHODS

2.1 | Study design

A retrospective cohort study was conducted using data from an employment-based health insurance claims database in Japan constructed by JMDC (Tokyo, Japan).²¹⁻²⁴ The database can track individual medical encounters and healthcare resource consumption covered by health insurance across multiple medical institutions on an individual basis as long as people are enrolled in a single health insurance coverage. Members withdraw from health insurance associations at the time of their retirement, which usually occurs at 65 years of age in Japan where lifetime employment has been the norm, and change insurers at the time of changing jobs.

The information in the database is irreversibly anonymized when the claims records are retrieved from the payers, and individual patients are not identified. The study used data from the period April 1, 2018 to April 30, 2019.

2.2 | Ethical and regulatory considerations

The study was in compliance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects and the Guidance for the Ethical Guidelines, and was approved by the Keio University Faculty of Pharmacy Ethics Committee for Research Involving Humans (No. 200713-1). Informed consent was waived because of the use of anonymous data. The study was registered in the University Hospital

Medical Information Network (UMIN) Clinical Trial Registration System (UMIN000041568).

2.3 | Study patients and episodes

The study included outpatients diagnosed with influenza episodes according to the International Classification of Diseases 10th revision (ICD-10) procedure and diagnostic codes (2013) codes J09, J10, and J11 between October 1, 2018 and April 11, 2019.²¹

The day when any of the above ICD-10 codes for influenza and any medical care, including medical consultation, procedures or prescriptions were recorded for a patient was designated as an index date for a single influenza episode. An index date had to be on or after October 1, 2018. This date was selected because the 2018/2019 season was the first full influenza season after the launch of baloxavir in Japan on March 14, 2018. To be eligible for inclusion, the patient had to have an index date, and at least 6 months' active history in the database prior to the index date, and at least 20 days of health insurance data available after the index date. Multiple records of influenza diagnosis in the same patient were counted as separate episodes unless the intervals between the recorded ICD-10 codes for influenza were less than 20 days. To test the robustness of the definition based on ICD-10 codes, different definitions for an influenza episode were employed, as follows: (a) diagnosis based on ICD-10 codes J09, J10, and J11 plus influenza diagnostic test (Standardized medical treatment ID code: 160042210, 160042310, 160169450, 160198010) performed on the index date; (b) diagnosis based on ICD-10 codes J09 and J10 plus influenza diagnostic test performed on the index date.²¹

Influenza episodes were excluded if the patient was hospitalized or first diagnosed with a bleeding event on an index date, or received more than one anti-influenza drug.

2.4 | Definition of exposure and diseases

The exposure group was defined as patients who received baloxavir on an index date. The comparator groups were defined as patients who received oseltamivir, zanamivir, peramivir, or laninamivir on an index date, or who received no treatment.

The study outcomes were bleeding events that occurred between 2 and 20 days after the index date, including: total bleeding events, intracranial bleeding events, gastrointestinal bleeding events, and other bleeding events. The details of ICD-10 codes for all bleeding episodes, including major events such as intracranial, upper and lower gastrointestinal, and others are provided in Tables S1 and S2.^{25,26} The following factors that may affect influenza progression and bleeding risk were empirically selected as potential adjustment covariates: age groups at the index date of 0–4, 5–17, 18–49, 50–64, or ≥65 years; sex; type of influenza virus, including A, B, A and B, or uncertain; treatments, including steroids, asthma medication, diabetes mellitus medication, anticoagulants, cancer therapy,

immunosuppressants, non-steroidal anti-inflammatory drugs (NSAIDs); previous diseases/comorbidities, including influenza, bleeding, chronic obstructive pulmonary disease, coronary heart disease, stroke, psychiatric/behavioral/ neurodevelopmental disorders, neurological diseases, anemia, immune deficiency, liver diseases, malignant neoplasms, hemophilia, leukemia, thrombocytopenia, gastric ulcer, ulcerative colitis, and hypertension; dialysis; respiratory co-infection; and Charlson comorbidity index.^{27–32} The ICD-10 codes for definitions of these variables are provided in Tables S3.1–S3.6. The cumulative effects of multiple influenza episodes on bleeding was not considered for adjustment.

2.5 | Statistical analysis

Background characteristics were summarized for each treatment group and for the total population, using numerical values (mean ± SD or median [range]), and categorical values (number [%]).

Primary risk indices of bleeding outcomes were incidence proportions and odds ratios of bleeding events for baloxavir compared to the other groups after exact matching to adjust for imbalances between the groups.³³ Risk of bleeding events was considered to be independent of the number of preceding influenza episodes. A control influenza episode was matched with a case episode at a 1:1 ratio without replacement, using all background information shown in Table 1 equally. For discrete variables such as Charlson comorbidity index, matching was done using the same value without allowance. In 1:1 sampling, when there were multiple candidates for control episodes, the matched control episode was randomly sampled. The 50th percentile for incidence proportions and 50th percentile (2.5th, 97.5th percentile) for odds ratio were calculated after 1000 exact matching sets were created in a simulation. The base value used for random number generation was $20\ 201\ 101 + i$ (where i = number of simulations).

In a sensitivity analysis we examined the effect of the different definitions for an influenza episode on the incidences and risk estimates of bleeding events. In addition, exclusion of the following influenza episodes was tested: (a) with bleeding events before the index date and within the same month as the index date; (b) with bleeding events within 14 days before the index date, with a claim during the same month or month prior to the index date; (c) with bleeding events within 28 days before the index date, with a claim during the same month or month prior to the index date; (d) with bleeding events other than the major bleeding events.

The following subgroup analyses were performed: (a) influenza episodes with known virus type; (b) influenza episodes in patients without a past history of bleeding; (c) influenza episodes in patients who did not receive anti-influenza prophylaxis for infection prevention (i.e., excluded episodes with OTV prescriptions for ≥7 days). An ad hoc subgroup analysis was also performed for influenza episodes limited only to the first influenza episodes. This eliminates the potential for cumulative effects associated with previous influenza episodes.

TABLE 1 Baseline characteristics by anti-influenza treatment group for the overall study population before exact matching

	BXM N = 207 630	OTV N = 143 722	ZNV N = 28 208	PRV N = 5304	LNV N = 113 373	Untreated N = 30 964	Total N = 529 201
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age							
0–4 years	3610 (1.74)	42 176 (29.35)	114 (0.40)	210 (3.96)	374 (0.33)	8023 (25.91)	54 507 (10.30)
5–17 years	67 307 (32.42)	43 166 (30.03)	18 227 (64.62)	1009 (19.02)	42 827 (37.78)	8099 (26.16)	180 635 (34.13)
18–49 years	101 839 (49.05)	42 386 (29.49)	8088 (28.67)	2802 (52.83)	53 825 (47.48)	11 464 (37.02)	220 404 (41.65)
50–64 years	32 209 (15.51)	14 635 (10.18)	1671 (5.92)	1151 (21.70)	15 168 (13.38)	3105 (10.03)	67 939 (12.84)
≥65 years	2665 (1.28)	1359 (0.95)	108 (0.38)	132 (2.49)	1179 (1.04)	273 (0.88)	5716 (1.08)
Sex							
Male	115 834 (55.79)	77 620 (54.01)	14 320 (50.77)	2985 (56.28)	61 238 (54.01)	17 083 (55.17)	289 080 (54.63)
Influenza virus type							
A	149 792 (72.14)	96 633 (67.24)	18 052 (64.00)	3875 (73.06)	78 929 (69.62)	11 541 (37.27)	358 822 (67.80)
B	1420 (0.68)	1035 (0.72)	270 (0.96)	71 (1.34)	983 (0.87)	218 (0.70)	3997 (0.76)
A and B	54 (0.03)	27 (0.02)	4 (0.01)	2 (0.04)	23 (0.02)	12 (0.04)	122 (0.02)
Unknown	56 364 (27.15)	46 027 (32.03)	9882 (35.03)	1356 (25.57)	33 438 (29.49)	19 193 (61.98)	166 260 (31.42)
Medications							
Corticosteroid	1006 (0.48)	592 (0.41)	96 (0.34)	57 (1.07)	582 (0.51)	116 (0.37)	2449 (0.46)
Anticoagulant	2517 (1.21)	1789 (1.24)	192 (0.68)	114 (2.15)	1390 (1.23)	373 (1.20)	6375 (1.20)
Anticancer drug	561 (0.27)	298 (0.21)	47 (0.17)	29 (0.55)	343 (0.30)	80 (0.26)	1358 (0.26)
Immunosuppressant	474 (0.23)	272 (0.19)	68 (0.24)	28 (0.53)	338 (0.30)	66 (0.21)	1246 (0.24)
NSAIDs (including aspirin)	12 947 (6.24)	4909 (3.42)	1119 (3.97)	664 (12.52)	5722 (5.05)	3034 (9.80)	28 395 (5.37)
Same day ^a	2278 (1.10)	1245 (0.87)	170 (0.60)	88 (1.66)	1218 (1.07)	252 (0.81)	5251 (0.99)
Disease history							
Previous influenza infection	1536 (0.74)	1841 (1.28)	394 (1.40)	62 (1.17)	1040 (0.92)	1246 (4.02)	6119 (1.16)
History of bleeding	5383 (2.59)	3592 (2.50)	727 (2.58)	192 (3.62)	3151 (2.78)	780 (2.52)	13 825 (2.61)
Asthma	36 599 (17.63)	50 701 (35.28)	6590 (23.36)	1074 (20.25)	19 117 (16.86)	8522 (27.52)	122 603 (23.17)
Diabetes	3403 (1.64)	1706 (1.19)	172 (0.61)	136 (2.56)	1746 (1.54)	353 (1.14)	7516 (1.42)
COPD	1896 (0.91)	1419 (0.99)	173 (0.61)	99 (1.87)	1040 (0.92)	291 (0.94)	4918 (0.93)
Cardiovascular disease	2537 (1.22)	1833 (1.28)	231 (0.82)	100 (1.89)	1366 (1.20)	446 (1.44)	6513 (1.23)
Cerebrovascular disease	1914 (0.92)	981 (0.68)	122 (0.43)	79 (1.49)	976 (0.86)	263 (0.85)	4335 (0.82)
Psychiatric disease including dementia	13 295 (6.40)	8919 (6.21)	1598 (5.67)	446 (8.41)	6875 (6.06)	2060 (6.65)	33 193 (6.27)
Neurological disease	16 555 (7.97)	8564 (5.96)	1554 (5.51)	668 (12.59)	8787 (7.75)	2238 (7.23)	38 366 (7.25)
Anemia	5012 (2.41)	3482 (2.42)	656 (2.33)	179 (3.37)	3106 (2.74)	943 (3.05)	13 378 (2.53)
Immunodeficiency	294 (0.14)	283 (0.20)	62 (0.22)	19 (0.36)	204 (0.18)	55 (0.18)	917 (0.17)
Liver disease	6858 (3.30)	3600 (2.50)	492 (1.74)	288 (5.43)	3747 (3.31)	910 (2.94)	15 895 (3.00)
Malignant tumor	2515 (1.21)	1235 (0.86)	184 (0.65)	104 (1.96)	1344 (1.19)	303 (0.98)	5685 (1.07)

TABLE 1 (Continued)

	BXM N = 207 630 n (%)	OTV N = 143 722 n (%)	ZNV N = 28 208 n (%)	PRV N = 5304 n (%)	LNV N = 113 373 n (%)	Untreated N = 30 964 n (%)	Total N = 529 201 n (%)
Hemophilia	21 (0.01)	18 (0.01)	2 (0.01)	0	16 (0.01)	3 (0.01)	60 (0.01)
Leukemia	109 (0.05)	83 (0.06)	21 (0.07)	3 (0.06)	58 (0.05)	14 (0.05)	288 (0.05)
Thrombocytopenia	131 (0.06)	120 (0.08)	19 (0.07)	3 (0.06)	79 (0.07)	20 (0.06)	372 (0.07)
Gastric ulcer	4737 (2.28)	2320 (1.61)	397 (1.41)	191 (3.60)	2618 (2.31)	668 (2.16)	10 931 (2.07)
Ulcerative colitis	470 (0.23)	206 (0.14)	40 (0.14)	24 (0.45)	319 (0.28)	54 (0.17)	1113 (0.21)
Hypertension	12 693 (6.11)	6273 (4.36)	734 (2.60)	499 (9.41)	6514 (5.75)	1356 (4.38)	28 069 (5.30)
Dialysis	28 (0.01)	177 (0.12)	5 (0.02)	1 (0.02)	29 (0.03)	24 (0.08)	264 (0.05)
Respiratory co-infection	134 134 (64.60)	89 445 (62.23)	18 005 (63.83)	3925 (74.00)	72 344 (63.81)	22 240 (71.83)	340 093 (64.27)
Charlson comorbidity index	Mean (SD)	0.3 (0.7)	0.4 (0.7)	0.4 (0.9)	0.3 (0.7)	0.4 (0.7)	0.3 (0.7)
	Median (min, max)	0.0 (0, 12)	0.0 (0, 15)	0.0 (0, 11)	0.0 (0, 12)	0.0 (0, 12)	0.0 (0, 15)

Abbreviations: BXM, baloxavir; COPD, chronic obstructive pulmonary disease; LNV, laninamivir; N, number of influenza episodes; NSAIDs, non-steroidal anti-inflammatory drugs; OTV, oseltamivir; PRV, peramivir; ZNV, zanamivir.

^aReceived on same day as anti-influenza medication.

Statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC, United States).

3 | RESULTS

Among 567 953 patients with influenza in the JMDC database between October 1, 2018 and April 11, 2019, a total of 529 719 influenza episodes met the criteria for inclusion (Figure 1). Among 529 201 influenza episodes after October 1, 2018 in the analysis set, 498 237 (94.1%) involved prescription of an anti-influenza drug and 30 964 (5.9%) did not. Baloxavir was the most common anti-influenza drug used ($n = 207 630$; 39.2%), followed by oseltamivir ($n = 143 722$; 27.2%) and laninamivir ($n = 113 373$; 21.4%); zanamivir and peramivir were dispensed less often ($n = 28 208$; 5.3% and $n = 5304$; 1.0%, respectively) (Figure 1 and Table 1).

The most prevalent influenza virus across all study groups was type A (67.8% overall, before exact matching) (Table 1). Few patients were aged ≥ 65 years. Compared to other treated groups, the oseltamivir group had a greater proportion of patients aged 0–4 years (29.4% vs. 0.3%–4.0%, respectively), and the peramivir group had a greater proportion of patients aged ≥ 18 years (77.0% vs. 35.0%–65.8%). The untreated group also had a high proportion of patients aged 0–4 years (25.9%). The proportion of patients who received NSAIDs on the same day as anti-influenza drugs was highest in the peramivir group (12.5%), followed by baloxavir (6.2%), and laninamivir (5.1%), compared with $<4\%$ of the oseltamivir and zanamivir groups.

The overall incidence of bleeding events was similar among the treatment groups (Table 2), although the incidence proportion was slightly higher in recipients of peramivir and in untreated patients (0.21% and 0.30%, respectively) than in the other groups (all 0.19%).

Baseline characteristics after exact matching are summarized in Table S4. The exact-matched numbers of influenza episodes for baloxavir were 107 010 compared with laninamivir, followed by oseltamivir ($n = 98 018$), zanamivir ($n = 27 257$), peramivir ($n = 4808$), and the untreated group ($n = 24 249$) (Tables 3 and S4). The overall incidence proportion of bleeding events (50th percentile) was lower with baloxavir compared with the untreated group (0.16% vs. 0.30%), with a 50th percentile odds ratio of 0.53 (2.5th–97.5th percentile 0.39–0.69) (Table 3). There was no difference in odds ratios between baloxavir and the other anti-influenza drugs for any bleeding events, except for gastrointestinal hemorrhage versus laninamivir; the 50th percentile odds ratio was 0.79 (2.5th–97.5th percentile 0.59–0.97) in this simulation (Table 3). The ad hoc analysis for major bleeding based on the previous study found that major bleeding events were similar to those for all bleeding events (Table S5).

The results of sensitivity analyses examining the effects of different definitions of influenza episodes and the effect of different exclusion periods for prior bleeding events were consistent with the results of the main analysis (data not shown). Similar results were also obtained in subgroup analyses involving only patients with a known virus type, patients with no past history of bleeding, patients who did

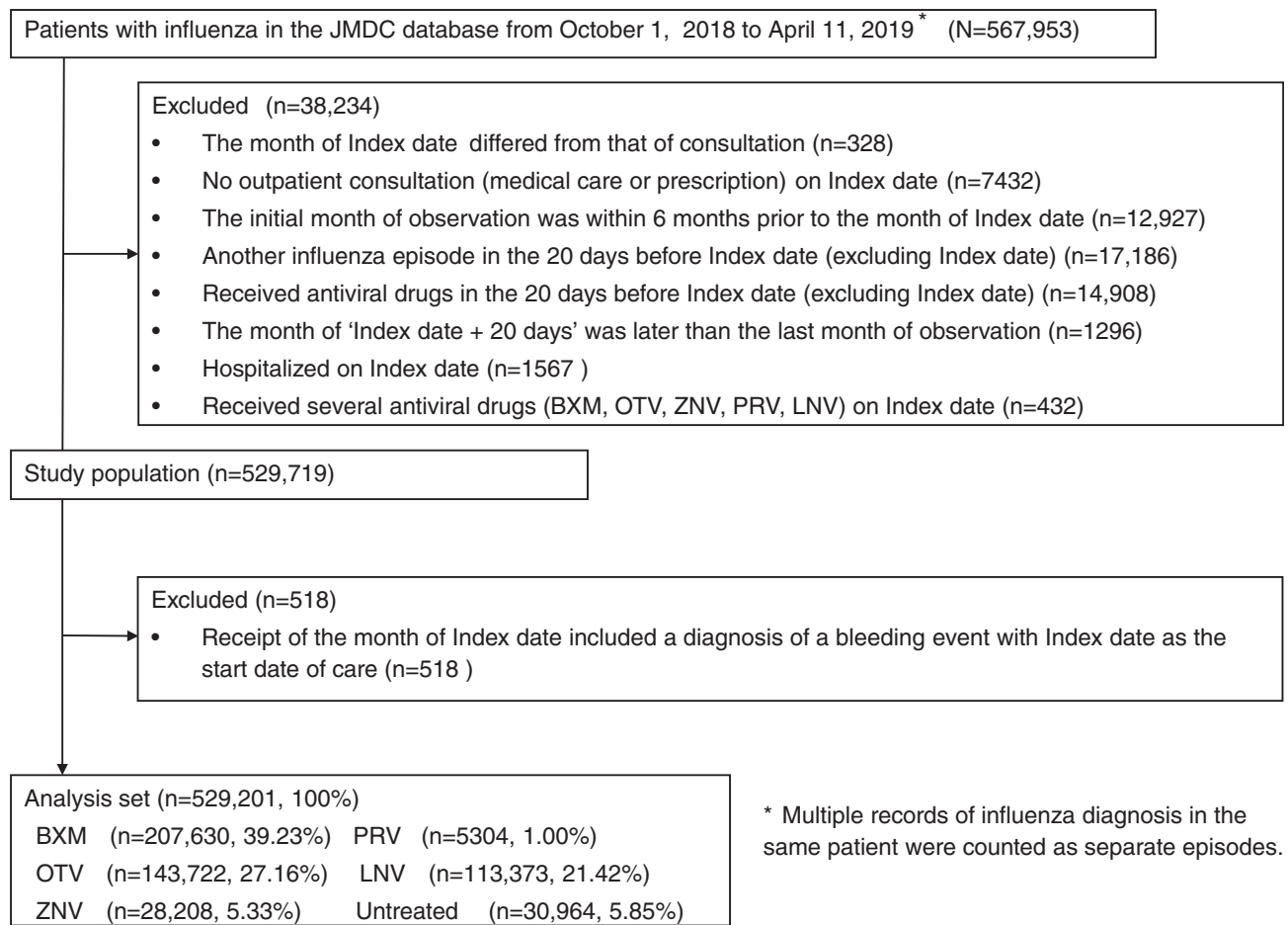


FIGURE 1 Patient flow chart. BXM, baloxavir marboxil; LNV, laninamivir; OTV, oseltamivir; PRV, peramivir; ZNV, zanamivir

TABLE 2 Incidence proportions of bleeding events and odds ratios, by anti-influenza treatment group before exact matching

	BXM N = 207 630	OTV N = 143 722	ZNV N = 28 208	PRV N = 5304	LNV N = 113 373	Untreated N = 30 964	Total N = 529 201
Bleeding (overall), n (%)	397 (0.19)	268 (0.19)	55 (0.19)	11 (0.21)	214 (0.19)	94 (0.30)	1039 (0.20)
Intracranial hemorrhage, n (%)	10 (0.00)	4 (0.00)	0 (0.00)	1 (0.02)	7 (0.01)	3 (0.01)	25 (0.00)
Gastrointestinal hemorrhage, n (%)	60 (0.03)	40 (0.03)	9 (0.03)	1 (0.02)	42 (0.04)	16 (0.05)	168 (0.03)
Other bleeding, n (%)	330 (0.16)	226 (0.16)	46 (0.16)	9 (0.17)	169 (0.15)	76 (0.25)	856 (0.16)

Abbreviations: BXM, baloxavir; LNV, laninamivir; N, number of influenza episodes; OTV, oseltamivir; PRV, peramivir; ZNV, zanamivir.

not receive prophylactic anti-influenza therapy, and in patients with only a first influenza episode (data not shown).

4 | DISCUSSION

Our study is the first to examine whether there is an association between anti-influenza agents and bleeding risk using an employment-based healthcare insurance database. We found no difference in the incidence of bleeding between anti-influenza drugs used to treat influenza outpatients, including baloxavir and neuraminidase inhibitors.

There has been no evidence to suggest an association between baloxavir and bleeding events based on the results of pre-clinical and clinical studies obtained in the pre-registration stage. A preclinical study of the repeated-dose toxicity of baloxavir in rats reported findings of prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT). However, this prolongation was unlikely to be related to baloxavir, since it is often observed in laboratory rats due to lack of vitamin K. This was subsequently confirmed by a study in which vitamin K supplementation reduced the effects on PT and APTT.¹⁵ No increase in bleeding risk was seen in clinical trials or post-marketing studies. Pooled incidence proportions of bleeding events in pre-registration clinical trials

TABLE 3 Incidence proportions of bleeding events and odds ratios, by anti-influenza treatment group after exact matching

	BXM N = 98 018	OTV N = 98 018	BXM N = 27 257	ZNV N = 27 257	BXM N = 4808	PRV N = 4808	BXM N = 107 010	LNV N = 107 010	BXM N = 24 249	Untreated N = 24 249
Bleeding (overall)	n (%) 163 (0.17)	165 (0.17)	44 (0.16)	48 (0.18)	9 (0.19)	10 (0.21)	185 (0.17)	189 (0.18)	38 (0.16)	72 (0.30)
	OR 0.99 [0.88, 1.09]		0.92 [0.69, 1.15]		0.90 [0.40, 1.50]		0.98 [0.89, 1.06]		0.53 [0.39, 0.69]	
Intracranial hemorrhage	n (%) 2 (0.00)	1 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.02)	3 (0.00)	5 (0.00)	0 (0.00)	2 (0.01)
	OR 2.00 [0.33, 5.00]		1.00 [1.00, 3.00]		0.33 [0.33, 1.00]		0.60 [0.20, 1.00]		0.20 [0.20, 0.50]	
Gastrointestinal hemorrhage	n (%) 21 (0.02)	21 (0.02)	5 (0.02)	6 (0.02)	1 (0.02)	1 (0.02)	26 (0.02)	34 (0.03)	4 (0.02)	11 (0.05)
	OR 1.00 [0.73, 1.30]		0.83 [0.17, 1.50]		1.00 [0.33, 3.50]		0.79 [0.59, 0.97]		0.36 [0.09, 0.73]	
Other bleeding	n (%) 141 (0.14)	144 (0.15)	39 (0.14)	42 (0.15)	8 (0.17)	8 (0.17)	158 (0.15)	154 (0.14)	34 (0.14)	59 (0.24)
	OR 0.98 [0.87, 1.09]		0.93 [0.67, 1.19]		1.00 [0.37, 1.63]		1.03 [0.92, 1.13]		0.58 [0.41, 0.75]	

Note: Incidence proportions are 50th percentile and odds ratio are 50th [2.5th, 97.5th] percentiles for baloxavir versus comparator group.

Abbreviations: BXM, baloxavir; LNV, laninamivir; N, number of influenza episodes; OR, odds ratio; OTV, oseltamivir; PRV, peramivir; ZNV, zanamivir.

of baloxavir are shown in Table S6. The incidence of bleeding events in the pooled analysis was 0.8% (14 events among 1810 patients) in baloxavir recipients, 0.9% (10/1136) in placebo recipients, and 0.6% (8/1234) in oseltamivir recipients (unpublished data). In a post-marketing surveillance study of baloxavir (JapicCTI-183 882), bleeding events were 0.13% (4 of 3094 cases, unpublished data). Although the results of these studies cannot be compared directly due to the differences in definitions of bleeding events and data collection methods, these studies did not suggest an increased risk of bleeding, in agreement with the results of quantitative, concurrent comparative assessments made in the present study.

The validity of untreated cases with untyped influenza seems to be suboptimal, considering a situation where patients diagnosed with influenza usually receives anti-influenza drugs in Japan and the recorded ICD-10 diagnostic codes which indicate a lack of decisive testing for influenza types. Therefore, we regard that the untreated group, which included a large number of patients with the code of untyped influenza, is likely to be composed of patients with heterogeneous backgrounds, making it difficult to interpret in comparison with the treatment groups.

Almost the same incidence of bleeding was observed across all treatment groups; however, there were some significant differences with regard to demographic factors, for example, in the peramivir group. Differences in the age distribution observed between anti-influenza drug groups in the study, including a high proportion of children aged ≤ 4 years in the oseltamivir group and a high proportion of patients aged ≥ 18 years in the peramivir group, may be attributable to the different types of available formulation and administration route. The untreated group also had a high proportion of patients aged 0–4 years; it is possible that many of them were infants who have difficulties with drug administration.

Since NSAIDs can be associated with bleeding,³⁴ we analyzed the effect of NSAIDs on the incidence of bleeding in the study population by comparing the proportions of NSAIDs used in each group with and without bleeding events. However, no clear association was observed because of the small number of patients with bleeding events (data not shown). After eliminating the cumulative effects of multiple influenza infections on bleeding, no impact of a cumulative effect of multiple influenza episodes on bleeding events was observed and, furthermore, most patients had only one influenza episode (data not shown).

The incidences of different types and severities of bleeding that were evaluated in the study, including intracranial, gastrointestinal, and other bleeding events, were similar among all treatment groups. However, it should be noted that the number of cases for several types of hemorrhage were small. Although an increase in site-specific bleeding risk is unlikely regardless of the severity, based on the potential mechanism of bleeding after influenza infection, which is a coagulation cascade triggered by the virus, further studies with larger sample sizes to ensure sufficient power to analyze low-incidence site-specific bleeding events are warranted.

When considering the methods used for the current study, an aspect that deserves comment is the matching that was performed to eliminate imbalances in background patient characteristics. A good

match indicated by the standardized differences less than 0.1 was not achieved for multiple covariates between baloxavir and any other group when propensity score matching was attempted, potentially due to the presence of non-positivity.³⁵ This was particularly evident when attempting matching between baloxavir and the smaller groups in the study, including zanamivir, peramivir and untreated patients. In the exact matching analysis, the absolute number of patients with events who were excluded may have been greater in the baloxavir group because of the large difference in the number of patients in this group compared with other groups. Thus, the odds ratios were interpreted as the average treatment effect of baloxavir on the treated with a comparator group.

The study has several limitations that need to be considered. First, the JMDC database only includes employees and their dependents covered by the employee's health insurance, and therefore the number of individuals aged ≥ 65 years in the database is small and none were aged >75 years. The data from the study population cannot be generalized to the elderly and those insured under other types of insurance.²³ Second, patients with influenza were defined based on ICD-10 codes, not a definitive diagnostic tool such as the polymerase chain reaction method. A validation study to confirm the accuracy of the diagnoses was not undertaken; in Japan influenza is often diagnosed by a rapid testing kit as well as by symptoms, and therefore more accurate diagnoses could be expected in combination with a claim record for rapid testing.²¹ Furthermore, similar results were obtained in sensitivity analyses based on different diagnostic criteria. The presence of imperfect sensitivity and specificity in defining diagnoses/conditions does not bias the relative indexes such as odds ratio when sensitivity and specificity are not differential between comparison groups. Third, the definitions of bleeding events in the present study were based on the ICD-10 codes from a preceding study using the JMDC database.²⁵ A validation study of these definitions was not performed; however, some diagnoses obtained from hospital administrative data has been validated in other studies in Japan.³⁶ Fourth, as this was an observational study, bias due to unmeasured confounding is unavoidable and totality of data cannot be achieved. It is not possible to conclude whether there is a causal relationship between a drug and bleeding events or not based on this study alone. However, similar results were obtained in sensitivity analyses that addressed different exclusion periods for previous bleeding events and a subgroup analysis in patients with no history of bleeding.

As usual for claims record-based studies, other limitations related to misclassification include: the time from onset of influenza to treatment start, adherence to prescribed medication, the severity of influenza symptoms at baseline, and the actual results of diagnostic tests being unavailable. Finally, influenza varies by season, but our study was based on data from a single season, which may limit the interpretation of the results.

5 | CONCLUSION

The incidence of bleeding was similar across recipients of different anti-influenza drugs. Bleeding events were also observed at a slightly

higher frequency in patients who did not receive anti-influenza drugs. Based on this study, there is no evidence to suggest that anti-influenza drugs, including baloxavir and neuraminidase inhibitors, are associated with an increased incidence of bleeding in influenza patients.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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