Research Paper

Adverse reaction profiles of hemorrhagic adverse reactions caused by direct oral anticoagulants analyzed using the Food and Drug Administration Adverse Event Reporting System (FAERS) database and the Japanese Adverse Drug Event Report (JADER) database

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Abstract

Direct oral anticoagulants (DOACs) are used in anticoagulant therapy. The purpose of this study was to evaluate the association of DOAC-induced gastrointestinal (GI) and nervous system hemorrhage using the FDA's Adverse Event Reporting System (FAERS) database and the Japanese Adverse Drug Event Report (JADER) database.

We identified and analyzed the reports of hemorrhagic reactions between 2004 and 2016 from the FAERS and JADER databases, and calculated the adjusted reported odds ratio (ROR) using the multiple logistic regression method. Additionally, we used the time-to-onset analysis.

In the FAERS database, the adjusted ROR of apixaban, rivaroxaban, and dabigatran for GI hemorrhage was 6.79 (5.84–7.91), 19.58 (18.85–20.34), and 14.51 (13.58–15.51), respectively. In the JADER database, the adjusted ROR of apixaban, rivaroxaban, edoxaban, and dabigatran for GI hemorrhage was 11.80 (9.50–14.64), 11.03 (9.18–13.26), 10.17 (6.95–14.88), and 9.85 (7.23–13.42), respectively. We found that the association of GI hemorrhage with DOACs was affected by sex (female). Additionally, 30% of GI hemorrhage was observed after 30 days.

Hemorrhagic reactions of both GI and nervous systems were observed in both the spontaneous reporting system databases. We recommend that female patients who experience symptoms related to GI hemorrhage should be closely monitored and advised to adhere to an appropriate care plan. Additionally, our results show that patients should be closely monitored for hemorrhage even after a month.

Key words: direct oral anticoagulant, hemorrhage, adverse reaction, FAERS, JADER

Introduction

Direct oral anticoagulants (DOACs) are used for anticoagulant therapy to prevent stroke associated with atrial fibrillation and for the prevention and treatment of venous thromboembolic disease [1–4]. DOACs directly inhibit thrombin (dabigatran [5]) or factor Xa (rivaroxaban [6], apixaban [7], and edoxaban [8]) to exert their anticoagulant effect. DOACs have advantages over vitamin K antagonists (e.g., warfarin), such as a more rapid anticoagulant effect, fewer individual differences in therapeutic effect, fixed-dose administration, less drug–drug interactions, and limited dietary restrictions [1–4,9]. Randomized clinical trials (dabigatran (Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial) [1], rivaroxaban (Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial) [2], apixaban (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial) [3], and edoxaban (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction study 48 (ENGAGE AF TIMI-48) trial) [4]) have demonstrated that DOACs are associated with lower risk of intracranial hemorrhage than that with warfarin.

Renal function is an important factor in DOAC therapy, because each DOAC has varying degrees of renal elimination. The urinary excretion rate of dabigatran, rivaroxaban, apixaban, and edoxaban is reported to be 80% [10], 36% [11], 27% [12], and 50% [13,14], respectively. Moderate to severe renal impairment could increase the risk for hemorrhage due to the accumulation of drugs in the serum, affecting dabigatran the most and apixaban the least [15,16]. Renal impairment is more often observed among elderly patients compared with that in the general population. Because atrial fibrillation is largely a disease of the elderly population, the risk of stroke and hemorrhage with DOAC therapy increases with age. The possible association of DOAC with gastrointestinal (GI) hemorrhage is of interest in elderly patients. Because ischemic strokes and systemic embolisms have greater clinical significance than nonfatal hemorrhage (e.g., GI hemorrhage), higher doses of DOACs (e.g., dabigatran) are more favorable in elderly patients [1]. However, both acute and chronic GI hemorrhages have a negative effect on the patient's quality of life. A limitation of the standard-dose DOACs is an increase in the risk of GI hemorrhage [17–20]. Moreover, there have been concerns regarding the safety profile of DOACs relating to age and sex; for example, renal functions are affected by sex [21, 22].

To monitor the adverse drug reactions, a spontaneous reporting system (SRS) compiles reports of suspected adverse reactions (ARs) either voluntarily reported by patients, clinicians, pharmacists, and other healthcare professionals or mandatorily reported by various pharmaceutical manufacturers. SRS is a valuable tool in post-marketing surveillance that reflects the realities of clinical practice [23]. The US Food and Drug Administration (FDA) has developed the FDA Adverse Event Reporting System (FAERS). The Pharmaceuticals and Medical Devices Agency (PMDA), a regulatory authority in Japan, has developed the Japanese Adverse Drug Event Report (JADER) database.

Several researchers have evaluated hemorrhage risk associated with dabigatran using the FAERS database [24–26]. Southworth et al. [24] demonstrated that dabigatran and warfarin were associated with similar hemorrhage rates, which is consistent with the findings of the RE-LY study. McConeghy et al. [25] reported that the reporting rate of hemorrhage related to dabigatran and warfarin was 26% and 32%, respectively. They also reported that intracranial hemorrhage was low with dabigatran, but the rate of GI hemorrhage was increased compared to that with warfarin, both of which are consistent with the findings of RE-LY. We previously demonstrated that GI hemorrhage was significantly increased in patients over the age of 80 years [26]. Despite the insights that these trials provide, the effects of other DOACs on hemorrhagic ARs in a clinical setting are uncertain.

In this study, we evaluated the relationship between DOACs and hemorrhagic ARs using the reporting odds ratio (ROR) adjusted using the multiple logistic regression analysis [26–29]. Analysis of time-to-onset data has been proposed as a method to detect signals for ARs in SRS. We also analyzed the time-to-onset of hemorrhagic ARs [30–32].

Methods

Data source

All data from the SRS database were fully anonymized by the regulatory authorities before we used them. Data from January 2004 to December 2016 in the FAERS database are publicly available and can be downloaded from the FDA website (http://www.fda.gov/). The FAERS database permits contributors to register drugs under any name, including a trade name and an abbreviation. The DrugBank database contains information of drugs used globally, including the FDA-approved small molecule drugs; it was utilized as a resource for

batch conversion and compilation of drug names [33]. We followed the FDA's recommendation to adopt the most recent CASE number to identify duplicate reports of the same patient from different reporting sources and excluded them from the analysis [34].

Data from April 2004 to November 2016 in the JADER database were extracted from the PMDA website (www.pmda.go.jp). We built a database that integrated data from the FAERS and JADER databases and the DrugBank using FileMaker Pro 13 software (FileMaker, Santa Clara, CA, U.S.A.) following the international safety reporting guidelines (International Council on Harmonization, E2B).

Definition of hemorrhage reactions

The AR definitions used in this study corresponded to those provided by the Medical Dictionary for Regulatory Activities (MedDRA)/Japanese version 19.0 (MedDRA/J, www.pmrj.jp/jmo/php/indexj.php) [35]. To evaluate the effect of DOACs on hemorrhagic reactions, we used a standardized MedDRA inquiry (SMQ) for hemorrhage reactions (SMQ code: 20000039) and the System Organ Class (SOC) for GI disorder, and extracted only reports that met both criteria. The number of selected preferred terms for hemorrhagic reactions, limited by SOC (GI disorder), was 152. Furthermore, to evaluate the nervous system hemorrhage, we used 88 preferred terms that matched the SMQ for hemorrhage reactions (SMQ code: 20000039) and the SOC for the nervous system disorder.

Analysis

To evaluate the effect of age on "hemorrhagic reactions," the reports were stratified into the following age groups: 0–59 years and more than 60 years. According to the definition of the World Health Organization (WHO) of the United Nations, elderly people are those who are aged 65 years or more.

Using established pharmacovigilance indices [23], we evaluated the ROR to establish the effects of DOACs on "hemorrhagic reactions." "Cases" were defined as patients who reported "hemorrhagic reactions," while "non-cases" consisted of patients associated with all other reports. The ROR is the ratio of the odds of reporting ARs versus all other reactions associated with DOACs compared with the reporting odds for all other drugs present in the database. To compare the "cases" and "non-cases," we calculated the RORs as (a:c) / (b:d). The RORs were expressed as point estimates with a 95% confidence interval (CI). The signal was considered positive if the lower limit of 95% CI was > 1 and the reported number was ≥ 2 [36].

The use of ROR allows adjustment using multiple logistic regression analysis and provides the advantage of controlling covariates [37,38]. In this analysis, the results were refined by dedicated correction to detect confounding factors that may be present in the database. We calculated the adjusted ROR to control the covariates using the multiple logistic regression analysis. The report was stratified according to age as follows: 0–59- and ≥ 60-year-old group. To construct a multiple logistic model that coded report year, sex, stratified age group, and drug, the following multiple logistic model was used for analysis:

$$\log(odds) = \beta_0 + \beta_1 Y + \beta_2 S + \beta_3 A + \beta_4 D$$
$$+ \beta_5 S * A + \beta_6 S * D + \beta_7 A * D$$

(Y = reporting year, S = sex, A = stratified age group, and D = drug (apixaban, rivaroxaban, edoxaban, and dabigatran)).

The adjusted ROR was calculated using the 0–59-year-old group as the control group. The effectiveness of explanatory variables was evaluated using a stepwise method with a significance level of 0.05 (forward, and backward) [27,28]. Using the likelihood ratio test, the influence of explanatory variables was evaluated. As the difference of -2log likelihood follows chi-square distribution with one degree of freedom, the results with p ≤ 0.05 were considered statistically significant. Data analysis was performed using JMP software version 12.0 (SAS Institute Inc., Cary, NC, USA).

Time-to-onset duration was calculated from the time of a patient's first prescription to the occurrence of hemorrhagic reactions. The records with completed AR occurrence and prescription start date were used for the time-to-onset analysis. It was necessary to consider right truncation when evaluating the time-to-onset of ARs. We determined an analysis period of 365 days after the start of administration. The median duration, quartiles, and Weibull shape parameters (WSPs) were used to evaluate the time-to-onset data. The scale parameter α of Weibull distribution determines the scale of the distribution function. A larger scale value (α) stretches the distribution, whereas a smaller scale value (α) shrinks data distribution. The WSP β of Weibull distribution determines the shape of distribution function. Larger and smaller shape values produce left- and right-skewed curves, respectively. The shape parameter β of Weibull distribution was used to indicate the level of hazard over time without a reference population. When β is equal to 1, the hazard is estimated to be constant over time. If β is greater than 1 and 95% CI of β excluded the value 1, the

hazard was considered to increase with time [30,31,39]. The time-to-onset analysis was performed using JMP software version 12.0 (SAS Institute Inc., Cary, NC, USA).

Results

The FAERS database contained 8,867,135 AR reports from January 2004 to December 2016. After excluding duplicates according to the FDA's recommendation, 7,348,357 reports were analyzed. The JADER database contained 430,587 reports from April 2004 to November 2016.

Gastrointestinal hemorrhage reaction

The reporting rate of GI hemorrhage related to apixaban, rivaroxaban, edoxaban, and dabigatran was 9.5%, 24.5%, 23.8%, and 22.2% in FAERS and 23.1%, 21.5%, 27.8%, and 25.7% in JADER, respectively (Table 1).

For the FAERS database, the crude ROR with 95% CI for GI hemorrhage for apixaban, rivaroxaban, edoxaban, and dabigatran was 5.83 (5.54–6.13), 20.04 (19.65–20.43), 17.18 (10.27–28.75), and 16.90 (16.51–17.30), respectively (Table 1). The crude ROR (95% CI) for dabigatran in 0–59-year-old group and ≥ 60-year-old group was 10.41 (9.29–11.66) and 19.52 (18.95–20.11), respectively (Table 1).

For the JADER database, the crude ROR with 95% CI for apixaban, rivaroxaban, edoxaban, and dabigatran was 12.24 (11.12–13.46), 11.20 (10.22–12.27), 15.14 (12.48–18.35), and 13.96 (12.55–15.52), respectively (Table 1). The crude ROR (95% CI) for dabigatran in 0–59-year-old group and ≥ 60-year-old group was 4.19 (2.02–8.70) and 14.66 (13.15–16.34), respectively (Table 1).

After excluding incomplete reports that lacked information on the report year, age and sex, 4,383,074 reports in FAERS and 398,645 reports in JADER were included in the multiple logistic regression analysis. Using a stepwise logistic regression model, we selected significant variables related to ARs among the reporting year, age, sex, and administered drugs (apixaban, rivaroxaban, edoxaban, and dabigatran), and examined the interaction between sex, age, and the administered drug (Table 2, Table S1).

	Adverse reaction of interest	All other adverse reaction of interest	Total
Drug of interest	a	b	a+b
All other drug of interest	c	d	c+d
Total	a+c	b+d	a+b+c+d

$$\text{Reporting Odds Ratio (ROR)} = \frac{a/c}{b/d} = \frac{ad}{bc}$$

$$\text{95\% confidence interval (CI)} = e^{\ln(ROR)\,\pm\,1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$$

Figure 1. Two-by-two contingency table for calculating the reporting odds ratio.

Table 1. Reported cases and crude ROR of gastrointestinal hemorrhage and nervous system hemorrhage with SMQ code and SOC

		FAERS					JADER				
		Total	Case	Non-case	Ratio (%)	Crude ROR (95% CI)	Total	Case	Non-case	Ratio (%)	Crude ROR (95% CI)
Gastrointentional hemorrhage[a)]											
	Total	7348357	130860	7217497	1.8		430587	10830	419757	2.5	
Apixaban	Total	18011	1705	16306	9.5	5.83 (5.54–6.13)	2485	574	1911	23.1	12.24 (11.12–13.46)
	0-59 y.o.	797	60	737	7.5	4.49 (3.45–5.84)	85	20	65	23.5	11.95 (7.23–19.73)
	≥ 60 y.o.	8184	1088	7096	13.3	8.52 (7.99–9.08)	2329	539	1790	23.1	12.23 (11.09–13.49)
Rivaroxaban	Total	59538	14596	44942	24.5	20.04 (19.65–20.43)	2874	618	2256	21.5	11.20 (10.22–12.27)
	0-59 y.o.	6669	1328	5341	19.9	13.84 (13.03–14.71)	134	25	109	18.7	8.91 (5.77–13.76)
	≥ 60 y.o.	26621	8111	18510	30.5	25.70 (25.02–26.39)	2658	573	2085	21.6	11.19 (10.18–12.30)
Edoxaban	Total	80	19	61	23.8	17.18 (10.27–28.75)	521	145	376	27.8	15.14 (12.48–18.35)
	0-59 y.o.	1	0	1	0.0	–[c)]	52	5	47	9.6	4.12 (1.64–10.37)
	≥ 60 y.o.	7	0	7	0.0	–[c)]	450	133	317	29.6	16.45 (13.42–20.16)
Dabigatran	Total	43392	9629	33763	22.2	16.90 (16.51–17.30)	1846	474	1372	25.7	13.96 (12.55–15.52)
	0-59 y.o.	2234	354	1880	15.8	10.41 (9.29–11.66)	82	8	74	9.8	4.19 (2.02–8.70)
	≥ 60 y.o.	23761	6009	17752	25.3	19.52 (18.95–20.11)	1711	456	1255	26.7	14.66 (13.15–16.34)
Nervous system hemorrhage[b)]											
	Total	7348357	32961	7315396	0.4		430587	6528	424059	1.5	
Apixaban	Total	18011	848	17163	4.7	11.23 (10.47–12.04)	2485	617	1868	24.8	23.59 (21.46–25.93)
	0-59 y.o.	797	27	770	3.4	7.79 (5.31–11.43)	85	29	56	34.1	33.79 (21.56–52.94)
	≥ 60 y.o.	8184	566	7618	6.9	16.76 (15.38–18.27)	2329	576	1753	24.7	23.31 (21.15–25.70)
Rivaroxaban	Total	59538	3546	55992	6.0	15.63 (15.08–16.20)	2874	666	2208	23.2	21.71 (19.83–23.76)
	0-59 y.o.	6669	257	6412	3.9	8.96 (7.90–10.15)	134	42	92	31.3	29.84 (20.7–43.02)
	≥ 60 y.o.	26621	2244	24377	8.4	21.85 (20.9–22.85)	2658	608	2050	22.9	21.14 (19.24–23.23)
Edoxaban	Total	80	3	77	3.8	8.65 (2.73–27.41)	521	89	432	17.1	13.55 (10.77–17.05)
	0-59 y.o.	1	0	1	0.0	–[c)]	52	7	45	13.5	10.11 (4.56–22.44)
	≥ 60 y.o.	7	0	7	0.0	–[c)]	450	81	369	18.0	14.43 (11.33–18.37)
Dabigatran	Total	43392	2167	41225	5.0	12.42 (11.88–12.98)	1846	229	1617	12.4	9.50 (8.25–10.93)
	0-59 y.o.	2234	86	2148	3.8	8.91 (7.18–11.05)	82	6	76	7.3	5.13 (2.23–11.79)
	≥ 60 y.o.	23761	1335	22426	5.6	13.73 (12.98–14.52)	1711	217	1494	12.7	9.73 (8.42–11.24)

[a)] Gastrointestinal hemorrhage defined with "haemorrhage terms (excl laboratory terms)" of SMQ (code: 20000039) and "gastrointestinal disorder" of SOC

[b)] Nervous system hemorrhage defiend with "haemorrhage terms (excl laboratory terms)" of SMQ (code: 20000039) and "nervous system disorder" of SOC

[c)] Number of cases < 2

Table 2. Multiple-logistic regression analysis

| | FAERS | | JADER | |
	Adjusted ROR (95% CI)	p-value	Adjusted ROR (95% CI)	p-value
Gastrointestinal hemorrhage[a)]				
Reporting year	0.69 (0.69–0.69)	< 0.0001	1.45 (1.44–1.45)	< 0.0001
Age (≥ 60)	1.83 (1.75–1.92)	< 0.0001	1.60 (1.53–1.68)	< 0.0001
Sex (female)	0.65 (0.63–0.68)	< 0.0001	0.77 (0.74–0.81)	< 0.0001
Apixaban	6.79 (5.84–7.91)	< 0.0001	11.80 (9.50–14.64)	< 0.0001
Rivaroxaban	19.58 (18.85–20.34)	< 0.0001	11.03 (9.18–13.26)	< 0.0001
Edoxaban	–	–	10.17 (6.95–14.88)	< 0.0001
Dabigatran	14.51 (13.58–15.51)	< 0.0001	9.85 (7.23–13.42)	< 0.0001
Age (≥ 60)*Sex (female)	1.11 (1.08–1.14)	< 0.0001	–	–
Age (≥ 60)*Dabigatran	–	–	2.29 (1.05–5.01)	0.038
Sex (female)*Apixaban	1.40 (1.24–1.59)	< 0.0001	1.60 (1.31–1.97)	< 0.0001
Sex (female)*Rivaroxaban	1.36 (1.29–1.43)	< 0.0001	1.79 (1.47–2.17)	< 0.0001
Sex (female)*Dabigatran	1.52 (1.44–1.62)	< 0.0001	2.01 (1.61–2.51)	< 0.0001
Nervous system hemorrhage[b)]				
Reporting year	0.62 (0.62–0.62)	< 0.0001	0.83 (0.82–0.84)	0.0001
Age (≥ 60)	2.03 (1.92–2.14)	< 0.0001	1.85 (1.73–1.97)	< 0.0001
Sex (female)	0.61 (0.58–0.64)	< 0.0001	0.80 (0.75–0.85)	< 0.0001
Apixaban	13.64 (10.94–17.01)	< 0.0001	34.07 (28.02–41.42)	< 0.0001
Rivaroxaban	15.46 (14.31–16.70)	< 0.0001	29.58 (25.07–34.90)	< 0.0001
Edoxaban	–	–	17.63 (12.47–24.94)	< 0.0001
Dabigatran	11.75 (10.34–13.34)	< 0.0001	8.24 (5.48–12.40)	< 0.0001
Age (≥ 60)*Sex (female)	1.15 (1.09–1.22)	< 0.0001	–	–
Age (≥ 60)*Apixaban	–	–	0.36 (0.22–0.57)	< 0.0001
Age (≥ 60)*Rivaroxaban	1.15 (1.00–1.32)	0.0455	0.38 (0.26–0.57)	< 0.0001
Age (≥ 60)*Dabigatran	0.76 (0.61–0.95)	0.0162	–	
Sex (female)*Apixaban	1.65 (1.39–1.96)	< 0.0001	–	–
Sex (female)*Rivaroxaban	1.29 (1.18–1.41)	< 0.0001	–	–
Sex (female)*Dabigatran	1.37 (1.22–1.53)	< 0.0001	–	–

[a)] Gastrointestinal hemorrhage defined with "haemorrhage terms (excl laboratory terms)" of SMQ (code: 20000039) and "gastrointestinal disorder" of SOC
[b)] Nervous system hemorrhage defiend with "haemorrhage terms (excl laboratory terms)" of SMQ (code: 20000039) and "nervous system disorder" of SOC

For the FAERS database, the result of the final model indicated that reporting year (p < 0.0001), age (≥ 60 years, p < 0.0001), sex (female, p < 0.0001), and the administered drug [apixaban (p < 0.0001), rivaroxaban (p < 0.0001), and dabigatran (p < 0.0001)] had significant effects (Table 2). The adjusted ROR of apixaban, rivaroxaban, and dabigatran was 6.79 (5.84–7.91), 19.58 (18.85–20.34), and 14.51 (13.58–15.51), respectively. The interaction of age (≥ 60)*sex (female) (p < 0.0001), sex (female)*apixaban (p < 0.0001), sex (female)*rivaroxaban (p < 0.0001), and sex (female)*dabigatran (p < 0.0001) was also significant. The adjusted ROR for sex (female)*apixaban, sex (female)*rivaroxaban, and sex (female)*dabigatran was 1.40 (1.24–1.59), 1.36 (1.29–1.43), and 1.52 (1.44–1.62), respectively.

For the JADER database, significant contributions were observed for reporting year (p < 0.0001), age (≥ 60 years, p < 0.0001), sex (female, p < 0.0001), and the administered drug [apixaban (p < 0.0001), rivaroxaban (p < 0.0001), edoxaban (p < 0.0001), and dabigatran (p < 0.0001)] (Table 2). The adjusted ROR of apixaban, rivaroxaban, edoxaban, and dabigatran was 11.80 (9.50–14.64), 11.03 (9.18–13.26), 10.17 (6.95–14.88), and 9.85 (7.23–13.42), respectively. The adjusted ROR for age (≥ 60)*dabigatran (p = 0.0380), sex (female)*apixaban (p < 0.0001), sex (female)*rivaroxaban (p < 0.0001), and sex (female)*dabigatran (p < 0.0001) was 2.29 (1.05–5.01), 1.60 (1.31–1.97), 1.79 (1.47–2.17), and 2.01 (1.61–2.51), respectively.

The time-to-onset profiles in the JADER database are demonstrated in Fig. 2. The median and quartiles of GI hemorrhage after the use of apixaban, rivaroxaban, edoxaban, and dabigatran were 26.0 (7.0–89.0), 47.5(12.0–141.8), 12.0 (6.0–68. 0), and 30.0 (10.0–82.0) days, respectively (Fig. 2). GI hemorrhage during the first 30 days after the use of apixaban, rivaroxaban, edoxaban, and dabigatran was 52.2%, 40.9%, 62.4%, and 49.0%, respectively.

Nervous system hemorrhage reaction

The reporting rate of nervous system hemorrhage related to apixaban, rivaroxaban, edoxaban, dabigatran was 4.7%, 6.0%, 3.8%, 5.0% in FAERS and 24.8%, 23.2%, 17.1%, 12.4% in JADER, respectively (Table 1).

For the FAERS database, the crude ROR with 95% CI for nervous system hemorrhage for apixaban, rivaroxaban, edoxaban, and dabigatran was 11.23 (10.47–12.04), 15.63 (15.08–16.20), 8.65 (2.73–27.41), and 12.42 (11.88–12.98), respectively (Table 2). The crude ROR (95% CI) for dabigatran in 0–59-year-old group and ≥ 60-year-old group was 8.91 (7.18–11.05) and 13.73 (12.98–14.52), respectively (Table 1).

For the JADER database, the crude ROR with 95% CI for apixaban, rivaroxaban, edoxaban, and dabigatran was 23.59 (21.46–25.93), 21.71 (19.83–23.76), 13.55 (10.77–17.05), and 9.50 (8.25–10.93), respectively (Table 1).

Using a stepwise logistic regression model, important variables relevant to GI hemorrhage and nervous system hemorrhage were selected (Table 2). For FAERS, reporting year (p < 0.0001), age (≥ 60 years, p < 0.0001), sex (female, p < 0.0001), and the administered drug [apixaban (p < 0.0001), rivaroxaban (p < 0.0001), and dabigatran (p < 0.0001)] showed significant effect. The adjusted ROR for apixaban, rivaroxaban, and dabigatran was 13.64 (10.94–17.01), 15.46 (14.31–16.70), and 11.75 (10.34–13.34), respectively. The interaction of age (≥ 60)*sex (female) (p < 0.0001), age (≥ 60)*rivaroxaban (p = 0.0455), age (≥ 60)*dabigatran (p = 0.0162), sex (female)*apixaban (p < 0.0001), sex (female)*rivaroxaban (p < 0.0001), sex (female)*dabigatran (p < 0.0001) was significant. The adjusted ROR for age (≥ 60)*sex (female), age (≥ 60)*rivaroxaban, age (≥ 60)*dabigatran, sex (female)*apixaban, sex (female)*rivaroxaban, and sex (female)*dabigatran was 1.15 (1.09–1.22), 1.15 (1.00–1.32), 0.76 (0.61–0.95), 1.65 (1.39–1.96), 1.29 (1.18–1.41), and 1.37 (1.22–1.53), respectively.

For JADER, the adjusted ROR of apixaban (p < 0.0001), rivaroxaban (p < 0.0001), edoxaban (p < 0.0001), and dabigatran (p < 0.0001) was 34.07 (28.02–41.42), 29.58 (25.07–34.90), 17.63 (12.47–24.94), and 8.24 (5.48–12.40), respectively (Table 2).

For the JADER database, the median and quartiles of nervous system hemorrhage after the use of apixaban, rivaroxaban, edoxaban, and dabigatran were 49.0 (12.3–174.5), 94.0 (30.3–185.8), 55.0 (9.5–117.0), and 48.0 (9.0–144.0) days, respectively (Fig. 3). Nervous system hemorrhage within the first 30 days after the use of apixaban, rivaroxaban, edoxaban, and dabigatran was 37.5%, 23.9%, 43.1%, and 41.9%, respectively.
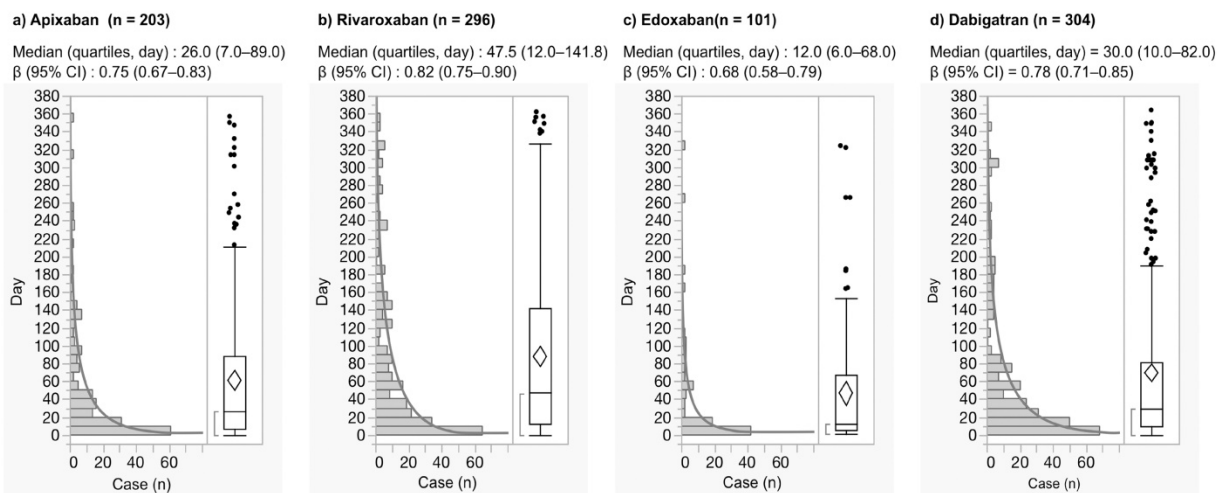

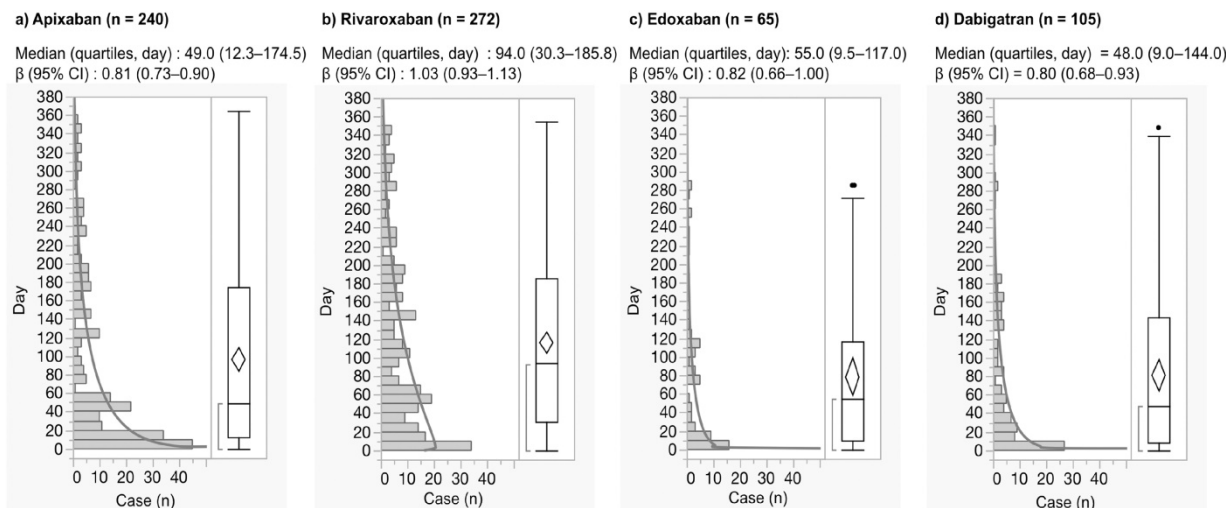**Figure 2.** Histogram and Weibull shape parameter of gastrointestinal hemorrhage.

Figure 3. Histogram and Weibull shape parameter of nervous system hemorrhage.

Discussion

In this study, we evaluated the association between DOAC and hemorrhagic reactions using data from the SRS databases. As the crude RORs of hemorrhagic reactions such as GI hemorrhage and nervous system hemorrhage were higher than one in both the SRS databases, our results suggest that DOACs increase the adverse hemorrhagic reactions.

Renal function is affected by age, sex, body weight, clinical condition, and medication. The effect of age on ARs associated with DOAC therapy has been widely reported. We applied the multiple logistic regression analysis to validate the results. The interaction term of age ($\geq$ 60)*dabigatran for GI hemorrhage was significant in the JADER databases. Dabigatran presented high renal excretion rate [21]. Because the renal excretion may be compromised, GI hemorrhage was increased in the elderly patients [21]. Increased adjusted ROR suggested that dabigatran increases ARs with advanced age; this also supports previous observations on GI hemorrhage reactions related to dabigatran [26].

We provided insights into the association between hemorrhagic reactions and sex in the SRS dataset—the results obtained after adjusting the ROR suggested that sex (female) may influence hemorrhagic reactions. Sex-specific differences in creatinine clearance and renal function exist [22]. Creatinine clearance, and presumably renal clearance of drugs, in women tends to be approximately 85% of that in men of the same age and body weight [40]. As women generally have less renal function, the risk of hemorrhagic reaction might be considered higher in females than in males. The interaction of the majority of DOACs and sex (female) in GI hemorrhage was observed in both the FAERS and JADER databases. Although the doses of DOACs are optimized according to the renal function of each patient based on the established guideline and package insert, the sex difference observed in our study should be evaluated further.

After a single 20 mg apixaban administration, the mean C_{max} and AUC_{∞} were 18% and 15% higher, respectively, in females than in males [41]. As no clinically meaningful age- or sex-related difference in the pharmacokinetics and pharmacodynamics of apixaban has been reported, apixaban is considered safe and well tolerated in both elderly and young subjects of both sexes [41]. Previously, dose adjustment was not required on the basis of body weight, age, or sex alone [41,42]. However, our results suggest that caution is warranted in the presence of unknown additional factors such as renal impairment that could increase GI hemorrhage risk in females.

For rivaroxaban-associated GI hemorrhage, aging (over 60 years) showed no effects in both the FAERS and JADER databases. It has been previously reported that the influence of age and sex on rivaroxaban therapy was small [43]. Neither age nor sex appeared to significantly influence the E_{max}, time course of inhibition of Factor Xa activity, or prolongation of prothrombin time [43]. Rivaroxaban has been approved for clinical use without dose-adjustment for age or sex alone [43]. Clinical studies have demonstrated that the half-life of rivaroxaban is 7–11 h and 11–13 h for young and elderly patients [44–46]. In the J-ROCKET-AF study, 15 mg rivaroxaban instead of 20 mg was used [47], because in Japanese patients, 15 mg rivaroxaban provided exposures comparable to 20 mg dose in Americans [48]. The trial results demonstrated that 15 mg rivaroxaban was non-inferior as compared with warfarin and it lowered intracranial bleeding, suggesting the use of a reduced dose of rivaroxaban (15 mg) for evaluation in Japanese patients with AF [47]. Our study supports the results of these previous reports.

It was difficult to interpret the data of edoxaban, because the number of case reports was small in the FAERS. Edoxaban exposure is affected by the efflux transporter (P-glycoprotein) inhibitors and inducers (amiodarone, quinidine, ketoconazole) [49–51]. The effect of concomitantly administered drugs should be investigated in the future.

We also applied time-to-onset analysis to validate the results, which provided novel insights into the time-to-onset of GI hemorrhage, that is, over 30% of GI hemorrhage was observed after 30 days in the real-world data set.

We evaluated nervous system hemorrhage as intracranial hemorrhage. It has been reported that Asians are prone to intracranial hemorrhage [52]. For all DOACs, the reporting rates in JADER were higher than those in FAERS. Sex is likely to be a significant factor in DOAC therapy. The interaction terms with DOACs (apixaban, rivaroxaban, and dabigatran) and sex (female) were significant in the FAERS, but not in the JADER.

From the reports of early post-marketing phase vigilance in Japan, severe hemorrhagic ARs in first one month after the use of apixaban, rivaroxaban, and dabigatran were 56.0%, 85.2%, and 56.5%, respectively [53–55]. The time-to-onset profile showed that more than 50% of nervous system hemorrhage was observed after 30 days.

Asian patients tended to have lower body weight, lower proportions of prior myocardial infarction, vitamin K antagonist experiences, and concomitant use of gastric antacid drugs, and higher

proportion of impaired renal function, prior stroke, nonparoxysmal atrial fibrillation, and antiplatelet medication use [56–58]. The differences in safety and efficacy between Asian and Caucasians should be carefully evaluated in the future.

The analysis using SRS such as the FAERS and JADER databases has several notable limitations. The SRS is subject to over-reporting, under-reporting, missing data, exclusion of healthy individuals, lack of a denominator, and the presence of confounding factors [36]. However, reports in the SRS databases could also reflect real-life scenarios. The duration of surveillance period could have been increased to strengthen the data obtained in this study. This might be a future consideration. Nomura et al. reported that there were differences in the reported number of ARs between the FAERS and JADER; however, the number of shared reports between the FAERS and JADER is unknown [59]. It is improbable to evaluate the "true" risk of ARs without information concerning the total number of patients administered DOACs. In general, ROR cannot be used to infer the comparative strength of causality. However, it offers a rough indication of the signal strength that can be used to generate hypotheses to search for unknown potential ARs [60,61]. Patients using any one of the four DOACs (i.e., dabigatran, rivaroxaban, apixaban, and edoxaban) have different risk factors for hemorrhage, and failing to adjust would bias the results. Careful attention must be paid to the interpretation of results. We partially refined the results with a dedicated correction to detect possible confounders present in the database, using multiple logistic regression technique.

Conclusions

We have reviewed hemorrhagic adverse drug reactions from the SRS databases, real-world registries of patients receiving DOACs. The signals of hemorrhagic reactions such as GI hemorrhage and nervous system hemorrhage were observed in both the SRS databases. Despite the limitations inherent to SRS, we demonstrated that the association of GI hemorrhage induced by DOACs was affected by sex (female). To the best of our knowledge, no time-to-onset analysis of hemorrhagic ARs has been performed using the SRS databases. The aim of the time-to-onset analysis was to obtain new information and compare the risks and onset profiles of hemorrhagic ARs for prescription drugs in the real world. We recommend that female patients who experience symptoms related to GI hemorrhage should be closely monitored and advised to adhere to an appropriate care plan. Additionally, our results show that patients should be closely monitored for hemorrhage even after a month. Results of the present study offer practical considerations for the avoidance and management of GI hemorrhage associated with DOACs. These data will be potentially useful to clinicians for improving the management of ARs associated with DOACs.

Supplementary Material

Supplementary table.
http://www.medsci.org/v16p1295s1.pdf

Acknowledgements

Competing Interests

JA is an employee of Medical Database Co., Ltd. The other authors have no conflict of interest.

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