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ORIGINAL RESEARCH

Trend of Reported Bleeding in Warfarin Compared with Direct Oral Anticoagulants in Japan

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Background: Evidence on bleeding events associated with oral anticoagulants in real-world settings is limited. Thus, we compared the incidence rate of oral anticoagulant-associated bleeding between warfarin and direct oral anticoagulants (DOACs).

Methods: This is a retrospective observational study using the Japanese Adverse Drug Event Report Database (JADER) and the nationwide health insurance claims database. We investigated the number of case reports with "bleeding" or "hemorrhage" using the JADER. The drugs of interest included warfarin, dabigatran, edoxaban, rivaroxaban, or apixaban. Main outcome measures included the number of case reports of bleeding and the estimated annual incidence rate of oral anticoagulant-associated bleeding using the Japanese Adverse Drug Event Report (JADER) and the nationwide estimated number of patients with prescriptions.

Results: In JADER, we found 16,125 oral anticoagulant-associated bleeding in 15,970 case reports of patients between April 1, 2004, and March 31, 2024. The most common suspected oral anticoagulant administered to patients was apixaban (33.4%), followed by rivaroxaban (26.0%), warfarin (16.6%), edoxaban (13.3%), and dabigatran (10.7%). The incidence rates of anticoagulant-associated bleeding in patients who were prescribed dabigatran, edoxaban, rivaroxaban, and apixaban were higher compared to those in patients who were prescribed warfarin. The estimated annual incidence rate was remarkably high in patients who received apixaban, reaching 1976.90 per 1,000,000 patients.

Conclusion: Compared with warfarin, the incidence rates of oral anticoagulant-associated bleeding were higher with dabigatran, edoxaban, rivaroxaban, or apixaban. In a real-world setting in Japan, the risk of oral anticoagulant-associated bleeding appears to be higher with DOACs than with warfarin.

Keywords: oral anticoagulants, direct oral anticoagulants (DOACs), Japanese adverse drug event report (JADER), drug safety, bleeding

Introduction

A decade has passed since the direct oral anticoagulants (DOACs)-dabigatran (Prazaxa), edoxaban (Lixiana), rivaroxaban (Xarelto), and apixaban (Eliquis) became available on the market in Japan. DOACs are categorized into two classes: dabigatran is a direct thrombin inhibitor, while edoxaban, rivaroxaban, and apixaban are direct factor Xa inhibitors. Anticoagulation pharmacotherapy with DOACs has been widely used to prevent thrombosis in several cardiovascular contexts. Those drugs demonstrated superiority or noninferiority to prior standards of anticoagulation pharmacotherapy with vitamin K antagonists (warfarin) with similar or reduced bleeding risks in Phase III trials.[1–6] Although the efficacy and safety of DOACs have been demonstrated, those pivotal randomized clinical trials were powered to assess efficacy; thus, the sample sizes may not have been enough to detect safety signals. In addition, patients enrolled in those clinical trials had to meet strict inclusion criteria and may not reflect the general patient population seen in real-world clinical practice. In addition, most patients in those trials were non-Japanese, and reports on Japanese populations treated with DOACs remain limited.

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Since the evidence of the safety of newly approved drugs, especially, is often limited, post-marketing surveillance and pharmacovigilance studies are essential to assess the safety profile of drugs used in routine clinical practice. The Japanese Adverse Drug Event Report Database (JADER) is a spontaneous reporting system for drug adverse events managed by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan.[7] This database has been widely used for pharmacovigilance studies in Japan. A few studies have reported on the bleeding risks of DOACs using JADER;[8,9] however, to the best of our knowledge, no pharmacovigilance studies have compared the bleeding risks of DOACs and warfarin in Japan. Moreover, the incidence rate of bleeding events associated with those drugs in real-world settings remains uncertain.

In this study, we investigated the number of oral anticoagulant-associated bleeding reports in the JADER. We also calculated the estimated incidence rate of oral anticoagulant-associated bleeding using the nationwide health insurance claims database provided by JMDC Inc. (JMDC database).[10]

Methods

Study Design and Data Source

This was a retrospective observational cohort study using the JADER[7] and the JMDC databases.[10] The JADER database contains serious adverse events which have even been noticed in the package inserts. All adverse drug events recorded in the JADER are reported mainly by marketing authorization holders and healthcare institutions. The database consists of four files: patient background information (DEMO), drug information (DRUG), adverse reactions (REAC), and medical history (HIST).

The nationwide estimated number of patients was obtained from the JMDC database. This database includes patients' characteristics (age and sex), prescribed or dispensed medications, procedures, and diagnoses for 17 million insured Japanese people. It is the largest anonymized database of claims data in Japan, and it has been widely used for health economics, epidemiology, and outcomes research.

Definitions of Case Reports and Drugs of Interest

From the JADER, adverse event data recorded between fiscal year (FY) 2004 and FY2023 (fiscal year: from April 1 to March 31 of the following year) were obtained. Case reports with bleeding were identified using the preferred terms "bleeding" and "hemorrhage" according to MedDRA version 28.0J. The drugs of interest included warfarin, dabigatran, edoxaban, rivaroxaban, and apixaban (Table S1).

Data Analysis

All bleeding case reports associated with the suspected drugs between FY2004 and FY2023 were identified. The patient characteristics and the number of oral anticoagulant-associated bleeding reported to the JADER were presented in a descriptive manner. The overall number of patients receiving study drugs was estimated from the JMDC database between FY2011 and FY2023, and the incidence rate was calculated from the number of bleeding reports extracted from JADER. To estimate the number of patients prescribed the drugs of interest, we used government statistical data to calculate the estimated numbers, adjusted for age (one-year increments) and gender (male and female), based on prescription rates obtained from the JMDC database using the direct standardization method.[11] In the following formula, "N Japan male/female" means the number of males and females in Japan for each analysis year, "N jmdc male/female" means the number of males and females in the JMDC database for each analysis year, and "N' jmdc male/female" means the number of prescriptions per male and female in the JMDC database for each analysis year, and "i" means age. If there was any prescription record within the fiscal year, it counted as one, and each drug of interest counted separately. The rate of oral anticoagulant-associated bleeding incidences between patients who were prescribed warfarin and those who were prescribed dabigatran, edoxaban, rivaroxaban, or apixaban between FY2011 and FY2023 was compared. Since statistical power was not calculated and bleeding incidence was rare, we decided to present the data descriptively.

Nationwide estimated number of patients =

$$\left\{\sum_{i=x}^{n}\left(N'_{jmdcmalei}\times\frac{N_{japanmalei}}{N_{jmdcmalei}}\right)+\sum_{i=x}^{n}\left(N'_{jmdcfemalei}\times\frac{N_{japanfemalei}}{N_{jmdcfemalei}}\right)\right\}$$

Ethics Approval

Ethics approval was not applicable to this study based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labour and Welfare (MHLW), since only completely encrypted data were used.

Results

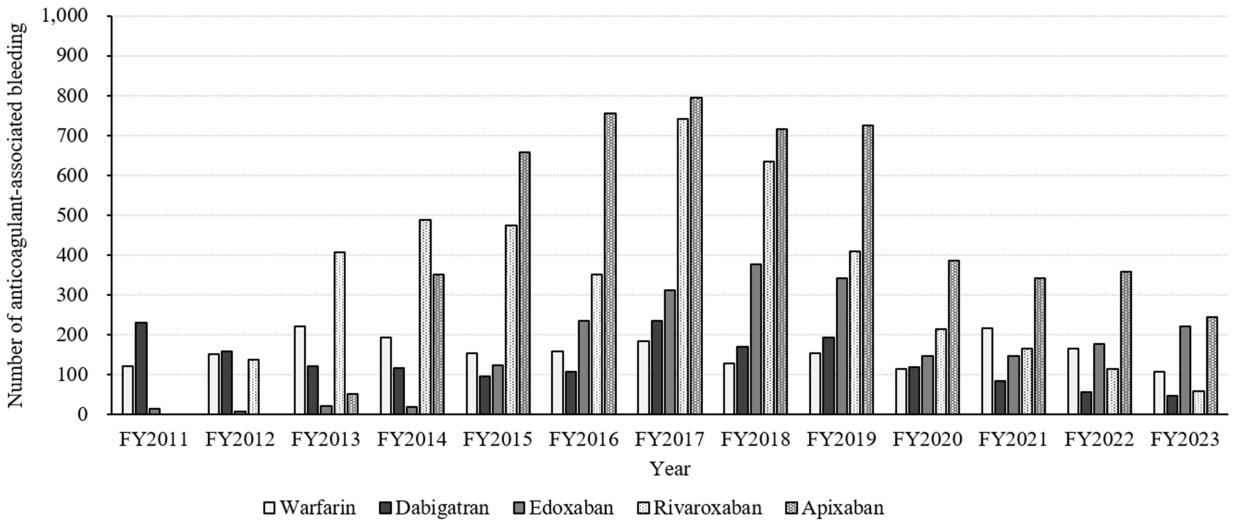
Between FY2004 and FY2023 (between April 1, 2004, and March 31, 2024), there were 903,869 case reports, of which we identified 50,276 with bleeding. Among them, we identified 16,125 oral anticoagulant-associated bleeding in 15,970 case reports. The characteristics of patients in those case reports are summarized in Table 1. More than half (54.3%) were male, and 69.5% was over 70 years old. The most common suspected oral anticoagulant was apixaban (33.4%), followed by rivaroxaban (26.0%), warfarin (16.6%), and edoxaban (13.3%).

The trend in the reported number of oral anticoagulant-associated bleeding between FY2011 and FY2023 is shown in Figure 1. The number of reported oral anticoagulant-associated bleeding for warfarin was within the 100–200 range

Table 1 Patient Characteristics of 15,970 Case Reports

	N=15,970	
Gender, n(%)		
Male	8,669	54.3%
Female	6,113	38.3%
Unknown	1,188	7.4%
Age group, n(%)		
<20	68	0.4%
20s	57	0.4%
30s	77	0.5%
40s	282	1.8%
50s	631	4.0%
60s	2,280	14.3%
70s	5,081	31.8%
80s	4,950	31.0%
90s	1,033	6.5%
100s	31	0.2%
Unknown	1,480	9.2%
Anticoagulants, n(%)		
Warfarin	2,675	16.6%
Dabigatran	1,724	10.7%
Edoxaban	2,144	13.3%
Rivaroxaban	4,195	26.0%
Apixaban	5,387	33.4%

Note: * Includes duplicates.



	FY2011	FY2012	FY2013	FY2014	FY2015	FY2016	FY2017	FY2018	FY2019	FY2020	FY2021	FY2022	FY2023
Warfarin	121	152	222	193	154	159	183	129	154	115	216	165	106
Dabigatran	230	158	120	116	95	106	234	171	192	118	83	55	46
Edoxaban	14	7	21	20	123	235	311	377	343	147	147	178	221
Rivaroxaban	-	137	407	488	475	351	741	634	409	215	165	114	59
Apixaban	-	-	52	351	659	756	796	715	726	385	343	359	245

Figure 1 Number of oral anticoagulant-associated bleeding between FY2011 and FY2023. Blanks (-) indicate no available data because these drugs were not yet available on the market.

throughout the period. On the other hand, the number of reported oral anticoagulant-associated bleeding for rivaroxaban and apixaban was high; both reached a peak of over 700 in FY2017. Overall, the number of reported oral anticoagulant-associated bleeding tended to decrease from FY2020.

The estimated number of patients prescribed oral anticoagulants, calculated from the JMDC database by gender and age group, is summarized in Table 2. In this table, data for FY2023, the latest available, are presented. The proportion of male patients who were prescribed oral anticoagulants tended to be higher than that of females, and the majority of patients were aged 70 years or older. The incidence rates of oral anticoagulant-associated bleeding in patients who were prescribed oral anticoagulants are summarized in Table 3. The incidence rates of anticoagulant-associated bleeding in patients who were prescribed dabigatran, edoxaban, rivaroxaban, and apixaban were higher compared to those in patients who were prescribed warfarin. The incidence rate of oral anticoagulant-associated bleeding in patients prescribed warfarin remained below 1000 per 1,000,000/year throughout the study period. In contrast, the incidence exceeded this threshold for dabigatran, edoxaban, rivaroxaban, and apixaban in several fiscal years.

Table 2 Number of Estimated Patients Prescribed Oral Anticoagulants Calculated Using the JMDC Database in FY2023

	Total		**Warfarin**		**Dabigatran**		**Edoxaban**		**Rivaroxaban**		**Apixaban**	
Number of patients n (%)	1,790,468	(100)	279,280	(15.6)	95,990	(5.4)	735,425	(41.1)	354,110	(19.8)	325,663	(18.2)
Gender, n (%)												
Male	1,141,567	(63.8)	189,783	(68.0)	72,870	(75.9)	415,385	(56.5)	255,741	(72.2)	207,788	(63.8)
Female	648,901	(36.2)	89,497	(32.0)	23,120	(24.1)	320,040	(43.5)	98,369	(27.8)	117,875	(36.2)

(*Continued*)

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Table 2 (Continued).

	Total		Warfarin		Dabigatran		Edoxaban		Rivaroxaban		Apixaban	
Age group, n (%)												
<20 years	7,417	(0.4)	6,338	(2.3)	20	(<0.1)	354	(<0.1)	559	(0.2)	146	(<0.1)
20s	7,073	(0.4)	3,609	(1.3)	131	(0.1)	1,806	(0.2)	748	(0.2)	779	(0.2)
30s	14,381	(0.8)	6,115	(2.2)	362	(0.4)	4,325	(0.6)	1,913	(0.5)	1,666	(0.5)
40s	45,306	(2.5)	13,647	(4.9)	2,240	(2.3)	15,751	(2.1)	7,056	(2.0)	6,612	(2.0)
50s	146,161	(8.2)	30,826	(11.0)	8,390	(8.7)	57,119	(7.8)	26,584	(7.5)	23,242	(7.1)
60s	350,767	(19.6)	55,053	(19.7)	20,698	(21.6)	147,326	(20.0)	67,713	(19.1)	59,977	(18.4)
>70 years	1,219,363	(68.1)	163,692	(58.6)	64,149	(66.8)	508,744	(69.2)	249,537	(70.5)	233,241	(71.6)

Note: FY, fiscal year (the Japanese fiscal year is from April 1 to March 31 of the following year).

Discussion

We conducted a retrospective observational study using the JADER and JMDC databases to investigate the number of oral anticoagulant-associated bleeding reports and their annual incidence rate. Our study showed that oral anticoagulants were mainly prescribed to patients aged 70 years or older, and the risk of oral anticoagulant-associated bleeding was higher in those prescribed dabigatran, edoxaban, rivaroxaban, or apixaban than in those prescribed warfarin.

Oral anticoagulant-associated bleeding was more commonly reported in elderly patients (those aged 70 years or older) in our study (78.7%). Our study also showed that the majority of patients prescribed DOACs were elderly, ranging from 66.8% to 71.6% of the total (based on FY2023 data); in contrast, the proportion of elderly patients prescribed warfarin was only 58.6% (based on FY2023 data). These findings confirm several studies showing that anticoagulation pharmacotherapy increases the bleeding risk in elderly patients.[12–17] The Japanese local clinical guidelines also mention that age over 75 years is one of the factors associated with significant bleeding during anticoagulation therapy.[18] However, anticoagulation pharmacotherapy using DOACs in the elderly population is less extensively studied, and the clinical impact of anticoagulation-related bleeding in elderly patients remains uncertain. Thus, the risk of bleeding, particularly in the elderly population treated with DOACs, needs further investigation.

Although package inserts of DOACs precaution against the risk of bleeding,[19–22] a number of serious bleeding events have been reported in the JADER. In our study, bleeding risk was higher in those who were prescribed DOACs compared to those who were prescribed warfarin. Compared to the Western population, the bleeding risk in the East Asian population treated with anticoagulation pharmacotherapy has been reported to be higher.[23–26] Moreover, the pharmacokinetic profiles of some DOACs differ in the Japanese population compared to those in Western populations.[27,28] Therefore, the risk of bleeding, specifically in the Japanese population treated with DOACs, should be more carefully determined.

Previous real-world studies conducted outside Japan have consistently shown that DOACs are associated with a lower or comparable risk of bleeding compared with warfarin. In a large observational study conducted in the United States, apixaban and dabigatran were associated with a lower risk of major bleeding compared with warfarin.[29] Furthermore, a large cohort study involving approximately 200,000 patients in the United Kingdom also reported that apixaban was associated with a significantly lower risk of major bleeding compared with warfarin in clinical practice.[30] Similar findings have been reported in Asian populations. A meta-analysis of studies involving Asian patients with atrial fibrillation demonstrated that DOAC therapy was associated with a lower risk of major bleeding compared with warfarin.[31] Furthermore, a cohort study using electronic health records and claims data from 372 acute care hospitals in Japan showed that DOACs were associated with a lower risk of major bleeding compared with warfarin.[32] In contrast to these findings, our analysis using the JADER database showed that the frequency of reported serious bleeding events tended to be higher with DOACs than with warfarin. This apparent discrepancy may be explained by the inherent

Table 3 Incidence Rates of Oral Anticoagulant-Associated Bleeding in Patients Who Were Prescribed Oral Anticoagulants

		FY2011	FY2012	FY2013	FY2014	FY2015	FY2016	FY2017	FY2018	FY2019	FY2020	FY2021	FY2022	FY2023
Warfarin	Oral anticoagulant-associated bleeding	121	152	222	193	154	159	183	129	154	115	216	165	106
	Number of patients*	1,818,436	1,703,219	1,510,551	1,357,269	1,205,278	934,703	800,805	696,361	581,099	476,747	435,606	342,686	279,280
	Incidence rate per 1,000,000	66.54	89.24	146.97	142.20	127.77	170.11	228.52	185.25	265.02	241.22	495.86	481.49	379.55
Dabigatran	Oral anticoagulant-associated bleeding	230	158	120	116	95	106	234	171	192	118	83	55	46
	Number of patients*	182,189	368,965	372,348	320,471	271,775	206,536	194,358	191,369	182,064	149,412	146,274	124,904	95,990
	Incidence rate per 1,000,000	1,262.43	428.22	322.28	361.97	349.55	513.23	1,203.96	893.56	1,054.57	789.76	567.43	440.34	479.22
Edoxaban	Oral anticoagulant-associated bleeding	14	7	21	20	123	235	311	377	343	147	147	178	221
	Number of patients*	13,588	55,277	51,074	94,370	211,349	334,851	469,579	595,526	649,268	678,600	794,970	765,547	735,425
	Incidence rate per 1,000,000	1,030.32	126.63	411.17	211.93	581.98	701.80	662.30	633.05	528.29	216.62	184.91	232.51	300.51
Rivaroxaban	Oral anticoagulant-associated bleeding	-	137	407	488	475	351	741	634	409	215	165	114	59
	Number of patients*	-	31,424	275,116	382,659	473,654	482,858	501,273	503,509	488,764	453,096	457,153	406,516	354,110
	Incidence rate per 1,000,000	-	4,359.73	1,479.38	1,275.29	1,002.84	726.92	1,478.24	1,259.16	836.80	474.51	360.93	280.43	166.61
Apixaban	Oral anticoagulant-associated bleeding	-	-	52	351	659	756	796	715	726	385	343	359	245
	Number of patients*	-	-	401,75	230,743	363,062	386,668	402,650	413,095	407,381	394,563	418,861	374,850	325,663
	Incidence rate per 1,000,000	-	-	1,294.34	1,521.17	1,815.12	1,955.17	1,976.90	1,730.84	1,782.12	975.76	818.89	957.72	752.31

Notes: *Number of estimated patients calculated using the JMDC database. Blanks (-) indicate no available data because these drugs were not yet available on the market. FY, fiscal year (the Japanese fiscal year is from April 1 to March 31 of the following year).

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limitations of spontaneous reporting systems, including reporting bias,[33,34] whereby adverse events associated with newly marketed drugs may be reported more frequently, whereas well-known adverse events related to long-established drugs may be underreported. Therefore, the low frequency of reported bleeding events with warfarin in JADER may not reflect the actual bleeding risk and should be interpreted in conjunction with findings from other studies.

The majority of oral anticoagulant-associated bleeding was reported between FY2015 and FY2019, while far fewer cases were reported between FY2020 and FY2023. A decrease in the oral anticoagulant-associated bleeding events in FY2020 and thereafter might be due to the COVID-19 pandemic. MHLW reports that the average daily outpatient visits fell dramatically in 2020 and then did not recover to pre-COVID-19 pandemic levels even in 2023.[35]

Limitations

Our study had several limitations. Underreporting, overreporting, and data entry errors can occur in any spontaneous adverse event reporting system, including the JADER. To interpret our study results using the JADER, reporting and notoriety bias should be taken into account. Regarding the JMDC database, it primarily includes health insurance data for employees of large companies. Also, the proportion of the elderly aged 65 years and older included in the database is significantly lower than in the Japanese population. Thus, caution is needed when generalizing our findings from the JMDC database. Although our study had such limitations, showing differences in oral anticoagulant-associated bleeding risks among drugs and their incidence rates among Japanese patients receiving oral anticoagulants in real-world settings is informative.

Future Directions

Further studies with more inclusive datasets would be warranted for a better understanding of oral anticoagulant-associated bleeding risks.

Conclusions

Our study demonstrated that oral anticoagulant-associated bleeding was more commonly reported in elderly patients aged 70 years or older. Moreover, the risk of oral anticoagulant-associated bleeding might be higher with DOACs than with warfarin in the real-world setting in Japan. Further assessment would be warranted to understand the risk-benefit of DOACs.

Data Sharing Statement

The datasets generated for this manuscript are available in the JADER database (https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0004.html).

Ethics Statement

Ethics approval was not applicable to this study, and informed consent was not required based on the Ethical Guidelines for Medical and Biological Research Involving Human Subjects issued by the MHLW, since only completely anonymized data were used.

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Akina Takami and Ataru Igarashi are members of the Department of Health Policy and Public Health. Gen Terashima and Takumi Tajima are employees of JMDC, Inc. Koki Yamashita is the president of Maxwell International, Inc.,

wherein he provides medical writing and clinical study consultation services to academic, pharmaceutical, biotechnology, and medical device entities. Ataru Igarashi reports receiving remuneration from AstraZeneca K.K., Eisai Co., Ltd., Daiichi Sankyo Co., Ltd., Takeda Pharmaceuticals, and Mitsubishi Tanabe Pharma Co. He also reports grants and/or personal fees from Bayer Yakuhin, Ltd., Nippon Boehringer Ingelheim Co., Ltd., Pfizer Japan Inc., Moderna Inc., GlaxoSmithKline K.K., Eli Lilly Japan K.K., and illumina Inc., outside the submitted work. The authors report no other conflicts of interest in this work.

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