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Research Paper

Evaluation of Dabigatran- and Warfarin-Associated Hemorrhagic Events Using the FDA-Adverse Event Reporting System Database Stratified by Age

Junko ABE[1,2], Ryogo UMETSU[1], Yamato KATO[1], Natsumi UEDA[1], Yoko NAKAYAMA[1], Yukiya SUZUKI[1], Toshiyuki SUZUKI[1], Hideko NAGASAWA[3], Yasutomi KINOSADA[4], Mitsuhiro NAKAMURA[1] ✉

1. Laboratory of Drug Informatics, Gifu Pharmaceutical University
2. Medical Database Co., LTD
3. Laboratory of Pharmaceutical and Medical Chemistry, Gifu Pharmaceutical University
4. Department of Biomedical Informatics, Gifu University Graduate School of Medicine, JAPAN

✉ Corresponding author: Mitsuhiro Nakamura, Laboratory of Drug Informatics, Gifu Pharmaceutical University, 1-25-4, Daigaku-Nishi, Gifu, 501-1196, JAPAN, Tel: +81-58-230-8100, Fax: +81-58-230-8105, E-mail: mnakamura@gifu-pu.ac.jp

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Abstract

Dabigatran and warfarin are oral anticoagulant drugs widely used for the prevention of stroke in patients with atrial fibrillation. The objective of this study was to evaluate the interaction between aging and dabigatran- and warfarin-induced gastrointestinal (GI) and nervous system hemorrhage using data available in the FDA Adverse Event Reporting System (FAERS) database.

We analyzed reports of hemorrhagic events in the GI and nervous system recorded in the FAERS database between 2004 and 2014 using an adjusted reporting odds ratio (ROR).

We demonstrated that dabigatran-associated GI hemorrhage was significantly increased in patients over the age of 80 years. The RORs of dabigatran increased with increasing age, although aging had little effect on warfarin-associated GI hemorrhage. The ROR for anticoagulant-associated nervous system hemorrhage was not significantly affected by aging, as compared to GI hemorrhage.

Our results indicate that the excretion of dabigatran may be affected by aging, as compared to warfarin, likely due to renal function decline. Our results emphasize the need for physicians to closely monitor GI bleeding in aging patients, because it is closely related to renal function deterioration.

Key words: dabigatran, warfarin, hemorrhagic events, adverse event reporting system

Introduction

Dabigatran is a new oral anticoagulant drug used widely for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation [1]. The Food and Drug Administration (FDA) approved dabigatran based on the results the phase III, prospective, randomized, open-label multi-national Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) clinical trial [2]. In the RE-LY trial, the rate of stroke and systemic embolism was similar between dabigatran and warfarin [2]. Major bleeding was significantly reduced with dabigatran (110 mg), as compared to warfarin, whereas 150 mg showed an effect similar to warfarin. Furthermore, dabigatran was associated with lower rates of major bleeding and intracranial bleeding than warfarin treatment [2].

Dabigatran is primarily excreted unmetabolized by the kidneys [3]. It was reported that dabigatran concentrations increase approximately two- to three-fold in patients with moderate renal impair-

ment, as compared to patients with normal renal function [4]. Indeed, gastrointestinal (GI) bleeding was increased with 150 mg dabigatran, but not 110 mg dabigatran [2]. Thus, higher blood concentrations of dabigatran may increase the risk of GI bleeding [5].

The effects of dabigatran on GI bleeding are of interest in older patients, because atrial fibrillation is largely a disease of the elderly, and the risk of stroke and bleeding increases with advanced age. In the RE-LY trial, Eikelboom *et al.* reported that, in patients older than 75, the risk of intracranial bleeding was lower, but the risk of extra-cranial bleeding was similar or higher with both doses (150 mg and 110 mg) of dabigatran, as compared to warfarin [5]. Because ischemic strokes and systemic embolisms have greater clinical significance than nonfatal bleeding, such as GI bleeding, higher doses of dabigatran are more favorable in elderly patients [2]. However, acute and chronic GI bleeding has a negative effect on a patient's quality of life.

The FDA Adverse Event Reporting System (FAERS) database, a spontaneous reporting system, is the primary tool used for pharmacovigilance. The FAERS is a rich resource, and data mining indices provide a powerful means to identify potential associations between drugs and adverse events. Dabigatran is a direct oral thrombin inhibitor, and is administered in a fixed dose, without laboratory monitoring [6]. Initially, it was expected to be an alternative therapy to warfarin; however, reports of serious and fatal bleeding events associated with dabigatran use increased in the FAERS database after approval [7]. Thus, the effects of dabigatran use on internal bleeding remain unclear. In the RE-LY study, patients with severe renal impairment were excluded [2, 6]. In contrast, the FAERS database contains information on patients with varying renal function, ranging from normal to severe dysfunction. Thus, evaluation of GI bleeding events using the FAERS database is valuable, because it reflects the realities of clinical practice.

Recently, data mining algorithms have been developed for use in spontaneous adverse event reporting databases, such as the FAERS database, to identify drug-associated adverse events by disproportionality analysis [8, 9]. The crude reporting odds ratio (ROR) is used by the Pharmaceuticals and Medical Devices Agency in Japan and the Netherlands Pharmacovigilance Center [10]. The crude ROR is an applicable technique that allows for adjustments through logistic regression analyses and control of covariates [11]. We hypothesized that it may be possible to adjust for the above-mentioned reporting bias using this approach.

The effects of aging on dabigatran- and warfarin-induced bleeding have not yet assessed using RORs adjusted by logistic regression analyses. The purpose of this study was to evaluate the relationship between aging and dabigatran-associated hemorrhage, and to compare the data with that obtained from warfarin using the FAERS database.

Methods

Data sources

The FAERS database, which covered the period from January 2004 to March 2014, was obtained from the FDA website (www.fda.gov). The FAERS structure complies with the international safety reporting guidelines, ICH E2B. The adverse events are coded according to the terminology preferred by the Medical Dictionary for Regulatory Activities (MedDRA) [12].

The drugs selected for this investigation were dabigatran and warfarin. The FAERS database permits contributors to register drugs under any name, including a trade name and an abbreviation. The DrugBank database contains drug information used globally, including 1,447 FDA-approved small molecule drugs [13], and was utilized as a dictionary for the batch conversion and compilation of drug names. For duplicate entries, we followed the FDA's recommendation as described on the FAERS website, to adopt the most recent case number to identify duplicate reports from the same patient and excluded them from the analysis.

Definition of hemorrhage events

This study relied on definitions provided by MedDRA version 17.1. To evaluate dabigatran- and warfarin-associated hemorrhagic events in the GI system, we utilized the Standardized MedDRA Query (SMQ) for *hemorrhages events* (SMQ code: 20000038) and the System Organ Class (SOC) for *gastrointestinal disorder*, and selectively extracted reports that met both criteria. The number of selected preferred terms for *hemorrhages*, limited by the SOC (*gastrointestinal disorder*), was 71. Furthermore, to evaluate dabigatran- and warfarin-associated hemorrhagic events in the nervous system, such as intracranial hemorrhage, we utilized 35 preferred terms that matched the SMQ for *hemorrhages events* (SMQ code: 20000038) and the SOC (*nervous system disorder*).

Analysis

Using established pharmacovigilance indices, we evaluated the reporting odds ratio (ROR) to establish the effects of dabigatran and warfarin on "hemorrhagic events." "Cases" were defined as patients who reported "hemorrhagic events," while "non-cases" consisted of patients associated with all other reports. The reporting odds ratio (ROR) is the

ratio of the odds of reporting adverse events versus all other events associated with dabigatran or warfarin compared to 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). RORs were expressed as point estimates with a 95% confidence interval (CI). To evaluate the effect of age on "hemorrhagic events," the reports were stratified into age groups: 0–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, and greater than 90.

For signal detection, general qualitative judgments were used. The detection of a signal was dependent on the signal indices exceeding a predefined threshold. ROR values < 1 indicated no exposure-event association, and estimates > 1 indicated exposure-event safety signals. Safety signals are considered significant when the ROR estimates and the lower limits of the corresponding 95% CI are ≥ 2. [10]

We refined the signal with a dedicated correction to detect possible confounders present in the database using logistic regression analysis. After adjusting for gender, reporting year, and stratified age groups, the RORs were calculated using logistic regression analysis. To construct the logistic model, the drugs and stratified age groups were coded. The following logistic model was used for analysis:

$$\text{Log (odds)} = \beta_0 + \beta_1 G + \beta_2 Y + \beta_3 D + \beta_4 A + \beta_5 D^{*} A \quad \ldots(1)$$

(G = gender, Y = reporting year, D = drug (dabigatran or warfarin), and A = stratified age group)

The adjusted RORs were calculated using the 40–49 year old group as a reference group. This model can be compared with a model in which no interaction term is present. A likelihood ratio test can be used to evaluate the effect of adding this term. Because the difference in -2 log likelihood follows a chi-square distribution with one degree of freedom after adding the interaction term, a probability (p) value of 0.05 or less was considered statistically significant. Data analyses were performed using JMP, version 11.0 (SAS Institute Inc., Cary, NC, USA).

Results

The FAERS database contains 5,597,297 reports from the first quarter of 2004 through the end of the first quarter of 2014. After excluding duplicates according to the FDA recommendation and extracting reports that contained the age and the gender of the patients, 2,143,443 reports were analyzed. The RORs of dabigatran and warfarin are summarized in Table 2. The RORs (95% CI) of hemorrhage associated with dabigatran, limited by the SOC (GI disorders), in patients age 40–49, 70–79, 80–89, and ≥ 90 were 4.88 (3.26–7.31), 13.55 (12.79–14.35), 19.34 (18.30–20.44), and 26.18 (23.05–29.74), respectively. The RORs for gastrointestinal hemorrhage increased with advancing age after dabigatran treatment (Figure 1). The RORs (95% CI) of hemorrhage associated with warfarin, limited by the SOC (GI disorders), in patients age 40–49, 70–79, 80–89, and ≥ 90 were 2.95 (2.55–3.41), 4.74 (4.46–5.03), 5.80 (5.42–6.20), and 5.39 (4.42–6.57), respectively. The ROR signal for GI hemorrhage in elderly patients treated with dabigatran was higher than in patients treated with warfarin.

The RORs (95% CI) of hemorrhage associated with dabigatran, limited by the SOC (nervous system disorders), in patients age 40–49, 70–79, 80–89, and ≥ 90 were 3.54 (1.46–8.57), 9.57 (8.54–10.72), 10.44 (9.31–11.71), and 10.11 (7.63–13.40), respectively (Table 3). The RORs (95% CI) of hemorrhage associated with warfarin, limited by the SOC (nervous system disorders), in patients age 40–49, 70–79, 80–89, and ≥ 90 were 2.79 (2.09–3.72), 4.92 (4.40–5.50), 6.58 (5.85–7.41), and 6.14 (4.34–8.69), respectively. The RORs for nervous system hemorrhage had no significant correlation with age.

Table 1. Characteristics of cases and non-cases, hemorrhage events (SMQ20000038) limited by SOC for gastrointestinal disorder and nervous system disorder

	Case	(%)	Non-Case	(%)	Total	Reporting Odds Ratio (95%CI)
Gastrointestinal disorder						
Total	43,758		2,099,685			
Gender Male	21325	(48.7)	795968	(37.9)	817293	1.56 (1.53 - 1.59)
Dabigatran	4541	(10.4)	15186	(0.7)	19727	15.89 (15.41 - 16.45)
Warfarin	4035	(9.2)	43596	(2.1)	47631	4.73 (4.64 - 4.95)
Mean age	60.8		53			
Nervous system disorder						
Total	10,868		2,132,575			
Gender Male	5479	(50.4)	811814	(38.1)	817293	1.65 (1.59 - 1.71)
Dabigatran	888	(8.2)	18839	(0.9)	19727	9.98 (9.30 - 10.70)
Warfarin	1098	(10.1)	46535	(2.2)	47631	5.04 (4.73 - 5.37)
Mean age	61.7		53.1			

Table 2. Characteristics of cases and non-cases, dabigatran or warfarin associated with hemorrhage events (SMQ20000038) limited by SOC for gastrointestinal disorder

Drug name	Age (year)	Total (n)	Cases (n)	Non-cases (n)	Rate (%)	Reporting odds Ratio (95%CI)
Dabigatran						
Reference						
	0-29	291711	4274	287437	9.77	0.76 (0.74 - 0.78)
	30-39	216892	2525	214367	5.77	0.60 (0.58 - 0.62)
	40-49	313483	3980	309503	9.10	0.65 (0.63 - 0.67)
	50-59	437570	6594	430976	15.07	0.78 (0.76 - 0.80)
	60-69	418434	8319	410115	19.01	1.10 (1.07 - 1.13)
	70-79	286535	7844	278691	17.93	1.62 (1.58 - 1.66)
	80-89	139953	4928	135025	11.26	2.07 (2.01 - 2.13)
	≥ 90	19138	753	18385	1.72	2.20 (2.04 - 2.37)
Dabigatran administration						
	0-29	104	24	80	0.05	14.40 (9.12 - 22.73)
	30-39	76	8	68	0.02	5.65 (2.72 - 11.76)
	40-49	282	26	256	0.06	4.88 (3.26 - 7.31)
	50-59	1148	167	981	0.38	8.20 (6.96 - 9.66)
	60-69	3620	649	2971	1.48	10.62 (9.75 - 11.57)
	70-79	7059	1515	5544	3.46	13.55 (12.79 - 14.35)
	80-89	6393	1785	4608	4.08	19.34 (18.30 - 20.44)
	≥ 90	1045	367	678	0.84	26.18 (23.05 - 29.74)
Warfarin						
Reference						
	0-29	290568	4243	286325	9.70	0.74 (0.72 - 0.76)
	30-39	215267	2450	212817	5.60	0.57 (0.55 - 0.59)
	40-49	310402	3812	306590	8.71	0.61 (0.59 - 0.63)
	50-59	432272	6324	425948	14.45	0.72 (0.70 - 0.74)
	60-69	411028	7981	403047	18.24	1.03 (1.00 - 1.06)
	70-79	280036	8165	271871	18.66	1.70 (1.66 - 1.74)
	80-89	137147	5738	131409	13.11	2.47 (2.40 - 2.54)
	≥ 90	19092	1010	18082	2.31	2.94 (2.76 - 3.13)
Warfarin administration						
	0-29	1247	55	1192	0.13	2.22 (1.69 - 2.91)
	30-39	1701	83	1618	0.19	2.46 (1.97 - 3.07)
	40-49	3363	194	3169	0.44	2.95 (2.55 - 3.41)
	50-59	6446	437	6009	1.00	3.51 (3.18 - 3.87)
	60-69	11026	987	10039	2.26	4.80 (4.49 - 5.13)
	70-79	13558	1194	12364	2.73	4.74 (4.46 - 5.03)
	80-89	9199	975	8224	2.23	5.80 (5.42 - 6.20)
	≥ 90	1091	110	981	0.25	5.39 (4.42 - 6.57)

Table 3. Characteristics of cases and non-cases, dabigatran or warfarin associated hemorrhage events (SMQ20000038) limited by SOC for nervous system disorder

Drug name	Age (year)	Total (n)	Cases (n)	Non-cases (n)	Rate (%)	Reporting odds Ratio (95%CI)
Dabigatran						
Reference						
	0-29	291711	904	290807	8.32	0.62 (0.58 - 0.66)
	30-39	216892	562	216330	5.17	0.52 (0.48 - 0.57)
	40-49	313483	938	312545	8.63	0.60 (0.56 - 0.64)
	50-59	437570	1587	435983	14.60	0.73 (0.69 - 0.77)
	60-69	418434	2180	416254	20.06	1.14 (1.09 - 1.20)
	70-79	286535	2164	284371	19.91	1.78 (1.70 - 1.87)
	80-89	139953	1469	138484	13.52	2.46 (2.33 - 2.60)
	≥ 90	19138	176	18962	1.62	1.98 (1.70 - 2.30)
Dabigatran administration						
	0-29	104	5	99	0.05	9.91 (4.03 - 24.34)
	30-39	76	4	72	0.04	10.91 (3.99 - 29.87)
	40-49	282	5	277	0.05	3.54 (1.46 - 8.57)
	50-59	1148	44	1104	0.40	7.85 (5.80 - 10.62)
	60-69	3620	144	3476	1.32	8.22 (6.95 - 9.72)
	70-79	7059	320	6739	2.94	9.57 (8.54 - 10.72)
	80-89	6393	315	6078	2.90	10.44 (9.31 - 11.71)
	≥ 90	1045	51	994	0.47	10.11 (7.63 - 13.40)
Warfarin						

Drug name	Age (year)	Total (n)	Cases (n)	Non-cases (n)	Rate (%)	Reporting odds Ratio (95%CI)			
Reference									
	0-29	290568	887	289681	8.16	0.62	(0.58	- 0.66	)
	30-39	215267	541	214726	4.98	0.51	(0.47	- 0.56	)
	40-49	310402	896	309506	8.24	0.58	(0.54	- 0.62	)
	50-59	432272	1495	430777	13.76	0.69	(0.65	- 0.73	)
	60-69	411028	2105	408923	19.37	1.13	(1.08	- 1.19	)
	70-79	280036	2160	277876	19.87	1.85	(1.76	- 1.94	)
	80-89	137147	1492	135655	13.73	2.59	(2.45	- 2.74	)
	≥ 90	19092	194	18898	1.79	2.22	(1.92	- 2.56	)
Warfarin administration									
	0-29	1247	22	1225	0.20	3.53	(2.31	- 5.38	)
	30-39	1701	25	1676	0.23	2.93	(1.97	- 4.35	)
	40-49	3363	47	3316	0.43	2.79	(2.09	- 3.72	)
	50-59	6446	136	6310	1.25	4.27	(3.60	- 5.07	)
	60-69	11026	219	10807	2.02	4.04	(3.53	- 4.62	)
	70-79	13558	324	13234	2.98	4.92	(4.40	- 5.50	)
	80-89	9199	292	8907	2.69	6.58	(5.85	- 7.41	)
	≥ 90	1091	33	1058	0.30	6.14	(4.34	- 8.69	)

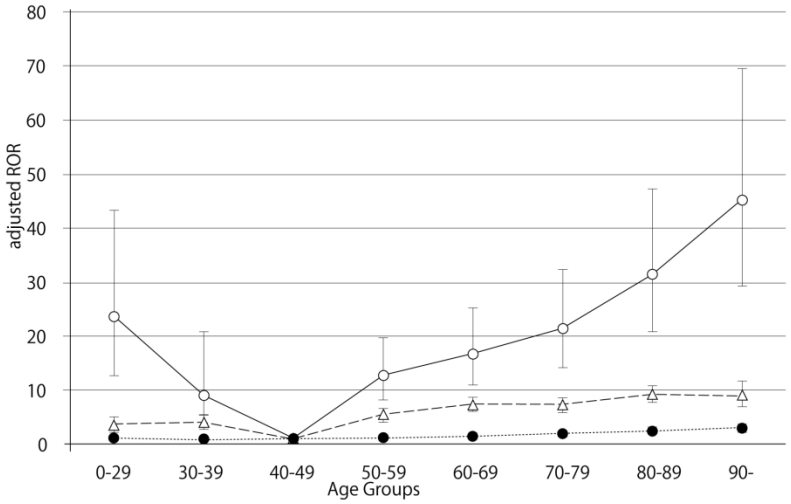

Figure 1: Adjusted reporting odds ratios and 95% confidence intervals for dabigatran- and warfarin- associated hemorrhagic events, limited by gastro-intestinal disorders. Open circles, dabigatran; triangles, warfarin; filled circles, control.

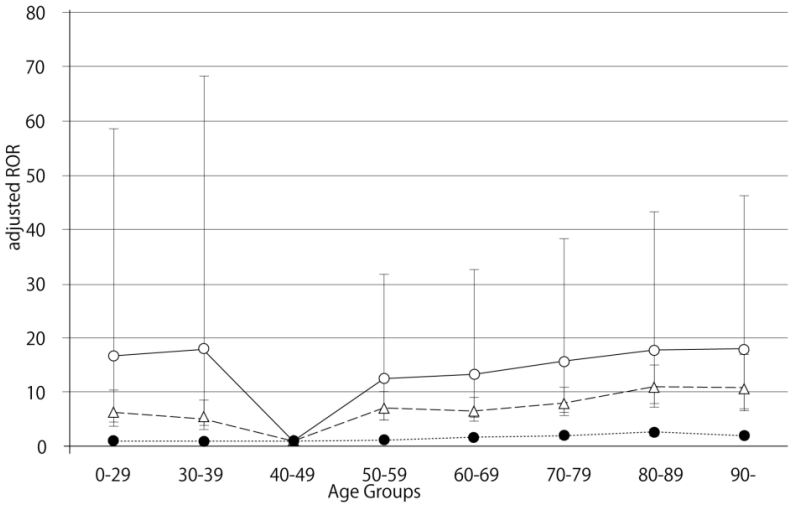

Figure 2: Adjusted reporting odds ratios and 95% confidence intervals, for dabigatran- and warfarin-associated hemorrhagic events, limited by nervous system disorders. Open circles, dabigatran; triangles, warfarin; filled circles, control.

The number of GI hemorrhage cases and crude RORs (95% CI) are summarized in Table 4. The crude RORs (95% CI) for GI hemorrhage in dabigatran-treated patients aged 80–89 and ≥ 90 were 10.61 (9.98–11.28) and 13.22 (11.42–15.30), respectively. The likelihood ratio test of the interaction terms dabigatran*60–69, dabigatran*80–89 and dabigatran*≥ 90 were statistically significant (Table 6). The adjusted RORs for dabigatran*60-69, dabigatran*80-89, and dabigatran*≥ 90, were 16.66 (95% CI, 11.01–25.23), 31.36 (95% CI, 20.81–47.26), and 45.14 (95% CI, 29.30–69.53), respectively. In contrast, the crude RORs (95% CI) for warfarin did not increase with advancing age (Table 5). The likelihood ratio test of the interaction term warfarin*70–79, warfarin*80–89, and warfarin*≥ 90 were statistically significant (Table 6). The adjusted RORs for warfarin*70-79, warfarin*80-89, and warfarin*≥ 90, were 7.33 (95% CI, 6.23-8.62), 9.21 (95% CI, 7.80–10.87), and 9.02 (95% CI, 6.96–11.69).

The crude ROR for dabigatran- and warfarin-associated nervous system hemorrhage did not increase with advancing age. Further, the likelihood ratio test of the interaction term was not statistically significant (Table 6).

Discussion

Bleeding is the most common complication associated with the use of anticoagulant drugs. We examined the association between hemorrhagic events in the GI and nervous system and anticoagulant drugs (dabigatran and warfarin) after stratification by age. In this study, we demonstrated that dabigatran-associated GI hemorrhage was significantly increased in patients over the age of 80 (Table 6). Evaluation of GI hemorrhage revealed that the adjusted RORs of dabigatran increased with advancing age, whereas aging had little effect on warfarin (Table 6 and Figure 1). The adjusted ROR for dabigatran-associated GI hemorrhage was higher than the adjusted ROR of warfarin. Our study supports the results of the RE-LY trials and the safety announcements issued by regulating authorities. In contrast, the RORs of dabigatran- and warfarin-associated nervous system hemorrhage were less affected by aging (Figure 2, Table 6). Since dabigatran is primarily excreted by the kidney and warfarin is metabolized in the liver by cytochrome P450 [14], the effect of dabigatran on GI hemorrhage may be affected by changes in kidney function due to aging.

Table 4. Stratified analysis of gastrointestinal hemorrhage

			Cases	Non-cases	Total	Crude ROR (95% CI)
Dabigatran						
	0-29 y.o.	Drug -	4274	287437	291711	
		Drug +	24	80	104	20.18 (12.78 - 31.88)
		Total	4298	287517	291815	
	30-39 y.o.	Drug -	2525	214367	216892	
		Drug +	8	68	76	9.99 (4.80 - 20.81)
		Total	2533	214435	216968	
	40-49 y.o.	Drug -	3980	309503	313483	
		Drug +	26	256	282	7.90 (5.27 - 11.84)
		Total	4006	309759	313765	
	50-59 y.o.	Drug -	6594	430976	437570	
		Drug +	167	981	1148	11.13 (9.43 - 13.14)
		Total	6761	431957	438718	
	60-69 y.o.	Drug -	8319	410115	418434	
		Drug +	649	2971	3620	10.77 (9.87 - 11.76)
		Total	8968	413086	422054	
	70-79 y.o.	Drug -	7844	278691	286535	
		Drug +	1515	5544	7059	9.71 (9.13 - 10.32)
		Total	9359	284235	293594	
	80-89 y.o.	Drug -	4928	135025	139953	
		Drug +	1785	4608	6393	10.61 (9.98 - 11.28)
		Total	6713	139633	146346	
	≥ 90 y.o.	Drug -	753	18385	19138	
		Drug +	367	678	1045	13.22 (11.42 - 15.30)
		Total	1120	19063	20183	
Warfarin						
	0-29 y.o.	Drug -	4243	286325	290568	
		Drug +	55	1192	1247	3.11 (2.37 - 4.08)

		Total	4298	287517	291815					
	30-39 y.o.	Drug -	2450	212817	215267					
		Drug +	83	1618	1701	4.46	(	3.56	-	5.58)
		Total	2533	214435	216968					
	40-49 y.o.	Drug -	3812	306590	310402					
		Drug +	194	3169	3363	4.92	(	4.24	-	5.71)
		Total	4006	309759	313765					
	50-59 y.o.	Drug -	6324	425948	432272					
		Drug +	437	6009	6446	4.90	(	4.43	-	5.42)
		Total	6761	431957	438718					
	60-69 y.o.	Drug -	7981	403047	411028					
		Drug +	987	10039	11026	4.97	(	4.64	-	5.33)
		Total	8968	413086	422054					
	70-79 y.o.	Drug -	8165	271871	280036					
		Drug +	1194	12364	13558	3.22	(	3.02	-	3.43)
		Total	9359	284235	293594					
	80-89 y.o.	Drug -	5738	131409	137147					
		Drug +	975	8224	9199	2.72	(	2.53	-	2.92)
		Total	6713	139633	146346					
	≥ 90 y.o.	Drug -	1010	18082	19092					
		Drug +	110	981	1091	2.01	(	1.63	-	2.47)
		Total	1120	19063	20183					

Table 5. Stratified analysis of nervous system hemorrhage

			Cases	**Non-cases**	**Total**	**Crude ROR (95% CI)**				
Dabigatran										
	0-29 y.o.	Drug -	904	290807	291711					
		Drug +	5	99	104	16.25	(	6.60	-	40.00)
		Total	909	290906	291815					
	30-39 y.o.	Drug -	562	216330	216892					
		Drug +	4	72	76	21.38	(	7.79	-	58.72)
		Total	566	216402	216968					
	40-49 y.o.	Drug -	938	312545	313483					
		Drug +	5	277	282	6.01	(	2.48	-	14.59)
		Total	943	312822	313765					
	50-59 y.o.	Drug -	1587	435983	437570					
		Drug +	44	1104	1148	10.95	(	8.07	-	14.86)
		Total	1631	437087	438718					
	60-69 y.o.	Drug -	2180	416254	418434					
		Drug +	144	3476	3620	7.91	(	6.66	-	9.39)
		Total	2324	419730	422054					
	70-79 y.o.	Drug -	2164	284371	286535					
		Drug +	320	6739	7059	6.24	(	5.54	-	7.03)
		Total	2484	291110	293594					
	80-89 y.o.	Drug -	1469	138484	139953					
		Drug +	315	6078	6393	4.89	(	4.32	-	5.54)
		Total	1784	144562	146346					
	≥ 90 y.o.	Drug -	176	18962	19138					
		Drug +	51	994	1045	5.53	(	4.02	-	7.60)
		Total	227	19956	20183					
Warfarin										
	0-29 y.o.	Drug -	887	289681	290568					
		Drug +	22	1225	1247	5.87	(	3.83	-	8.99)
		Total	909	290906	291815					
	30-39 y.o.	Drug -	541	214726	215267					

	Drug +	25	1676	1701	5.92	(3.95	-	8.87	)
	Total	566	216402	216968					
40-49 y.o.	Drug -	896	309506	310402					
	Drug +	47	3316	3363	4.90	(3.65	-	6.58	)
	Total	943	312822	313765					
50-59 y.o.	Drug -	1495	430777	432272					
	Drug +	136	6310	6446	6.21	(5.20	-	7.41	)
	Total	1631	437087	438718					
60-69 y.o.	Drug -	2105	408923	411028					
	Drug +	219	10807	11026	3.94	(3.42	-	4.53	)
	Total	2324	419730	422054					
70-79 y.o.	Drug -	2160	277876	280036					
	Drug +	324	13234	13558	3.15	(2.80	-	3.54	)
	Total	2484	291110	293594					
80-89 y.o.	Drug -	1492	135655	137147					
	Drug +	292	8907	9199	2.98	(2.62	-	3.38	)
	Total	1784	144562	146346					
≥ 90 y.o.	Drug -	194	18898	19092					
	Drug +	33	1058	1091	3.04	(2.09	-	4.42	)
	Total	227	19956	20183					

Table 6. Adjusted ROR for hemorrhagic events

	Gastrointestinal hemorrhage					Nerve system hemorrhage				
	Likelihood ratio test	Adjusted ROR	(95%CI)			Likelihood ratio test	Adjusted ROR	(95%CI)		
Dabigatran	< 0.0001	7.56	(4.92	-	11.11)	0.0028	5.61	(1.99	-	12.22)
Warfarin	< 0.0001	4.87	(4.19	-	5.64)	<.0001	4.83	(3.55	-	6.41)
Gender male	< 0.0001	1.42	(1.40	-	1.45)	<.0001	1.49	(1.44	-	1.55)
Reporting year	< 0.0001	0.97	(0.96	-	0.98)	0.0039	0.98	(0.97	-	0.99)
AGE										
0-29 y.o.	< 0.0001	1.18	(1.12	-	1.23)	0.4013	1.04	(0.95	-	1.14)
30-39 y.o.	0.0234	0.94	(0.90	-	0.99)	0.0224	0.88	(0.79	-	0.98)
40-49 y.o. (as reference)		1	1		1		1	1		1
50-59 y.o.	< 0.0001	1.16	(1.11	-	1.21)	0.0005	1.16	(1.07	-	1.26)
60-69 y.o.	< 0.0001	1.45	(1.39	-	1.51)	<.0001	1.63	(1.51	-	1.77)
70-79 y.o.	< 0.0001	1.96	(1.88	-	2.04)	<.0001	2.27	(2.09	-	2.46)
80-89 y.o.	< 0.0001	2.47	(2.36	-	2.59)	<.0001	3.08	(2.82	-	3.36)
≥ 90 y.o.	< 0.0001	3.02	(2.77	-	3.29)	<.0001	2.80	(2.33	-	3.33)
*interaction term dabigatran * AGE*										
dabigatran * *0-29 y.o.*	0.0021*	23.51	(12.75	-	43.34)	0.1135	16.52	(4.66	-	58.53)
dabigatran * *30-39 y.o.*	0.5924	8.99	(3.89	-	20.81)	0.0756	17.79	(4.63	-	68.30)
dabigatran * *40-49 y.o. (as reference)*		1	1		1		1	1		1
dabigatran * *50-59 y.o.*	0.0862	12.71	(8.20	-	19.70)	0.1427	12.41	(4.86	-	31.71)
dabigatran * *60-69 y.o.*	0.0366*	16.66	(11.01	-	25.23)	0.4010	13.20	(5.35	-	32.59)
dabigatran * *70-79 y.o.*	0.0622	21.45	(14.23	-	32.31)	0.6436	15.61	(6.37	-	38.21)
dabigatran * *80-89 y.o.*	0.0083*	31.36	(20.81	-	47.26)	0.9646	17.61	(7.19	-	43.16)
dabigatran * *≥ 90 y.o.*	0.0009*	45.14	(29.30	-	69.53)	0.7722	17.98	(6.98	-	46.26)
*interaction term warfarin * AGE*										
warfarin * *0-29 y.o.*	0.0045*	3.71	(2.72	-	5.06)	0.4350	6.20	(3.69	-	10.41)
warfarin * *30-39 y.o.*	0.4767	4.17	(3.18	-	5.45)	0.4437	5.19	(3.15	-	8.57)
warfarin * *40-49 y.o. (as reference)*		1	1		1		1	1		1
warfarin * *50-59 y.o.*	0.8923	5.59	(4.67	-	6.68)	0.1804	7.05	(5.00	-	9.96)
warfarin * *60-69 y.o.*	0.5166	7.45	(6.32	-	8.77)	0.2650	6.52	(4.70	-	9.05)
warfarin * *70-79y.o.*	0.0019*	7.33	(6.23	-	8.62)	0.0526	7.90	(5.75	-	10.87)
warfarin * *80-89 y.o.*	0.0019*	9.21	(7.80	-	10.87)	0.0640	10.85	(7.86	-	14.99)
warfarin * *≥ 90 y.o.*	0.0002*	9.02	(6.96	-	11.69)	0.3498	10.72	(6.61	-	17.40)

*Statistically significant

The RE-LY trial indicated that dabigatran is associated with a reduced risk of intracranial hemorrhage, as compared to warfarin [5]. Furthermore, new retrospective post-marketing studies also indicate that dabigatran is associated with a lower risk of intracranial hemorrhage [15, 16]. In contrast, the adjusted dabigatran RORs for nervous system hemorrhage did not indicate lower adjusted RORs compared to warfarin in our study (dabigatran: 5.61 [95% CI 1.99-12.22]; warfarin: 4.83 [95% CI 3.55-6.41]) (Table 6). Our results showd that the 95% CI of the adjusted dabigatran RORs was broad and not significant. We do not have a conclusive explanation for these data. We adjusted the crude ROR by coding the terms of gender, reporting year, drug, and stratified age groups in the logistic mode. However, our results from the FAERS database using this logistic model could not account for our observations. This contradiction could be considered the result of unobserved bias. Alternatively, differences in the definition of hemorrhagic adverse events in our study, the Preferred Terms (PTs) from MedDRA, and other studies could cause this effect. Furthermore, the manufacturer recommends that high-risk elderly patients (over 75 years of age) and those with chronic kidney disease should be given a lower dose of dabigatran; however, we could not determine whether dabigatran doses were lowered.

The pharmacokinetic profile of dabigatran can be affected by concomitant administration of several drugs. Dabigatran etexilate is a substrate for p-glycoprotein; thus, drugs that inhibit or induce p-glycoprotein could potentiate or attenuate the anticoagulant effect of dabigatran [3]. The effects of this drug-drug interaction should be evaluated with respect to anticoagulant-associated hemorrhage using a well-organized epidemiologic studies and/or the FAERS database.

After the approval of dabigatran, the FDA received numerous reports of severe dabigatran-related bleeding events [7]. Safety advisories have been issued by the FDA, the European Medicine Agency, and the Australian Therapeutic Goods Authority [17-19]. The reports of increased bleeding with dabigatran differed from those in the RE-LY trial, and were likely the result of passive reporting in the FAERS database, which can lead to reporting bias. Currently, the increase in severe bleeding events associated with dabigatran in the FAERS database is regarded as the result of reporting bias [7]. Thus, regulating authorities have not altered the safety profile of dabigatran, based on its overall benefit-risk profile [17, 20].

Several post-marketing studies provide more data on the bleeding risks among patients with atrial fibrillation [15, 16]. A large post-marketing study of dabigatran evaluating 134,414 elderly patients showed the comparative safety of dabigatran versus warfarin in general practice settings between October 2010 and December 2012 [16]. This analysis confirmed a reduced risk of major bleeding and intracranial hemorrhage with dabigatran. In a press release, Boehringer Ingelheim, Inc. pointed out that the FDA analysis supported the positive safety and efficacy profile of dabigatran in the RE-LY trial [21].

Another retrospective post-marketing study evaluating 9,404 Medicare patients over a 6-month follow-up period reported that dabigatran was associated with a higher incidence of major bleeding relative to warfarin, a higher risk of gastrointestinal bleeding, but a lower risk of intracranial hemorrhage [15]. Their results differed from the RE-LY trial, which showed no difference in the rates of major bleeding with dabigatran and warfarin. The risk of major bleeding among dabigatran users was especially high for African Americans and patients with chronic kidney disease. These results should be interpreted with caution, due to the relatively small size of the study.

Disproportionality analysis has several limitations that are inherent to the nature of the data and require consideration prior to drawing conclusions. In general, ROR cannot be used to infer the comparative strength of causality [22, 23]. Rather, it offers a rough indication of the signal strength, used to generate hypotheses to search for unknown potential adverse reactions [24]. It is impossible to evaluate the "true" risk of hemorrhage without information concerning the total number of patients administered dabigatran. Since dabigatran and warfarin users are very different in several factors that directly affect the risk of bleeding, failing to adjust would bias the results, as our unadjusted estimates indicate. While hemorrhagic events have been document in the FAERS database, careful attention must be paid to the interpretation of the results.

Recently, the use of quantitative measures, in addition to qualitative analysis, has become increasingly important in signal detection for pharmacovigilance [22]. Several researchers have demonstrated that disproportionality measures can provide new, causal insights. These studies each use an approach that might circumvent biases, such as selection and reporting biases. Mitigating the effect of confounding factors by such approaches enhances the robustness of results. For example, van Puijenbroek *et al.* evaluated the association between two drugs and a single event (drug-drug interactions) using a statistical interaction term in a logistic model to calculate the adjusted

RORs [11].

To our knowledge, reports on safety signal detection using logistic regression analyses focusing on age stratification are scarce. This study was the first to evaluate the association between aging and dabigatran and warfarin in GI and nervous system bleeding using the FAERS database by logistic regression. We adjusted the crude ROR by coding the terms of gender, reporting year, drug, and stratified age groups in the logistic model. In our logistic regression analysis, the adjusted RORs after adding adjusting terms were different than the crude RORs (Table 6). Thus, the adjustment of variables might influence the reporting ratio of adverse events. We demonstrated that the effect of age on the association between dabigatran and GI bleeding cannot be ignored in spontaneous adverse reporting. We consider our results valid, due to the appropriate analysis methods and the special attention paid to potential bias.

Until more evidence is available, prescribers should carefully monitor bleeding complications in elderly patients with renal impairment, a group that is known to have an increased risk of bleeding. This information could potentially be useful for improved management of GI bleeding during dabigatran treatment, and may be particularly beneficial to prescribers.

We sought to evaluate, using a real-world setting, any differences in bleeding between dabigatran users after adjusting for patient differences using appropriate analysis methods. Our study indicates the importance of comparing the safety profiles of newer and traditional drugs using post-marketing real-world data. After considering the causality in the current analysis, further epidemiological studies are recommended in elderly patients.

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Conflict of Interest

The authors declare no conflict of interest.

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