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Original article

Effectiveness and safety of long-term dabigatran among patients with non-valvular atrial fibrillation in clinical practice: J-Dabigatran Surveillance

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ABSTRACT

Background: The effectiveness and safety of dabigatran etexilate (DE) have not been elucidated thoroughly [illegible] clinical practice for Japanese patients with non-valvular atrial fibrillation (NVAF). In particular, the [illegible] of DE at reduced dose due to dose reduction recommendations (DRR) remain unknown.
Methods: NVAF patients who had newly initiated DE treatment for prevention of thromboembolic events between December 2011 and November 2013 were enrolled. They were followed until August [illegible] Outcome events included thromboembolism, major bleeding, and all-cause death.
Results: The study group consisted of 6443 patients (mean age, 70.9 years; male, 66.9%; and mean $\mathrm{CHADS_2}$ score, 1.8). During a follow-up period of 610 days (median), stroke, transient ischemic attack (TIA), and systemic embolism (SE) occurred at 1.4%/year for DE 110 mg twice daily (BID) (DE220, $n = 4759$) and 0.8% for dabigatran 150 mg BID (DE300, $n = 1571$, unadjusted $p = 0.0317$). Major bleeding occurred at 1.3 and 0.6%/year for DE220 and DE300, respectively (unadjusted $p = 0.0097$). All-cause death occurred at 1.5 and 0.5%/year for DE220 and DE300, respectively (unadjusted $p = 0.0005$). When patients were divided into four groups based on DRR and DE doses (DE300 groups meeting and not meeting DRR, and DE220 groups meeting and not meeting DRR), incidence rates of stroke/TIA/SE and major bleeding differed among the four groups (unadjusted $p = 0.0026$ and 0.0194 for trend, respectively); DE220 group meeting DRR had the highest rates (1.7% and 1.4%/year, respectively). However, in multivariate analysis, no differences between doses were observed regarding any outcomes.
Conclusions: The present results are indicative of the favorable benefit-risk profile of dabigatran in Japanese clinical practice. Dabigatran dose was not independently associated with thromboembolic and bleeding events in Japanese NVAF patients.

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Introduction

Dabigatran etexilate (DE) is a prodrug of dabigatran, which is an inhibitor of thrombin, a key element in the coagulation cascade. Thus, dabigatran prevents thrombin-induced thromboembolism. The RE-LY study showed the clinical effectiveness and safety of dabigatran compared with warfarin in patients with non-valvular atrial fibrillation (NVAF) [1]. The effectiveness and safety of dabigatran 110 mg or 150 mg twice daily (BID) were also shown in Japanese and Asian populations from the RE-LY study [2,3]. After the introduction of dabigatran into clinical practice, several studies in real-world settings in Europe, the USA, and Asia have further validated the effectiveness and safety of dabigatran [4–8]. However, the effectiveness and safety of dabigatran have yet to be elucidated in clinical practice in Japan [9–12].

In Japan, the standard dose of dabigatran is 150 mg BID (DE300), but 110 mg BID (DE220) may be considered when any of the dose reduction recommendations (DRR) are met: age ≥70 years, creatinine clearance (CrCl) of 30–50 mL/min, prior gastrointestinal bleeding, or concomitant use of oral P-glycoprotein inhibitors [13]. Japanese physicians tend to select lower doses of dabigatran [9,10], as well as warfarin [14,15], out of concern of an increased bleeding risk. Herein, we report results of a post-marketing surveillance (PMS) study, the J-Dabigatran Surveillance (ClinicalTrials.gov Identifier, NCT01491178), focusing on the effectiveness and safety of DE220 and DE300 in Japanese NVAF patients. In particular, we examined the impact of the Japanese DRR and the actual doses selected on disease outcomes.

Methods

Study design

Detailed methods of this PMS have been reported elsewhere [16]. Briefly, NVAF patients who had newly initiated dabigatran treatment for prevention of ischemic stroke and systemic embolism (SE) between December 12, [illegible] and November [illegible], 2013, were enrolled in this study within 14 days after the first administration of dabigatran. Patients were [illegible] subject to any exclusion criteria. The study was conducted according to the Declaration of Helsinki, the ministerial ordinance for the Good Post-marketing Study Practice (GPSP), the Japanese Good Vigilance Practice, and associated Japanese regulations. Approval of the institutional review board of each participating institution and written informed consent was not required because this PMS was conducted as a [illegible]ry and legal requirement in accordance with GPSP guidelines.

Doses of dabigatran were selected at the discretion of each physician. Patients were followed up until August 2016. Observations were made at the following time points: baseline before the first administration, at [illegible] and 104 weeks after the start of treatment, and at the occurrence of any adverse events, drop out from the study or discontinuation of dabigatran. In the present report, the following outcome events were analyzed: stroke, transient ischemic attack (TIA), SE, any bleeding, myocardial infarction (MI), and all-cause death. The diagnostic criteria for major bleeding have been detailed elsewhere [16].

Statistical analyses

Data are expressed as means ± standard deviations. Differences in ordinal variables were analyzed with Wilcoxon rank-sum test or Kruskal–Wallis test, and those in continuous variables were analyzed with *t*-test and ANOVA. Categorical variables were compared with chi-squared test. Cox proportional hazard analyses were performed to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CI) of outcome events. Explanatory variables for stroke, TIA, and SE included age, body weight, components of CHA_2DS_2-VASc score [heart failure, hypertension, diabetes mellitus, and history of stroke or TIA, vascular disease (prior MI in the present analysis), and female sex], types of NVAF, serum creatinine level, components of DRR (prior gastrointestinal bleeding and oral P-glycoprotein inhibitors), antiplatelet drugs, and dabigatran doses. Those for bleeding events, all-cause death, and a composite of stroke/TIA/SE, major bleeding, and all-cause death included prior intracranial bleeding, hepatic disorders, and variables that were selected for stroke/TIA/SE. Two-tailed *p*-values of <0.05 were considered statistically significant. All statistical analyses were performed with SAS software, version 9 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline clinical characteristics

Of 6772 patients enrolled, case report forms were not obtained from 144 (2[illegible]%) patients. Additionally, 185 (2.7%) patients were excluded from the analysis, and 6443 patients therefore constituted the study population (Fig. 1). The mean follow-up period was 460 ± 293 days (median, [illegible] days).

Table 1 and [illegible] Table 1 show the baseline characteristics of patients. Eight[illegible] patients receiving DE220 and one patient receiving DE300 [illegible] CrCl <30 mL/min, which is a contraindication for dabigatran treatment. However, those patients were included in the present analyses. Compared with patients at DE300, those at DE220 were older and more likely to be female, and had higher prevalences of heart failure, gastrointestinal disorders other than bleeding, CrCl ≤50 mL/min, and concomitant treatment with antiplatelet drugs ($p < 0.0001$ for each). Consequently, $CHADS_2$ [17], CHA_2DS_2-VASc [18], and HAS-BLED [19] scores were all higher at DE220 than at DE300 ($p < 0.0001$ for each).

Bleeding, MI, and gastrointestinal disorders

Incidence rates of major bleeding and MI were low with both dosages (Table 2). Overall, the incidence of non-bleeding gastrointestinal disorders was 10.5%/year; the rate was similar in the DE220 and DE300 populations.

Stroke, thromboembolic events, and all-cause death

Incidence rates of stroke, TIA, SE, and all-cause death are shown in Table 2. Overall, the incidence of stroke/TIA/SE was 1.3%/year,

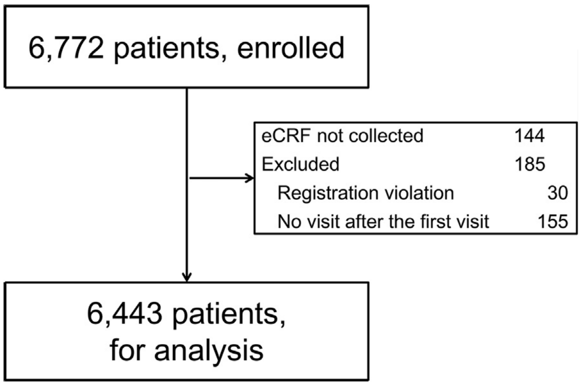

Fig. 1. Patient disposition. eCRF, electronic case report form.

Table 1
Baseline characteristics.

	Total[a] ($n = 6443$)	DE220 ($n = 4759$)	DE300 ($n = 1571$)	p-Value[b]
Men	4310 (66.9)	2990 (62.8)	1259 (80.1)	<0.0001
Age, years	70.9 ± 9.9	73.3 ± 8.7	63.1 ± 9.1	<0.0001
<65	1541 (23.9)	689 (14.5)	844 (53.7)	
65–74	2460 (38.2)	1823 (38.3)	605 (38.5)	
≥75	2442 (37.9)	2247 (47.2)	122 (7.8)	
≥70	3862 (59.9)	3447 (72.4)	322 (20.5)	
Body weight, kg	62.7 ± 12.3 ($n = 6272$)	61.0 ± 11.7 ($n = 4635$)	67.9 ± 12.6 ($n = 1530$)	<0.0001
Body mass index, kg/m^2	24.0 ± 3.6 ($n = 5293$)	23.8 ± 3.5 ($n = 3899$)	24.7 ± 3.7 ($n = 1309$)	<0.0001
Type of atrial fibrillation				0.0130
Paroxysmal	2728 (42.3)	1978 (41.6)	712 (45.3)	
Persistent	1687 (26.2)	1237 (26.0)	414 (26.4)	
Permanent	1615 (25.1)	1228 (25.8)	355 (22.6)	
Comorbidity				
Heart failure	1171 (18.2)	913 (19.2)	228 ([illegible])	<0.0001
Hypertension	4299 (66.7)	3233 (67.9)	99[illegible]0)	0.0004
Diabetes mellitus	1317 (20.4)	977 (20.5)	328 ([illegible])	0.7708
Prior stroke	1302 (20.2)	983 (20.7)	[illegible]97 (18.[illegible])	0.1065
Hepatic disorder	660 (10.2)	478 (10.0)	173 (11.0)	0.2724
Prior gastrointestinal bleeding	81 (1.3)	70 (1.5)	9 (0.6)	0.0051
Gastrointestinal disorder other than bleeding	969 (15.0)	779 (16.4)	[illegible]2 (10.9)	<0.0001
Serum creatinine, mg/dL	0.83 ± 0.20 ($n = 5957$)	0.84 ± 0.21 ($n = 4404$)	[illegible] ± 0.17 ($n = 1456$)	<0.0001
Creatinine clearance, mL/min	72.9 ± 26.2 ($n = 5840$)	67.6 ± 23.0 ($n = 4316$)	90[illegible]7.7 ($n = 1431$)	<0.0001
<30	21 (0.4)	18 (0.4)	1 (0.[illegible])	
30–50	1029 (17.6)	951 (22.0)	37 (2.6)	
>50	4790 (82.0)	3347 (77.5)	1393 (97.3)	
CHADS$_2$ score	1.8 ± 1.3	2.0 ± 1.3	1.4 ± 1.1	<0.0001
CHA$_2$DS$_2$-VASc score	3.0 ± 1.6	3.3 ± 1.6	2.1 ± 1.5	<0.0001
HAS–BLED score	2.1 ± 1.1	[illegible] ± 1.1	1.5 ± 1.0	<0.0001
Switched from warfarin	1809 (28.6) ($n = 6319$)	[illegible] (29.3) ($n =$ [illegible])	408 (26.4) ($n = 1545$)	0.0272
Concomitant drugs				
Antiplatelet drugs	870 (13.8) ($n = 6302$)	707 (15.2) ($n = 465$[illegible])	145 (9.4)($n = 1541$)	<0.0001
Proton pump inhibitors	617 (9.8) ($n = 6300$)	444 (9.6) ([illegible]647)	157 (10.2) ($n = 1542$)	0.4712
P-glycoprotein inhibitors	205 (3.3) ($n = 629$[illegible])	151 (3.2) ([illegible]645)	50 (3.2) ($n = 1541$)	0.9906

Number of patients (%) or mean ± standard deviation.
DE220, dabigatran 220 mg daily (110 mg BID); DE300, dabigatran 300 mg daily [illegible]mg BID).
[a] 113 patients received doses other than DE220 and DE300.
[b] Comparison between DE220 and DE300. Chi-squared test for categorical variables, [illegible]t-test for continuous variables.

Table 2
Incidences of outcome events.

	T[illegible] ($n = 6443$)	DE220 ($n = 4759$)	DE300 ($n = 1571$)	p-Value[b] (unadjusted)
Any bleeding	[illegible]73 (4.7)	295 (5.0)	69 (3.6)	0.0097
Major	[illegible]7 (1.1)	75 (1.3)	11 (0.6)	0.0114
Non-major	[illegible](3.8)	233 (4.0)	60 (3.1)	0.0869
Intracranial	2[illegible].3)	19 (0.3)	2 (0.1)	0.1182
Gastrointestinal	121 (1.5)	98 (1.6)	21 (1.1)	0.0753
Myocardial infarction	12 (0.2)	10 (0.2)	2 (0.1)	0.5255
Gastrointestinal disorders other tha[illegible]ding	807 (10.5)	597 (10.4)	197 (10.7)	0.9162
Stroke/TIA/SE	104 (1.3)	84 (1.4)	15 (0.8)	0.0317
Ischemic stroke	83 (1.0)	68 (1.1)	11 (0.6)	0.0314
Hemorrhagi[illegible]ke	8 (0.1)	7 (0.1)	1 (0.1)	0.4389
TIA	7 (0.1)	3 (0.1)	4 (0.2)	0.0654
SE	10 (0.1)	8 (0.1)	1 (0.1)	0.3664
All-cause death	106 (1.3)	91 (1.5)	9 (0.5)	0.0005
Composite events[c]	278 (3.5)	234 (3.9)	34 (1.8)	<0.0001

Number of patients (% per [illegible]r).
Composite of stroke/TIA/SE, major bleeding and all cause death.
DE220, dabigatran 220 mg daily (110 mg BID); DE300, dabigatran 300 mg daily (150 mg BID).
TIA, transient ischemic attack; SE, systemic embolism.
[a] 113 patients received doses other than DE220 and DE300.
[b] Comparison between DE220 and DE300.
[c] Composite of stroke/TIA/SE, major bleeding and all cause death.

and higher at DE220 than at DE300 (unadjusted $p = 0.0317$). Incidence rates of all-cause death and composite events (stroke/TIA/SE, major bleeding, and all-cause death) were also higher at DE220 than at DE300 (unadjusted $p = 0.005$ and $p < 0.0001$, respectively). Outcome events in patients in whom dabigatran treatment was contraindicated due to lower CrCl values are shown in Online Table 2. Because there were few patients with these events, formal statistical analyses were not performed.

Table 3
Baseline characteristics of four groups based on dose reduction recommendations and dabigatran doses.

	DE220 ($n = 4759$)		DE300 ($n = 1571$)		p-Value for trend[a]
	Recommended ($n = 3578$)	Non-Recommended ($n = 1181$)	Recommended ($n = 1196$)	Non-recommended ($n = 375$)	
Men	2098 (58.6)	892 (75.5)	976 (81.6)	283 (75.5)	<0.0001
Age, years	76.8 ± 6.0	62.4 ± 6.4	60.2 ± 7.3	72.5 ± 7.4	<0.0001
<65	60 (1.7)	629 (53.3)	806 (67.4)	38 (10.1)	
65–74	1271 (35.5)	552 (46.7)	390 (32.6)	215 (57.3)	
≥75	2247 (62.8)	0	0	122 (32.5)	
≥70	3447 (96.3)	0	0	322 (85.9)	
Body weight, kg	59.1 ± 10.9	67.1 ± 12.1	69.1 ± 12.5	64.1 ± 12.1	<0.0001
Body mass index, kg/m^2	23.5 ± 3.5	24.5 ± 3.6	24.8 ± 3.7	24.4 ± [illegible].8	<0.0001
Comorbidity					
Heart failure	726 (20.3)	187 (15.8)	155 (13.0)	[illegible]9.5)	<0.0001
Hypertension	2496 (69.8)	737 (62.4)	749 (62.6)	[illegible]1 (64.3)	<0.0001
Diabetes mellitus	749 (20.9)	228 (19.3)	252 (21.1)	[illegible]6 (20.[illegible]	0.6805
Prior stroke	813 (22.7)	170 (14.4)	214 (17.9)	[illegible]	<0.0001
Hepatic disorder	322 (9.0)	156 (13.2)	142 (11.9)	[illegible]	<0.0001
Prior gastrointestinal bleeding	70 (2.0)	0	0	9 (2[illegible]	<0.0001
Gastrointestinal disorder other than bleeding	650 (18.2)	129 (10.9)	113 (9.4)	59 (15[illegible]	<0.0001
Serum creatinine, mg/dL	0.84 ± 0.21	0.83 ± 0.20	0.81 ± 0.1[illegible]	0.81 ± 0.17	0.0001
Creatinine clearance, mL/min	61.3 ± 18.5 ($n = 3275$)	87.3 ± 24.4 ($n = 1041$)	94.9 ± 27.3 ($n = 1090$)	74.1 ± 22.8 ($n = 341$)	<0.0001
<30	18 (0.5)	0	[illegible]	[illegible]0.3)	
30–50	951 (29.0)	0	[illegible]	[illegible]7 (10.9)	
CHADS$_2$ score	2.2 ± 1.3	1.3 ± 1.1	[illegible]	1.8 ± 1.2	<0.0001
CHA$_2$DS$_2$-VASc score	3.7 ± 1.5	2.0 ± 1.3	[illegible] ± 1.3	3.0 ± 1.5	<0.0001
HAS–BLED score	2.5 ± 0.9	1.6 ± 1.1	[illegible]1.0	2.2 ± 1.0	<0.0001
Switch from warfarin	1082 (30.9) ($n = 3502$)	286 (24.6) (n [illegible])	29[illegible] ($n = 1172$)	113 (30.3) ($n = 373$)	<0.0001
Concomitant antiplatelet drugs	561 (16.1) ($n = 3493$)	146 (12.6[illegible]	96 [illegible] ($n = 1170$)	49 (13.2) ($n = 371$)	<0.0001
Concomitant P-glycoprotein inhibitors	151 (4.3) ($n = 3488$)	0	0	50 (13.4) ($n = 372$)	<0.0001

Number of patients (%) or mean ± standard deviation.
DE220, dabigatran 220 mg daily (110 mg BID); DE300, dabigatran 300 mg daily (1[illegible]g BID).
[a] Chi-squared test for categorical variables, and ANOVA for continuous variables.

Dose reduction recommendations, doses, and outcomes

Table 3 and Online Table 3 show the baseline characteristics of four groups of patients stratified [illegible] DRR and dabigatran dose. Of 4759 patients with DE220, 3578 ([illegible]5.2%) patients received the recommended DE220. [illegible] these, [illegible]1 patients had CrCl values of 30–50 mL/min, and 3[illegible] patients were ≥70 years of age. In the population with DE300, 375 (23.9%) patients had at least one DRR (non-recommended DE300); [illegible] patients had CrCl values of 30–50 mL/min, and 322 patients were ≥70 years of age. As expected, the baseline characteristics differed among the four groups (Table 3). The non-recommended DE220 had lower thromboembolic and bleeding risk scores than the recommended DE220, but had similar risk scores to the recommended DE300. Rates of bleeding, thromboembolic events, and all-cause death were higher at the recommended DE220 than at the non-recommended DE220 and the recommended DE300 (Table 4).

Table 4
Incidences of events i[illegible] groups [illegible] on dose reduction recommendations and dabigatran doses.

	DE220		DE300		p-Value for trend[a]
	Recommended ($n = 3578$)	Non-Recommended ($n = 1181$)	Recommended ($n = 1196$)	Non-Recommended ($n = 375$)	
Bleeding					
Major	62 (1.4)	13 (0.9)	7 (0.5)	4 (1.0)	0.0194
Intracranial	18 (0.4)	1 (0.1)	1 (0.1)	1 (0.2)	0.0543
Gastrointestinal	77 (1.7)	21 (1.4)	13 (0.9)	8 (1.8)	0.1266
Stroke/TIA/SE	74 (1.7)	10 (0.7)	13 (0.9)	2 (0.5)	0.0026
Ischemic stroke	60 (1.3)	8 (0.5)	10 (0.7)	1 (0.2)	0.0046
Hemorrhagic stroke	6 (0.1)	1 (0.1)	0	1 (0.2)	0.4327
TIA	3 (0.1)	0	3 (0.2)	1 (0.2)	0.2127
SE	6 (0.1)	2 (0.1)	1 (0.1)	0	0.7896
All-cause death	77 (1.7)	14 (0.9)	2 (0.1)	7 (1.6)	<0.0001
Composite events[b]	200 (4.5)	34 (2.3)	22 (1.5)	12 (2.7)	<0.0001

Number of patients (% per year).
DE220, dabigatran 220 mg daily (110 mg BID); DE300, dabigatran 300 mg daily (150 mg BID).
TIA, transient ischemic attack; SE, systemic embolism.
[a] Chi-squared test between four groups (not adjusted).
[b] Composite of stroke/TIA/SE, major bleeding, and all cause death.

Table 5
Multivariate analysis for variables associated with outcome events.

	Stroke/TIA/SE		Major bleeding		All-cause death		Composite events[c]	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
DE220[a]	1.03 (0.56–1.91)	0.9171	1.18 (0.58–2.38)	0.6541	1.71 (0.79–3.74)	0.1762	1.19 (0.80–1.78)	0.3945
Female	0.61 (0.35–1.07)	0.0833	0.83 (0.46–1.50)	0.5286	0.52 (0.30–0.91)	0.0206	0.69 (0.50–0.97)	0.0318
Age (per 10 years)	1.55 (1.15–2.10)	0.0039	1.59 (1.15–2.20)	0.0053	1.06 (1.17–2.19)	0.0030	1.55 (1.29–1.86)	<.0001
Body weight (per 10 kg)	0.89 (0.71–1.12)	0.3259	1.01 (0.79–1.28)	0.9480	0.59 (0.46–0.76)	<0.0001	0.80 (0.69–0.92)	0.0019
Persistent[b]	1.48 (0.88–2.47)	0.1381	0.88 (0.50–1.54)	0.6513	1.67 (0.98–2.85)	0.0617	1.33 (0.97–1.82)	0.0788
Permanent[b]	1.13 (0.65–1.95)	0.6716	0.77 (0.43–1.38)	0.3726	1.06 (0.58–1.92)	0.8533	1.01 (0.72–1.42)	0.9545
Stroke/TIA/SE	2.27 (1.47–3.49)	0.0002	1.67 (1.01–2.77)	0.0442	1.57 (0.97–2.52)	0.0641	1.82 (1.38–2.40)	<0.0001
Myocardial infarction	0.69 (0.25–1.96)	0.4921	2.47 (1.15–5.28)	0.0199	1.70 (0.65–4.43)	0.2757	1.44 (0.84–2.47)	0.1827
Intracranial bleeding	–		1.17 (0.28–5.01)	0.8279	0.45 (0.06–3.34)	0.4360	0.64 (0.24–1.77)	0.3930
Gastrointestinal bleeding	0.00 (0.00–∞)	0.9885	3.84 (1.49–9.86)	0.0052	2.25 (0.68–7.47)	0.1852	[illegible] (0.99–4.18)	0.0546
Hepatic disorder	–		0.78 (0.35–1.74)	0.5501	1.98 (1.11–3.53)	0.0204	[illegible] (0.79–1.78)	0.4018
Heart failure	1.27 (0.77–2.09)	0.3521	1.63 (0.97–2.75)	0.0650	1.84 (1.14–2.95)	0.0121	1.57 ([illegible]–2.10)	0.0027
Diabetes mellitus	1.07 (0.66–1.74)	0.7902	1.48 (0.90–2.43)	0.1245	1.15 (0.68–1.95)	0.59[illegible]	1.19 ([illegible]–1.61)	0.2535
Hypertension	1.04 (0.65–1.67)	0.8705	0.99 (0.59–1.66)	0.9798	0.81 (0.52–1.28)	0.371[illegible]	0.[illegible] (0.68–1.19)	0.4693
Serum creatinine (per 0.1 mg/dL)	0.97 (0.86–1.09)	0.5667	1.09 (0.97–1.22)	0.1409	1.07 (0.95–1.20)	[illegible]520	[illegible] (0.99–1.[illegible])	0.1251
Antiplatelet drug use	2.42 (1.52–3.86)	0.0002	1.27 (0.72–2.24)	0.4118	0.58 (0.29–1.19)	[illegible].1376	[illegible] (0.92[illegible])	0.1411
P-glycoprotein inhibitor use	1.98 (0.61–6.37)	0.2535	4.10 (1.82–9.19)	0.0006	0.99 (0.23–4.2[illegible])	0.9917	2[illegible]04)	0.0143

DE220, dabigatran 220 mg daily (110 mg BID); DE300, dabigatran 300 mg daily (150 mg BID); TIA, transient ischemic attack; [illegible] systemic embolism; HR, hazard ratio; CI, confidence interval.
[a] Versus DE300.
[b] Versus paroxysmal.
[c] Composite of stroke/TIA/SE, major bleeding and all-cause death.

Multivariate analysis

When adjusted for potential confounders in the whole patients, HRs (95% CIs) of DE220 versus DE300 for major bleeding, stroke/TIA/SE, all-cause death, and composite events were 1.18 (0[illegible]–2.39), 1.03 (0.56–1.90), 1.71 (0.79–3.74), and 1.19 (0.80–1.7[illegible]) respectively (Table 5), and thus, doses were not associated with outcome events. Rather, higher age and some comorbidities were independently associated with those events. Moreover, doses were not associated with outcome events, when multivariate analysis was performed in the recommended DE220 and recommended DE300 groups (Online Table 4). Higher age and [illegible] comorbidities were again independently associated with those events (Online Table 4).

Discussion

The present PMS is [illegible] largest observational study on effectiveness and safety of dabigatran ever reported in Japan [9,10,20,21] and [illegible] the following major findings. First, approximately three-quarters of all patients received the low dabigatran dose. In each of [illegible] low-dose (DE220) and high-dose (DE300) populations, approximately three-quarters of patients adhered to Japanese DRR [13]. Second, in an unadjusted analysis, patients receiving DE220 had higher thromboembolic and bleeding risk scores, [illegible] thereby, had higher event rates of stroke/TIA/SE, major bleeding, and all-cause death than those receiving DE300. Third, patients in the recommended DE220 had higher age and higher thromboembolic and bleeding risk scores than those in the other three groups. The recommended DE220 group had higher incidence rates of outcome events than the other three groups. However, when adjusted for potential confounders, no difference between the doses was observed regarding outcome events. This confirms the appropriateness of the recommendations for dose adjustments by age and clinical risk factors according to the drug label [13]. If DE300 were selected for prevention of thromboembolism in patients having DRR, incidence rates of major bleeding would have been much higher than that seen in the present recommended DE220 group.

Dose reduction recommendations and selected doses

In the present PMS, 73.9% of patients received DE220. This proportion is comparable with that in SAKURA AF registry in Japan (72.6%) [22], higher than that in a French study (65.6%) [23] and [illegible] studies (38–59%) [4,5,24,25], but lower than that in Taiwanese studies (88%) [7,26]. The DRR in Japan [13] differ from those in Europe (age >80 years; concomitant drugs, e.g. verapamil and aspirin; and higher bleeding risk: but age >75 years in Denmark) [4,5] and Taiwan (age ≥75 years, $CHADS_2$ score ≥3, body weight <50 kg, history of gastrointestinal bleeding, and CrCl 30–50 mL/min) [7]. The difference in age for dose reduction between Japan and Europe could contribute to the different distribution of dabigatran doses between Japanese [22] and European studies [4,23–25]. The DRR in Taiwan that included body weight of <50 kg could contribute to the higher prevalence of low dabigatran dose in Taiwan [7,26] as compared with the present study.

Patients receiving DE220 in the present PMS were older, more likely to be female, and at higher risk for thromboembolism and bleeding, and received antiplatelet drugs more frequently than those receiving DE300. This finding concerning standard dose versus reduced dose is consistent with that in European countries [4,5,23–25,27], and that for other non-vitamin K antagonist oral anticoagulants, i.e. rivaroxaban and apixaban [27–30].

Approximately 25% of our patients receiving DE220 did not have any DRR, a finding consistent with SAKURA AF registry [22]. However, in a Danish study, only 9.7% of patients receiving DE220 did not meet the European DRR [24]. In the present PMS, baseline clinical characteristics of patients that did not meet any DRR were similar between populations receiving DE220 and DE300. These findings suggest Japanese physicians prefer to select lower dabigatran doses in patients who do not meet any DRR and are therefore considered to be at lower thromboembolic risk.

Among patients receiving DE300, 23.9% had at least one DRR; this percentage was, again, comparable with that in SAKURA AF registry (28.2%) [22], but was lower than that in a Danish study (44.5%) [24]. Reasons for selecting DE300 in patients having at least one DRR were not determined in the present study. Of note, thromboembolic and bleeding risk scores of patients receiving the non-recommended DE300 ranged between those of the recommended DE220 and DE300 (Table 3).

Dabigatran doses and outcomes

In the Japanese population of the RE-LY study, incidence rate of stroke/SE was 0.67%/year and 1.38%/year for DE300 and DE220 groups, respectively [2]. The present PMS showed similar results. However, incidence rates in the present PMS were numerically lower than those in Danish (1.73%/year and 2.51%/year, respectively) [25] and French (1.0%/year and 2.3%/year, respectively) [23] studies. The difference could be attributed to the higher age and higher thromboembolic risk of the patients in these European studies [23,25].

As for major bleeding events, the present study showed numerically lower incidence rates at both doses (Table 2) as compared with the RE-LY study (DE300, 3.11%/year and DE220, 2.71%/year) [1] and the Japanese population of the RE-LY study (3.33%/year and 5.33%/year, respectively) [2]. Notably, the bleeding risk was comparable between the present study (HAS-BLED score, mean 2.1) and the RE-LY study (median 2) [31]. There are several possible explanations for the lower rates of major bleeding in the present study. First, the prevalence of concomitant use of antiplatelet drugs was lower in the present PMS (14%) as compared with the RE-LY study (39%–41% overall and 36% in the Japanese population) [1,2]. Second, patients in this PMS might have been followed more closely by measuring activated partial thromboplastin time [32] and renal function. Third, management of comorbidities (hypertension, diabetes mellitus, and others) might have been improved in the present PMS period (enrollment from 2011 to 2013) as compared with the RE-LY study period from 2005 to 2007) [1,2].

In the RE-LY study [1], in which patients were randomized to receive DE220, DE300, or warfarin, irrespective of their underlying stroke or bleeding risk factors, DE220 group showed a higher rate of stroke and SE but a lower rate of major bleeding events as compared with the DE300 group. This finding is suggestive of higher anticoagulation intensity with DE300 [illegible] with DE220. In contrast, in the present PMS, the crude incidence rates of major bleeding, as well as stroke/TIA/SE, were higher in DE220 than in DE300. This difference could be explained by the higher thromboembolic and bleeding risk in DE220 than in DE300 group in the present PMS. Although some inconsistent results were reported, European studies [23,25,27] showed that incidence rates or hazard ratios of both thromboembolism and bleeding were numerically higher in patients receiving DE220 than DE300 (Table 6). This was also true for rivaroxaban and apixaban; patients receiving reduced doses had numerically higher event rates of thromboembolism and bleeding as compared with those receiving the standard doses [29,30,25].

A clinically important finding in the present study is that incidence rates of stroke/TIA/SE, as well as major bleeding, were highest in the recommended DE220 group. This could be explained by a higher baseline thromboembolic and bleeding risk in the recommended DE220 than in the remaining groups. In ORBIT-AF II, patients receiving appropriately reduced dose of rivaroxaban or apixaban had higher incidence rates [illegible] thromboembolism, major bleeding, and mortality as compared with patients receiving standard dose of these drugs [illegible]. When adjusted for potential confounding variables, the dabigatran dose itself was not associated with thromboembolic or bleeding events in the present study (Table 5, Online Table 4). Physicians should be cautious when prescribing DE220 following DRR. In such cases, it is likely that patients would have higher thromboembolic and bleeding event rates compared with those receiving DE220 but without any DRR. For reduction of event rates, management of comorbidities should be optimized. For example, lower systolic blood pressures during the follow-up period [illegible] associated with lower risk of thromboembolism as well as major bleeding [33].

In multivariate analysis, age and some other clinical variables were identified as independent predictors for outcome events (Table 5, Online Table 4). As for stroke/TIA/SE, prior history of these events emerged as an independent predictor, as expected from factors that constitute risk score criteria [17,18]. Use of antiplatelet [illegible] also a predictor of thromboembolic events. This could be possibly caused by patient risk factors at prescription. Treating physicians would have prescribed antiplatelet drugs to their patients considered to be at higher thromboembolic risk, which might have been detected as a predictive factor in this context. Prior thromboembolic events and gastrointestinal bleeding were independently associated with major bleeding, again, as expected from factors that constitute the risk score criteria [19]. As stated in the precautions in the drug label [13], concomitant use of P-glycoprotein inhibitors could increase the plasma concentration of dabigatran, thereby increasing the risk of bleeding. The relation of prior MI with major bleeding events could be explained by

Table 6
Comparison of DE220 versus DE300 groups in the clinical practice.

Authors	Dose	Number of patients	Age (mean)	CHA2DS2-VASc (mean)	HAS-BLED (mean)	Thrombo-embolism[a]	Major bleeding[a]	Notes
Larsen et al. (2013) [4]	DE220	2739	74.7	1.27[a]	NA	2.7[b]	2.8	[a]CHADS2 score
	DE300	2239	67.4	0.96[a]	NA	3.5[b]	2.2	[b]Stroke
Sorensen et al. ([illegible]) [24]	DE220	1612	79.6	3.4	2.3	2.59	11.05	
	DE300	1114	67.9	2.9	1.9	3.74	3.75	
Larsen et al. (2014) [illegible]	DE220	3045	82 (median)	3.70	2.32	NA	3.7	
	DE300	4018	67 (median)	2.12	1.7	NA	2.7	
Maura et al. (2015) [23]	DE220	5895	77.4	3.6	2.4	2.3	3.6	
	DE300	2548	66.1	2.4	2	1.0	2.5	
Staerk et al. (2018) [25]	DE220	4414	81 (median)	4 (median)	2 (median)	2.51	3.9	
	DE300	7078	67 (median)	2 (median)	2 (median)	1.73	1.84	
Chan et al. (2018) [26]	DE220	17,760	77	3.93	2.97	Reference	Reference	[c]HR (95% CI)
	DE300	2319	71	3.48	2.83	1.11 (0.50–1.15)[c]	0.92 (0.54–1.57)[c]	
Hohnloser et al. (2018) [27]	DE220	2596	77.3	4.4	3.0	0.89 (0.70–1.13)[d]	0.71 (0.55–0.84)[d]	[d]HR (95% CI) versus phenprocoumon
	DE300	2526	66.0	2.9	2.2	0.48 (0.31–0.72)[d]	0.47 (0.30–0.74)[d]	
Present study	DE220	4759	73.3	3.3	2.3	1.4	1.3	
	DE300	1571	63.1	2.1	1.5	0.8	0.6	

DE220, dabigatran 220 mg daily; DE300, dabigatran 300 mg daily; NA, not addressed; HR, hazard ratio; CI, confidence interval; Thromboembolism, stroke + systemic embolism.
Superscript letters "a-d" in the column of Notes correspond to those in other columns in Table 6.
[a] % per year or per 100 person-years.

concomitant use of antiplatelet drugs in patients with MI, although antiplatelet drug use was not identified as an independent predictor of major bleeding events. Being female and having a lower body weight were associated with all-cause death, which is consistent with previous studies [34,35].

Limitations

The present study had several limitations. First, it was conducted as an observational study in clinical practice that lacked randomization. Dabigatran dose was selected at the discretion of treating physicians; therefore, comparisons of outcome events by dose are limited. Approximately, one-quarter of the patients in DE220 did not meet the Japanese DRR [13]. However, reasons for selecting DE220 in these patients were not studied. Likewise, reasons for selecting DE300 for patients meeting the DRR were not studied either. Second, a decline in the renal function during the course of treatment [36] could have led to changes in dabigatran doses. However, the present PMS did not examine changes in renal function, nor was consideration given to changes in dabigatran doses in the course of treatment. Rather, event rates were determined using the baseline dabigatran doses. Third, although the multivariate analysis was performed to clarify the relation of dabigatran dose with outcome events, some confounding factors not assessed in the present study could have affected the present results. Propensity score matching was not employed to adjust confounding factors in the present analysis. Patients in recommended DE300 group were all <70 years of age, but 96.3% of patients in recommended DE220 group were ≥70 years of age. The remaining 131 patients of recommended DE220 group were <70 years of age, but had at least one of DRR other [illegible] age. Patients in recommended DE300 group did not have any [illegible] by definition. Therefore, propensity score matching was not suitable to adjust confounding factors for determination of independent predictors of outcome events in the [illegible] analysis. Fourth, possible misclassifications of events cannot [illegible] out because assessments of events were [illegible] physicians and were not confirmed by an [illegible] tion committee, and as such, the [illegible] of the [illegible] results was limited. There is also the [illegible] reporting of minor adverse events, which [illegible] of the PMS study design.

Conclusion

Despite these limitations, [illegible] present [illegible] PMS demonstrated [illegible]. Even lower incidences of [illegible] were [illegible] in comparison with the RE-LY [illegible] [1,2], [illegible] a favorable drug profile. Components [illegible] are well-known risk factors for [illegible], [illegible], or both, which could increase incidence rates of [illegible] and bleeding events in patients receiving DE220 in the [illegible] study. However, when adjusted for potential confounders, dabigatran doses were not associated with thromboembolic and bleeding events in our Japanese population.

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Conflicts of interest

HI has received remuneration from Boehringer Ingelheim, Bayer Healthcare, Daiichi Sankyo, and Bristol-Myers Squibb; SU has received remuneration from Boehringer Ingelheim, Bayer Healthcare, Daiichi Sankyo, and Sanofi; HA has received remuneration from Boehringer Ingelheim and Daiichi Sankyo; KO has received remuneration from Boehringer Ingelheim, Bayer Healthcare, Daiichi Sankyo, and Pfizer; YK has received remuneration from Daiichi Sankyo, Boehringer Ingelheim, Bayer Healthcare, Bristol-Myers Squibb, and Pfizer; MY has received remuneration from Boehringer Ingelheim, Bayer Healthcare, and Daiichi Sankyo, and research funding from Boehringer Ingelheim; TY has received remuneration from Boehringer Ingelheim, Daiichi Sankyo, Bayer Healthcare, Pfizer, Bristol-Myers Squibb, and Eisai, and research funding from Boehringer Ingelheim and Daiichi Sankyo; AT and TF are employees of Nippon Boehringer Ingelheim.

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