American Heart Journal Plus: Cardiology Research and Practice 22 (2022) 100203

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Research paper

Twice- or once-daily dosing of direct oral anticoagulants and gastrointestinal bleeding in patient with atrial fibrillation

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ARTICLE INFO

Keywords:
Gastrointestinal bleeding
Direct oral anticoagulants
Atrial fibrillation
BID
QD

ABSTRACT

Aims: Direct oral anticoagulant (DOAC) is widely used for the prevention of embolic stroke in non-valvular atrial fibrillation (NVAF) patients. However, the gastrointestinal bleeding risk in several DOAC regimens was higher than warfarin, especially in once-daily regimens.

Methods and results: We conducted a single-center prospective registry of patients with NVAF treated with DOACs: the DIRECT registry (N = 2216; follow-up duration 650 [IQR 103–1574] days, UMIN000033283). All patients were divided into 2 groups: the twice-daily (BID) regimen group (dabigatran and apixaban) versus the once-daily (QD) regimen group (rivaroxaban and edoxaban). Out of 2216 patients, we successfully matched 904 patients in the QD group and 904 patients in the BID group using propensity score. The primary endpoint was gastrointestinal bleeding defined as any bleeding in the gastrointestinal tract that was identified through medical records regardless of bleeding site or severity. The BID group showed a significantly lower gastrointestinal bleeding rate than the QD group (3.5/100 person-year vs. 6.2/100 person-year, log-rank P < 0.0001). The secondary endpoints were all death, stroke, major bleeding, and any bleeding. The rate of major bleeding was significantly lower in patients with BID regimen group (log-rank P = 0.040). In contrast, all death, stroke, and any bleeding did not differ between both groups (log-rank P = 0.280, 0.520 and 0.066, respectively).

Conclusions: The BID regimen as compared with the QD regimen was associated with reduced risk of gastrointestinal bleeding.

1. Introduction

In recent era, direct oral anticoagulants (DOACs) are widely used for non-valvular atrial fibrillation (NVAF). Four landmark phase 3 trials have shown that each DOAC was more or equally effective for stroke prevention and also had almost similar safety profile with respect to bleeding events in patients with NVAF compared with vitamin K antagonist (warfarin) [1–4]. However, in these trials, rates of gastrointestinal bleeding were higher than warfarin in several DOAC regimens, especially in once-daily regimens. The peak level of drug concentration is thought to be associated with bleeding events [5–7]. The peak level would be higher in the once-daily [QD (quaque die)] regimens than in the twice-daily [BID (bis in die)] regimens. Furthermore, in contrast to warfarin, DOAC has active anticoagulation effect within the lumen of gastrointestinal tract after oral intake [8]. These points may explain the reason why rivaroxaban and edoxaban (both QD regimen) were associated with the higher risk of gastrointestinal bleeding compared with warfarin in the clinical trials [2,4]. Twice-daily dosing (BID) rather than once-daily dosing (QD) may theoretically suppress the peak level of drug concentration in the gut lumen and blood plasma. The range of drug concentration can be narrower in the BID regimen than in the QD regimen (Fig. 1), which may theoretically result in a better safety profile [9].

It remains unclear whether BID regimen shows the theoretical superiority over QD regimen in the real-world clinical data. The purpose of this study was to investigate the impact of once- or twice-daily regimen on the gastrointestinal bleeding in the real-world patients treated with DOACs.

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https://doi.org/10.1016/j.ahjo.2022.100203
Received 29 July 2022; Accepted 6 September 2022
Available online 9 September 2022

2. Methods

2.1. Study population

We conducted a single-center prospective observational registry of NVAF patients with DOACs: Safety and effectiveness of 4 Different dIrect oRal anticoagulants, dabigatran, rivaroxaban, apixaban and edoxaban in the rEal-world Clinical pracTice: [DIRECT registry (UMIN000033283)]. All serial adult patients (aged ≥18 years) in our institution with NVAF who were users of dabigatran, rivaroxaban, apixaban, or edoxaban from June 2011 to November 2017 were enrolled. If a patient ever used DOAC during the study period, the first fill of DOAC was defined as the index medication. The treatment period was defined as the time from the first administration of a drug to last follow-up or 2 days after the trial drugs were discontinued if the patient stopped taking the medication. In the present study, we divided all patients into 2 groups: BID regimen (dabigatran and apixaban) group and QD regimen (rivaroxaban and edoxaban) group.

2.2. Endpoints

The primary endpoint in the current study was gastrointestinal bleeding. Gastrointestinal bleeding was defined as any bleeding in the gastrointestinal tract that was identified through medical records regardless of bleeding site or severity.

The secondary endpoints were all death, stroke, major bleeding, and any bleeding. Stroke was defined as a neurologic deficit persisting ≥24 h attributed to an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria, as clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 2 g/dL or transfusion of at least 2 units of packed red cells, occurring at a critical site, or resulting in death [10]. Any bleeding was defined as a composite of major bleeding and clinically relevant non-major bleeding according to ISTH criteria. Clinical events were monitored by questioning, physical examination, and laboratory test at each outpatient visit every 2–4 months.

2.3. Statistical analysis

All analyses were performed using R software (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria). P value of <0.05 was considered statistically significant. Data are presented with listwise deletion. Categorical variables are expressed as counts (percentages) and compared with the chi-squared test or Fisher's exact test. Continuous variables are expressed as mean (standard deviation) or median [interquartile range] and compared using Student's *t*-test or the Mann–Whitney *U* test as appropriate. Because excluding missing data cases can cause bias in this analysis and loss of power for detecting a statistical difference, we performed random imputation using the "missForest" method. The method we used for imputation, "missForest", is a package in the R statistical software. The function missForest is used to impute missing values particularly in the case of mixed-type data [11]. Because dose of DOAC was not randomly selected, potential confounding factors were eliminated through a propensity score-matching technique. Propensity scores for the estimated probability of the BID regimen of DOAC with reference to the QD regimen in each patient were generated using a multiple logistic regression model. The final model included following 14 variables based on the clinical consensus: age, sex, body weight, antiplatelet use, hemoglobin, creatinine, diabetes mellitus, hypertension, dyslipidemia, histories of heart failure, bleeding, stroke, atherosclerosis, liver dysfunction. The area under the receiver operating characteristics (ROC) curve (AUC) was 0.601 (95 % CI: 0.577–0.624) for this model. We successfully matched 904 patients treated with QD regimen and 904 patients with BID regimen. The balance between the groups was assessed with a standardized mean difference (SMD). The SMD within 10 % is considered a negligible imbalance between 2 groups [12]. Outcomes were assessed according to the 2 groups, BID regimen group and QD regimen group, in a time-to-first-event fashion with the Kaplan-Meier method and compared with log-rank test. Impact of the BID regimen as compared to the QD regimen was estimated with Cox proportional hazard model. Subgroup analysis was done in the following subpopulations: elderly patients (age ≥ 75), sex, diabetes mellitus, hypertension, and dyslipidemia.

3. Results

3.1. Subjects

Patient selection flowchart is shown in Fig. 2. A total of 2216 patients [dabigatran (N = 648), apixaban (N = 599), rivaroxaban (N = 538) and edoxaban (N = 431)] were enrolled in the present registry. BID regimen (dabigatran and apixaban) group and QD regimen (rivaroxaban and edoxaban) group consist of 1247 and 969 patients, respectively. Median follow-up duration in the whole population was 650 days (IQR, 103–1574 days). Baseline characteristics of the BID and QD regimen groups are presented in Table 1. We successfully matched 904 patients treated with QD regimen and 904 patients with BID regimen using propensity score. After propensity score matching the baseline characteristics were well-balanced (Table 2).

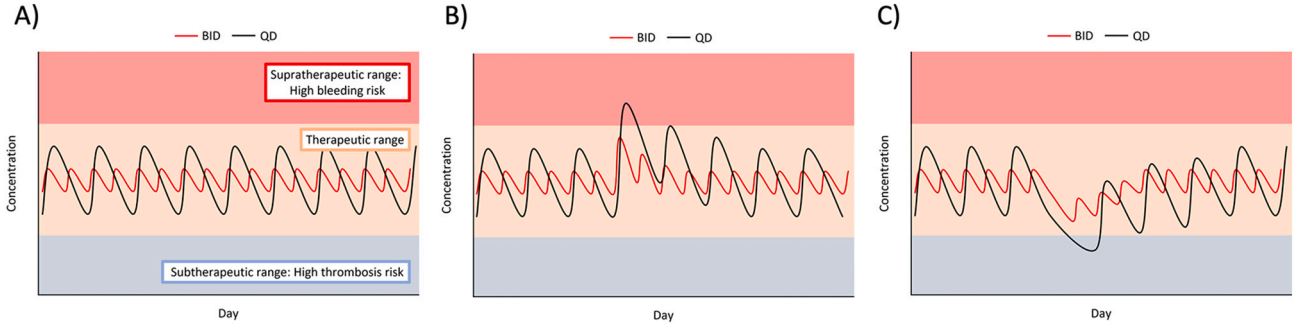

Fig. 1. Theoretical pharmacokinetic profile of a drug.
These schematic graphs illustrate the theoretical pharmacokinetic profile of a drug in serum and gastrointestinal lumen: a dose X administered once-daily (QD, black line), and a dose X/2 administered twice-daily (BID, red line). A) Taking proper regimen. B) Taking an extra tablet may result in a higher peak in the QD than in the BID regimen. C) A single miss of DOAC may deviate the concentration downward from the therapeutic range more severely in the QD regimens than in the BID regimens. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

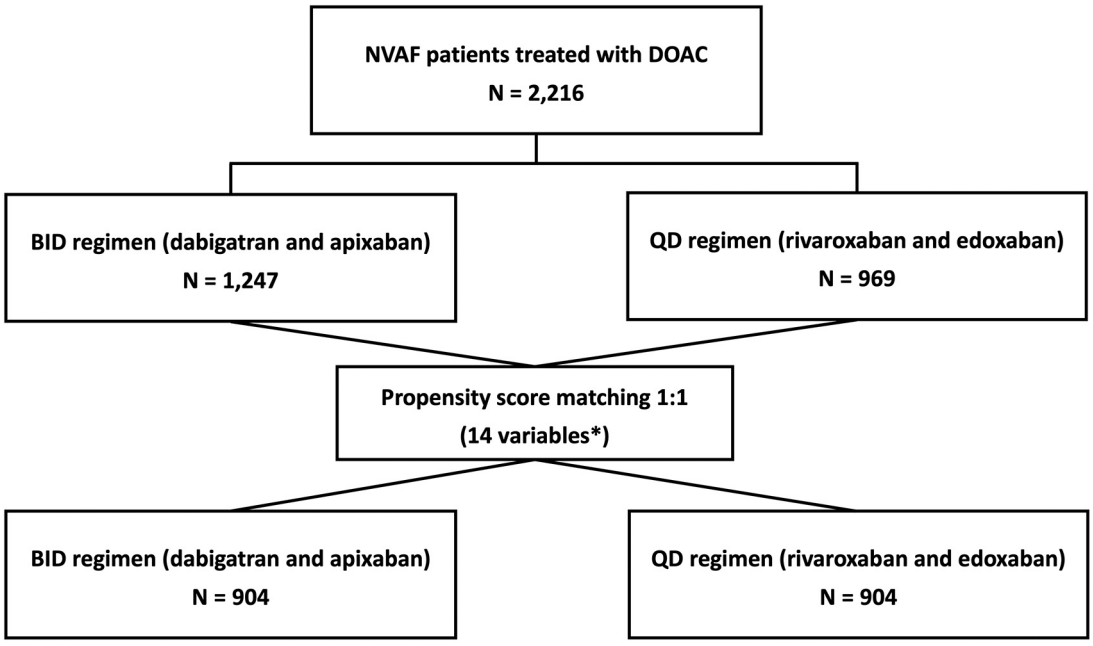

Fig. 2. Patient selection flowchart.
*A propensity score was calculated by a logistic regression model with the parameters of age, sex, body weight, antiplatelet use, hemoglobin, creatinine, diabetes mellitus, hypertension, dyslipidemia, a history of heart failure, a history of bleeding, a history of stroke, atherosclerosis, and liver dysfunction. Abbreviations: NVAF = non-valvular atrial fibrillation; DOAC = direct oral anticoagulants; BID = twice-daily dosing; QD = once-daily dosing.

Table 1
Overall cohort: Patient background.

Variable	BID (N = 1247)	QD (N = 969)	SMD	Missing (%)
Age (years)	72.00 [65.00, 79.00]	73.00 [66.00, 80.00]	0.076	0
Body weight (kg)	60.50 [51.20, 69.45]	60.00 [50.00, 70.00]	0.002	1.5
Woman	456 (36.6 %)	350 (36.1 %)	0.009	0
Hypertension	903 (72.4 %)	725 (74.8 %)	0.055	0
Diabetes mellitus	336 (26.9 %)	283 (29.2 %)	0.050	0
Dyslipidemia	820 (65.8 %)	624 (64.4 %)	0.030	0
Antiplatelets use	282 (22.6 %)	195 (20.1 %)	0.061	0
History of heart failure	289 (23.2 %)	236 (24.4 %)	0.028	0
History of bleeding	288 (23.1 %)	313 (32.3 %)	0.207	0
History of atherosclerosis	310 (24.9 %)	256 (26.4 %)	0.036	0
History of stroke	250 (20.0 %)	197 (20.3 %)	0.007	0
Liver dysfunction	355 (28.5 %)	382 (39.4 %)	0.233	0
Creatinine (mg/dL)	0.84 [0.69, 1.01]	0.83 [0.70, 1.00]	0.047	0
Hemoglobin (g/dL)	13.40 [12.10, 14.80]	13.20 [11.90, 14.70]	0.107	0

Data are expressed as n (%) or median [interquartile range]. BID = twice-daily dosing; QD = once-daily dosing; SMD = standard mean difference.

Table 2
Patient background after propensity score matching.

Variable	BID (N = 904)	QD (N = 904)	SMD
Age (years)	73.00 [66.00, 79.00]	73.00 [66.00, 80.00]	0.026
Body weight (kg)	60.10 [50.86, 69.00]	60.00 [50.00, 70.00]	0.011
Woman	330 (36.5 %)	330 (36.5 %)	<0.001
Hypertension	665 (73.6 %)	669 (74.0 %)	0.010
Diabetes mellitus	269 (29.8 %)	260 (28.8 %)	0.022
Dyslipidemia	600 (66.4 %)	586 (64.8 %)	0.033
Antiplatelets use	188 (20.8 %)	187 (20.7 %)	0.003
History of heart failure	209 (23.1 %)	219 (24.2 %)	0.026
History of bleeding	277 (30.6 %)	269 (29.8 %)	0.019
History of atherosclerosis	251 (27.8 %)	233 (25.8 %)	0.045
History of stroke	181 (20.0 %)	180 (19.9 %)	0.003
Liver dysfunction	309 (34.2 %)	326 (36.4 %)	0.039
Creatinine (mg/dL)	0.83 [0.68, 1.00]	0.83 [0.70, 1.00]	0.015
Hemoglobin (g/dL)	13.30 [12.00, 14.60]	13.30 [12.00, 14.70]	0.016

Data are expressed as n (%) or median [interquartile range]. BID = twice-daily dosing; QD = once-daily dosing; SMD = standard mean difference.

3.2. Clinical endpoints

Figs. 3 and 4 depict Kaplan-Meier curves for the primary and secondary endpoints. Table 3 tabulates the outcomes in the BID and QD regimen groups. Event rate of gastrointestinal bleeding was significantly lower in the BID regimen group than in the QD regimen group (3.5/100 person-years vs. 6.2/100 person-years, log-rank $P < 0.0001$). Furthermore, the rate of major bleeding was also significantly lower in patients with BID regimen group (log-rank $P = 0.040$). On the other hand, all death, stroke and any bleeding did not differ between BID and QD regimen groups (log-rank $P = 0.280$, 0.520 and 0.066). In the overall population, the risk of gastrointestinal bleeding was lower in the BID group (hazard ratio [HR]: 0.556; 95 % CI 0.416–0.743, $P < 0.001$). The superiority of BID regimen was consistent across various subgroups (Table 4).

4. Discussion

The main findings of this study can be summarized as follows: 1) The BID regimen group had a significantly lower gastrointestinal bleeding risk than the QD regimen group; 2) the BID regimen group showed a lower rate of major bleeding than the QD regimen group; 3) both groups did not have a significant difference in all death, stroke, and any bleeding rates.

In the last several years, DOACs have been approved as a first-line therapy for stroke prevention in NVAF patients. Compared with

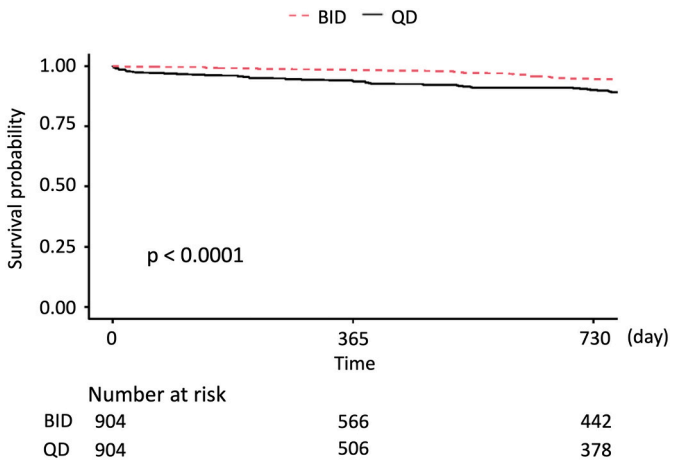

Fig. 3. Kaplan-Meier estimates for gastrointestinal bleeding.
Kaplan-Meier analysis for gastrointestinal bleeding according to QD vs. BID regimens of DOAC in the propensity score-matched population. Patient with BID regimen group less frequently had gastrointestinal bleeding than those with QD regimen group (log-rank P < 0.0001). Abbreviations: GI = gastrointestinal; DOAC = direct oral anticoagulants; BID = twice-daily dosing; QD = once-daily dosing.

warfarin, DOACs have rapid onset and offset action, predictable pharmacodynamics obviating regular therapeutic monitoring, and fewer food-drug or drug-drug interactions [8]. However, gastrointestinal bleeding remains major concern of DOAC use.

4.1. Pathophysiology of gastrointestinal bleeding caused by DOAC

The mechanisms of DOAC-related gastrointestinal bleeding could be summarized as following factors: (1) systemic anticoagulant effect; (2) focal anticoagulant effect; and (3) inhibition of mucosal healing and direct caustic effect [5,8]. The systemic anticoagulant effect is not a specific issue of DOACs, whereas focal anticoagulant effect and focal effect of inhibition of mucosal healing are specific for DOAC. Warfarin is well absorbed and has a bioavailability of over 95 %. Non-absorbed warfarin within the gastrointestinal lumen has no anticoagulant activity. In patients with warfarin, the risk of gastrointestinal bleeding reflects the systemic anticoagulant activity of drug. In contrast, the absorption of DOACs ranges from 7 % to 66 % (Dabigatran; 7 %, Apixaban; 50 %, Edoxaban; 62 %, Rivaroxaban; 66 %) [13] and non-absorbed DOACs within the gastrointestinal lumen has focal anticoagulant effect. Even in healthy volunteers, gastric erosions are noted in 5–10 % [14] and small bowel erosions are noted in 10–15 % [15]. The focal effect of DOACs may promote the gastrointestinal bleeding in these asymptomatic patients. The mucosal healing inhibition of DOACs may directly increase gastrointestinal bleeding. Dabigatran targets the protease, trypsin, while Rivaroxaban and Apixaban target chymotrypsin. Rivaroxaban targets matriptase as well [16]. Trypsin and chymotrypsin, and matriptase are digestive enzymes found within the gastrointestinal tract and their secretion leads to mucosal vulnerability that makes the gastrointestinal tract more prone to gastric bleeding. Through binding interactions with the DOACs, these enzymes become trapped within the gastrointestinal tract and lead to increased mucosal vulnerability and thus increased rates of gastrointestinal bleeding. Dabigatran is the only DOAC to contain an acid and would be the only DOAC to lead to gastrointestinal bleeding through a direct caustic effect [16]. This

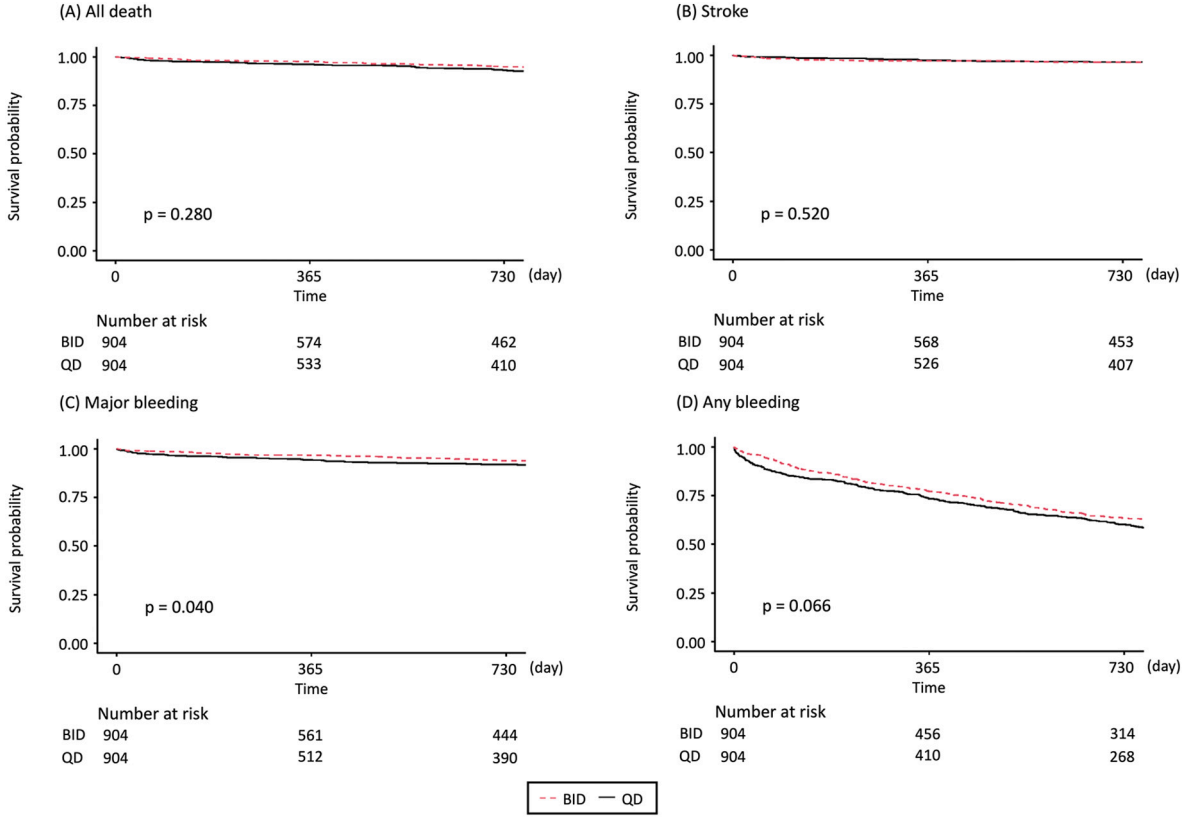

Fig. 4. Kaplan-Meier estimates for secondary endpoints.
Kaplan-Meier analysis for secondary endpoints according to QD vs. BID regiments of DOAC in the propensity score-matched population. There was no significant difference between the BID regimen group and the QD regimen group in each endpoint in all death (A), stroke (B), and any bleeding (D). Patients with the QD regimens experienced major bleeding more frequently than those with the BID regimens (C) (log-rank P = 0.040). Abbreviations: DOAC = direct oral anticoagulants; BID = twice-daily dosing; QD = once-daily dosing.

Table 3
Outcomes in the BID and QD groups.

	BID (N = 904)			QD (N = 904)			P value*
	Patients with event, n	Follow-up, person-year	Rate/100 person-year	Patients with event, n	Follow-up, person-year	Rate/100 person-year	
Gastrointestinal bleeding	80	2286	3.5	110	1781	6.2	<0.0001
All death	54	2400	2.3	56	1924	2.9	0.280
Stroke	36	2357	1.5	27	1903	1.4	0.520
Major bleeding	63	2321	2.7	74	1834	4	0.040
Any bleeding	350	1651	21.2	340	1342	25.3	0.066

BID = twice-daily dosing; QD = once-daily dosing.
* P value for log rank test.

Table 4
Subgroup analysis of the primary endpoint (gastrointestinal bleeding).

	HR (95 % CI)	P value	P value for interaction
Overall	0.556 (0.416, 0.743)	<0.001	
Age			0.292
≥75 years	0.482 (0.319, 0.729)	<0.001	
<75 years	0.618 (0.411, 0.930)	0.021	
Sex			0.561
Men	0.581 (0.403, 0.837)	0.004	
Women	0.521 (0.323, 0.838)	0.007	
Diabetes mellitus			0.548
Present	0.620 (0.381, 1.010)	0.055	
Absent	0.520 (0.362, 0.747)	<0.001	
Hypertension			0.675
Present	0.540 (0.391, 0.745)	<0.001	
Absent	0.652 (0.334, 1.27)	0.209	
Dyslipidemia			0.024
Present	0.684 (0.487, 0.960)	0.028	
Absent	0.312 (0.171, 0.567)	<0.001	

Hazard ratio for gastrointestinal bleeding was assessed in multiple subgroups.
BID = twice-daily dosing; QD = once-daily dosing.

pathophysiology may explain the reason why DOACs have higher gastrointestinal bleeding risk than warfarin. However, only edoxaban targets neither trypsin nor chymotrypsin [16]. Nevertheless, it showed the higher risk of gastrointestinal bleeding than warfarin [4]. This suggested that the first two factors, systemic anticoagulant effect and focal anticoagulant effect, may play a major role in the gastrointestinal bleeding in patients treated with DOACs. We hypothesized that the BID regimen rather than the QD regimen keeps the systemic anticoagulant effect and focal anticoagulant effect more stable and therefore provides better safety since it keeps drug concentration in the gut lumen and vessels more stable in the narrow range (Fig. 1).

4.2. BID versus QD regimen of DOAC

In the pivotal trials, gastrointestinal bleeding rates of DOACs were higher than those of warfarin especially in QD DOAC regimens: rivaroxaban (20 mg once-daily) [2] and edoxaban (60 mg once-daily) [4]. One of the possible reasons would be their relatively high peak level of plasma drug concentration which is reportedly associated with gastrointestinal bleeding [5–7]. Change in the focal drug concentration inside the gut lumen would also be similar to the plasma drug concentration. The BID regimen should theoretically minimize daily fluctuation in plasma and focal concentration, consequently lower the peak level of plasma and focal drug concentration. We depicted the theoretical pharmacokinetic profile of a drug: a dose X administered QD, and a dose X/2 administered BID (Fig. 1). Twice daily dosing may be safer than once daily dosing when a patient takes the medicine mistakenly. If a patient takes an extra dose incidentally, drug concentration level easily exceeds safety therapeutic range which could lead gastrointestinal bleeding in the QD regimen group. Alternatively, the concentration level of BID drug regimen could be sustained within the optimal therapeutic range. In contrast to clinical trials, adherence to anticoagulation therapy is one of the big issues in the real-world setting. BID regimen could be beneficial for maintaining the drug concentration in the therapeutic range even in patients with suboptimal adherence. These may explain the results that BID regimen decreased gastrointestinal bleeding risk compared with QD regimen [17]. A large-scale retrospective cohort study (N = 581,451) reported that the QD rivaroxaban was associated with a significantly increased risk of hemorrhagic events compared with the BID apixaban, including gastrointestinal bleeding (35.2/1000 person-years vs. 16.3/1000 person-years; rate difference, 19.0 [95 % CI, 17.9 to 20.1]; hazard ratio, 2.09 [95 % CI, 2.01 to 2.18]) [18]. This result also supports our findings. It is of note that high-dose dabigatran (150 mg twice-daily) was related to high risk of gastrointestinal bleeding compared with warfarin [1]. There seems to be a reason specific for dabigatran. The pellets of dabigatran contain a tartaric acid core coated by dabigatran etexilate. This construction generates an acidic microenvironment, then increases drug dissolution and gastric absorption [19]. However, the tartaric acid in dabigatran etexilate is postulated to cause direct caustic injury [5]. Hence, high-dose dabigatran might have shown a relatively high risk of gastrointestinal bleeding in spite of its BID regimen superiority.

4.3. Study strength and limitation

The present prospective observational registry would have, to date, relatively large Asian cohort, and long follow-up period. Data of the fourth DOAC, edoxaban, was uniquely available due to the geographical reason. A few limitations, however, need to be acknowledged. First, the present study is a single center prospective registry. The institution is located in the urban area in Japan. Generalizability to other regions is limited. Second, there might be unknown and unmeasured relevant factors such as frailty which were not integrated into the adjustment of propensity score matching. The unexpected selection bias could not be totally eliminated in our study setting. Lastly, we could not evaluate the drug adherence and its difference between the BID and QD regimens. Previous studies revealed that patients' adherence was significantly higher for drugs with the QD regimens than the BID regimens [9,20,21]. Readers should keep in their mind that the current results reflect a "real-world" clinical data of Asians population and are just hypothesis-generating. The present study suggests the necessity of further prospective large-scale randomized controlled trials.

5. Conclusions

The BID regimen of DOAC as compared with the QD regimen was associated with reduced risk of gastrointestinal bleeding. Further prospective randomized clinical trials are warranted to confirm the superiority of the BID regimen over the QD regimen in the real-world settings.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Y. Sotomi, A. Hirata, Y. Sakata, A. Hirayama, and Y. Higuchi received grants, travel expenses, and speaker honorarium from Daiichi-Sankyo, Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb. The other authors have nothing to disclose.

Acknowledgements

The authors thank Ayaka Murakami, Tomoe Yamamoto, Ayako Fukao, and Yoko Inoue for their invaluable support in data collection and management.

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