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Original Article

Observational study of the effects of dabigatran on gastrointestinal symptoms in patients with non-valvular atrial fibrillation

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ABSTRACT

Background: Dyspepsia (including upper abdominal pain, abdominal pain, abdominal discomfort, epigastric discomfort, and dyspepsia) is a symptom that is carefully monitored during dabigatran treatment. However, detailed information on dyspepsia, including onset, duration, severity, and use of drug treatment, has not yet been established in Japanese patients.

Methods: We conducted a multi-center, prospective, open-label, randomized, and parallel-group-comparison observational study of 309 patients with non-valvular atrial fibrillation who had been newly prescribed dabigatran at 19 institutes in Japan. Gastrointestinal adverse events were evaluated using the Global Overall Severity (GOS) scale self-reports to describe symptoms and to assess frequency and severity of symptoms (Part 1). Thereafter, patients with a GOS score ≥ 3 were randomized to receive a 4-week course of a proton pump inhibitor, an H2-receptor antagonist or a gastric mucosal protective drug (Part 2).

Results: The incidence of dyspepsia symptoms due to dabigatran was 17.2% (53/309, 95% confidence interval 13.1–21.8%), with 77% of events occurring within 10 days of initiation. Five patients discontinued the study because of dyspepsia. At the end of the observation period, the mean GOS score of those reporting dyspepsia was 3.5 ± 1.7, with 11.3% (35/309) reporting a score ≥ 3. Substantial differences in the incidence of dyspepsia were observed between the study institutes (0–41%). In the multivariate regression analysis, no significant factor was found to affect incidence or severity of dyspepsia. The majority (83–100%) reported that symptoms improved with treatment (GOS score ≤ 2), and there was no significant difference between the three different treatment groups.

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Conclusions: The reported symptoms of dyspepsia were generally mild, but were moderate in approximately 10% of patients. Proton pump inhibitors, H2-receptor antagonists, and rebamipide seemed to be equally effective in relieving dabigatran-related dyspepsia (umin-CTR UMIN000007579).

1. Introduction

Dabigatran etexilate, an orally administered pro-drug, is rapidly converted by a serum esterase to dabigatran, a potent, direct, and competitive inhibitor of thrombin. It has an absolute bioavailability of 6.5% and a serum half-life of 12–17 h, with 80% of the administered dose being excreted by the kidneys. Dabigatran is reported to have low potential for drug–drug interactions, and no drug–food interactions. It also has the advantage of not requiring therapeutic monitoring [1]. The therapeutic effects of dabigatran in patients with atrial fibrillation (AF) have been evaluated in several clinical trials at doses of 220 mg twice daily and 300 mg daily [2–4].

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) [4] trial was designed to compare two fixed doses of dabigatran (110 mg or 150 mg twice daily) with open-label use of warfarin in 18,113 patients from 44 countries who had atrial fibrillation, and were at increased risk for stroke. The trial demonstrated that the incidences of stroke and hemorrhage were lower in patients administered dabigatran than in those administered warfarin. However, the only adverse effect (AE) that was significantly more common in dabigatran patients than in warfarin patients was dyspepsia (defined as upper abdominal pain, abdominal pain, abdominal discomfort, epigastric discomfort, and dyspepsia). An analysis of the 326 Japanese participants in the RE-LY trial found that the efficacy and safety profile of dabigatran were essentially the same in Japanese participants as the rest of the study population, but that the incidence of dyspepsia was higher [5]. The RE-COVER double-blind, double-dummy, randomized trial of 6 months of treatment with dabigatran (150 mg twice daily) compared with dose-adjusted warfarin in 2539 patients with AF reported a significantly higher incidence of dyspepsia in the dabigatran group (2.9%) versus the warfarin group (0.6%). However, the definition of dyspepsia differed from that chosen by the RE-LY investigators [6]. These large trials suggest that dyspepsia is a relatively common and important side effect of dabigatran treatment. However, none used dyspepsia-like symptoms as a pre-defined endpoint, nor did they record onset, time course and duration, symptom description and localization, or severity of the symptoms.

Joyce et al. [7] reported that patients with AF commonly reported dyspepsia. Self-reported dyspepsia is more common in those with more severe AF and a higher comorbidity burden. The extent of self-reported dyspepsia also correlated with a lower likelihood of reported administration of appropriate AF pharmacotherapy or anticoagulation for stroke prevention.

Consequently, we undertook a prospective observational study to evaluate and determine the incidence and severity of dyspepsia in Japanese patients with non-valvular atrial fibrillation (NVAF) at high risk of stroke who had been newly prescribed dabigatran. In addition, we evaluated the efficacy and safety of proton pump inhibitors, H2-receptor antagonists, and gastric mucosal protective drugs in patients who developed symptoms of severe dyspepsia (≥ 3 of on a Global Overall Severity, GOS score [8]) after commencing dabigatran by means of a randomized, open-labeled, parallel-group comparison study.

2. Material and methods

The study was approved by the institutional review board at each participating study site. Prior to commencing any study procedure, the purposes and methods of this study were explained to all participants. Written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki as well as the ethical guidelines for clinical studies [9].

2.1. Study design

This observational study was conducted using a multi-center, prospective, open-label, randomized, and parallel-group comparison design. The outline of the study schedule is shown in Fig. 1.

In the study, a total of 309 patients with NVAF who had been newly prescribed dabigatran between April 2012 and January 2013 at 19 institutes in Japan were enrolled. Each participant subjectively scored dyspepsia symptoms especially for digestive AEs of dabigatran using the GOS scale to evaluate frequency, description and severity (Table 1).

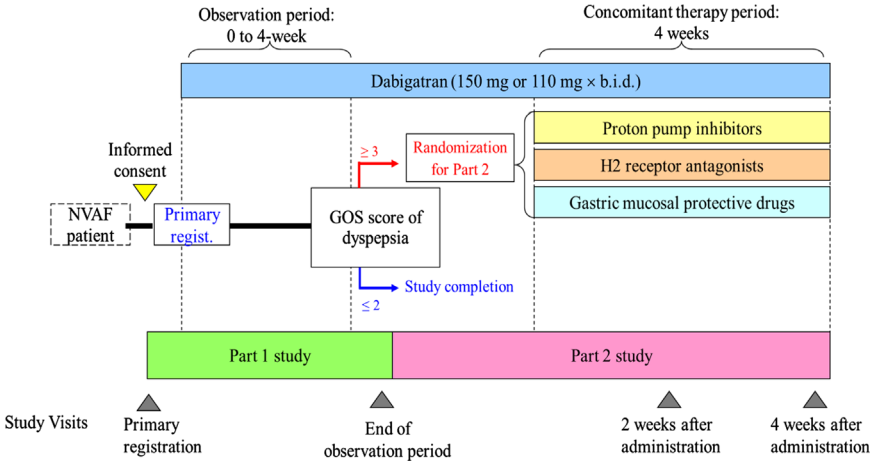

Fig. 1. Study protocol. b.i.d., twice daily; NVAF, non-valvular atrial fibrillation; and GOS, Global overall severity.

Table 1
Symptom severity in the global overall symptom (GOS) scale [8].

1. No problem
2. Minimal problem (can be easily ignored without effort)
3. Mild problem (can be ignored with effort)
4. Moderate problem (cannot be ignored but does not influence my daily activities)
5. Moderately severe problem (cannot be ignored and occasionally limits my daily activities)
6. Severe problem (cannot be ignored and often limits my concentration on daily activities)
7. Very severe problem (cannot be ignored and markedly limits my daily activities and often requires rest)

This study consisted of two parts: Part 1 was to investigate the incidence and severity of dabigatran-related dyspepsia symptoms targeted all enrolled patients and Part 2 was to evaluate the therapeutic efficacy and safety of proton pump inhibitors, H2-receptor antagonists, and gastric mucosal protective drugs prescribed to subjects who had experienced dyspepsia symptoms with a GOS score of 3 or higher during Part 1 of the study.

The primary endpoints were the frequency, description, and severity of dyspepsia symptoms during the observational study period, and the improvement rates of dyspepsia symptoms when patients were administered proton pump inhibitors, H2-receptor antagonists and gastric mucosal protective drugs.

The secondary endpoints of the study were

- Proportion of patients with improvement in the severity of dyspepsia symptoms by 2 points or more on the GOS scale.
- Proportion of patients with resolution of dyspepsia symptoms (where the resolution was defined as a reduction in GOS score to 1).
- Proportion of patients with improvement in dyspepsia symptoms (where improvement was defined as those patients who still had dyspepsia symptoms but the GOS score was reduced to 1 or 2).
- Post-treatment severity of dyspepsia symptoms compared with baseline (i.e., change in the GOS score from baseline).
- Safety, measured by the occurrence of stroke, systemic embolism, bleeding, and discontinuation of dabigatran administration because of any adverse events (AEs).

2.2. Study subjects

Male and female patients who were in- or out-patients at the study hospitals who met all of the following criteria were eligible to be enrolled in Part 1 of the study: (1) a diagnosis of NVAF (paroxysmal, persistent, or permanent); (2) dabigatran therapy was to be initiated to prevent ischemic stroke and systemic embolism associated with NVAF; (3) had no symptoms of dyspepsia at baseline (dyspepsia, upper abdominal pain, abdominal pain, abdominal discomfort, or epigastric discomfort); (4) aged 20 years or older at the time of giving consent; and (5) capable of providing written consent in person to participate in the study. For Part 2, participants in Part 1 who had met all the following criteria were eligible to proceed to Part 2 of the study: (1) administered dabigatran for prevention of ischemic stroke and systemic embolism associated with NVAF; and (2) had experienced symptoms of dyspepsia with a GOS score of 3 or higher during Part 1.

The key exclusion criteria were: (1) undergoing dialysis or diagnosis of a severe renal disorder (creatinine clearance < 30 mL/min): (2) on-going hemorrhage; (3) diagnosis of any organic lesion posing a clinically significant risk for bleeding (including onset of hemorrhagic stroke within the past 6 months); (4) having a spinal or epidural catheter in situ; and (5) use of oral itraconazole. Participants in Part 1 who met any of the following exclusion criteria were not eligible to proceed to Part 2: (1) use of proton pump inhibitors, H2-receptor antagonists or rebamipide during Part 1; (2) occurrence of dyspepsia symptoms not attributable to dabigatran, such as excess alcohol consumption, overeating, acute stress or being administered concomitant medication with other drugs known to cause dyspepsia; (3) diagnosis of upper gastrointestinal bleeding or peptic ulcer disease during Part 1; and (4) diagnosis of gastroesophageal reflux disease confirmed by endoscopy or radiograph during Part 1.

Eligible participants were prescribed oral dabigatran with 150 mg (75 mg capsule $\times 2$) administered twice daily or 110 mg (110 mg capsule $\times 1$) administered twice daily based on the dosage regimen approved in Japan. The daily dose of dabigatran was selected by the investigators, and was based on patients' renal function, age, and risk of bleeding. In cases when dabigatran replaced warfarin, dabigatran was initiated when the international normalized ratio (INR) was < 2.0.

The incidence and severity of dyspepsia symptoms were evaluated for 4 weeks, or until the GOS score for the severity of dyspepsia exceeded 2. At the end of the observation period (week 4), patients whose GOS score remained 2 or less were excluded the study. Patients eligible for the second registration were randomized to one of three treatment groups: a proton pump inhibitor group, a H2-receptor antagonist group or a mucosal protective agent group. A dynamic allocation method was applied with adjustment factors for age (< 70 years, ≥ 70 years), gender, and severity of dyspepsia symptoms (GOS score 3, 4, or ≥ 5).

Based on the treatment group randomized at the second registration, one drug from the treatment group listed below was administered for 4 weeks; generic products were acceptable. At the time of entry into the second registration, patients already taking a mucosal protective agent or other products to treat gastric ulcer or gastritis (including over-the-counter drugs) were asked to discontinue treatment to avoid concomitant administration.

Acceptable drugs were

(1) Proton pump inhibitors: omeprazole, lansoprazole, rabeprazole, or esomeprazole.
(2) H2-receptor antagonists: famotidine, ranitidine, nizatidine, lafutidine, cimetidine, or roxatidine.
(3) Mucosal protective agent: rebamipide.

2.3. Data analysis

The frequencies and summary statistics of demographic data were calculated for eligible patients at primary registration in patients with and without dyspepsia. The incidence and 95% confidence intervals (CIs), days to reporting of symptoms (mean $\pm$ standard deviation [SD]), and severity of symptoms (GOS score: mean $\pm$ SD) at the end of Part 1 were calculated. Adverse events and adverse drug reactions (ADRs) due to dabigatran were summarized by events. Factors that might have affected the incidence and severity of dyspepsia symptoms were subject to exploratory evaluation.

In Part 2 of the study, we analyzed the frequencies and summary statistics of demographic data of each treatment group to verify their homogeneity, the rate of improvement in symptoms of each group defined by the proportion achieving GOS severity scores of 1 or 2, and the occurrence of AEs and ADRs attributable to dabigatran summarized by the events and treatment group.

We estimated that a total of 500 patients were needed to establish the frequency and severity of dyspepsia symptoms

during administration of dabigatran. Based on the sub-group analysis of 326 Japanese patients in the RE-LY trial [5], the incidence of dyspepsia was approximately 25%. We estimated that the number of subjects for second registration was a total of 120 patients (40 patients for each group). We supposed that this target number of patients to perform an exploratory evaluation of the effects of treatment on dyspepsia symptoms in treated groups. Data analysis was conducted by Mebix Co. Ltd. (Tokyo, Japan) using the SAS program (ver. 9.3).

3. Results

This study was conducted from April 2012 to January 2013 at 19 institutes in Japan. We enrolled 309 patients with NVAF who had been newly prescribed dabigatran. The disposition of study patients is summarized in Fig. 2.

3.1. Part 1 of the study

3.1.1. Characteristics of study patients

Patients' characteristics at enrollment are summarized in Table 2. The mean age of the patients was 66.5 years, and 62.8% were female. Approximately 38% had a history of warfarin treatment. The mean $CHADS_2$ score was 1.3 [10].

3.1.2. Dosage and adherence to dabigatran

A daily dose of 220 mg (110 mg capsule × 2, b.i.d.) was the most common dabigatran dosage (264/309, 85.4%) followed by 300 mg (150 mg capsule × 2, b.i.d; 41, 13.3%) and 150 mg (75 mg capsule × 2, b.i.d; 4, 1.3%). The patient adherence to dabigatran was good; 278 (91.7%) patients administered 100% of the dosage and 21 (6.9%) administered ≥ 75% but no patient failed to take any dabigatran (1 administered ≥ 50%, and less than 75% and 3 for < 50%).

The total interruption rate of dabigatran treatment was 6.5% (20/309), and the breakdown in treatment was due to bleeding ADRs in 1.3% (gastrointestinal bleeding: 1 case, hematuria: 2 cases, ulorrhagia: 1 case, epistaxis: 1 case), other ADRs in 1.0% (skeletal muscle pain: 1 case, drug eruption: 1 case, and intolerance: 1 case), dyspepsia symptoms 1.6% (5 cases), development of complications 0.3% (intravitreal suspended solids: 1 case), and other reasons 2.3% (7 cases).

3.1.3. Incidence, days to reporting, and severity of dyspepsia symptoms

Incidences, days to expression, and severities of dyspepsia symptoms are summarized in Table 3.

In the total study patients ($n=309$), the incidence of dyspepsia symptoms was 17.2% (53/309, 95% CI: 13.1–21.8%), mean days to reporting of dyspepsia symptoms was 7.1 days (min.: 1 day, max.: 22 days, and median: 5 days), and the mean severity of symptoms (GOS score) at the end of Part 1 was 3.5 ± 1.7 (min.: 1.0, max.: 7.0, and median: 4.0). Nearly 80% (41/53) of the events occurred within 10 days after initiation of dabigatran treatment. A total of 11.3% (35/309, 95% CI: 8.0–15.4%) of patients had a GOS score ≥ 3 at the end of Part 1 of the study. Dyspepsia was most common (7.4%), followed by epigastric discomfort (5.5%), and abdominal discomfort (4.9%). Upper abdominal pain showed the shortest days to occurrence (min.: 2 days, max.: 15 days, and mean: 4.8 days) and abdominal discomfort showed the longest days to occurrence (min.: 1 day, max.: 22 days and mean: 9.5 days).

In patients who were administered continuous drug treatment for gastritis and gastric ulcer ($n=50$), the incidence of dyspepsia symptoms was 18.0% (95% CI: 8.6–31.4%), mean days to reporting of symptoms was 11.4 days (min.: 6 days, max.: 22 days, and median: 9 days), and mean severity of dyspepsia symptoms (GOS score) at the end of Part 1 was 4.2 (min.: 1.0, max.: 7.0, and median: 4.0). A comparison of each symptom showed abdominal discomfort had the highest incidence (10.0%, 5/50) following by dyspepsia (4.0%, 2/50) and epigastric discomfort (4.0%, 2/50), which were comparable figures to those for total patients.

3.1.4. Differences in incidence of dyspepsia symptoms among study institutes

The incidence of dyspepsia symptoms by study institute are summarized in Fig. 3. The highest incidence (41%) was shown in institute G followed by institute H (38%) and institute I (33%), while 6 institutes reported no incidence of dyspepsia symptoms.

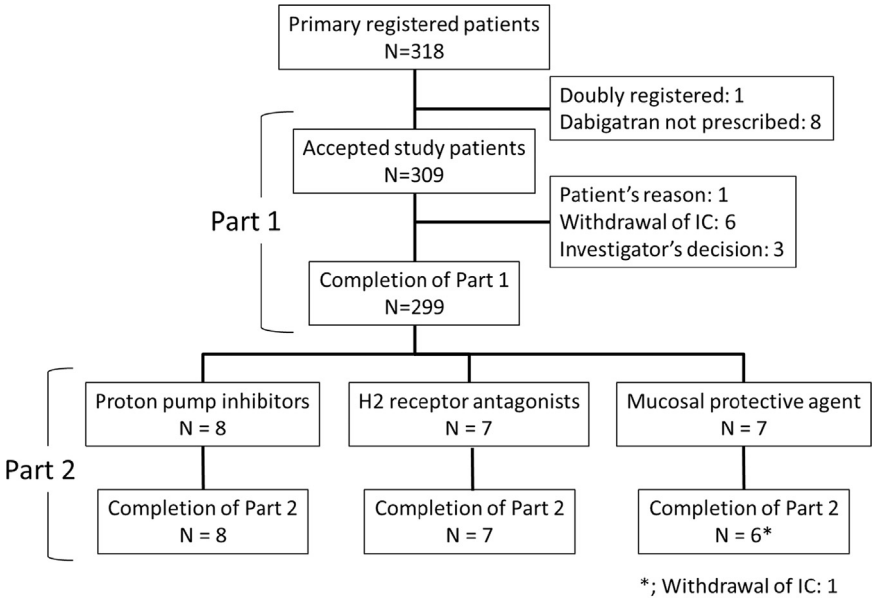

Fig. 2. Study participant flow chart. IC, informed consent.

Table 2
Participant baseline characteristics at enrollment.

Item	(*n*=309)	Item	(*n*=309)
Age (years)	66.5 ± 9.5[a]	Diabetes mellitus	46 (14.9%)
≥ 70 years	128 (41.4%)[b]	Hypertension	207 (67.0%)
Gender (Female)	194 (62.8%)	Hyperlipidemia	109 (35.3%)
BMI	24.0 ± 3.6	Ccr (mL/min)	80.2 ± 27.0
Atrial fibrillation		Ccr < 30	0 (0.0%)
Paroxysmal	174 (56.9%)	Ccr ≤ 50	24 (7.8%)
Persistent	60 (19.6%)	Ccr > 50	285 (92.2%)
Permanent	72 (23.5%)	History of warfarin use	118 (38.2%)
$CHADS_2$ score	1.3 ± 1.1	Use of drugs for gastric ulcer or gastritis	50 (16.2%)
History of gastroduodenal ulcer	18 (5.8%)	Proton pump inhibitors	27 (8.7%)
History of cerebrovascular disease	29 (9.4%)	H2-receptor antagonists	11 (3.6%)
History of coronary artery disease	22 (7.1%)	Rebamipide	12 (3.9%)
History of congestive heart failure	43 (13.9%)		

Abbreviations: BMI, body mass index; $CHADS_2$, a clinical prediction tool for estimating the risk of stroke in patients with non-rheumatic atrial fibrillation [10]; and Ccr: creatinine clearance.

[a] Mean ± standard deviation.
[b] Number of patients (percentage).

Table 3
Incidence, days to reporting, and severities of dyspepsia symptoms.

	Frequency[a] (patients)	Incidence (%, 95% CI)	Days to reporting	GOS score at the end of Part 1
(a) *Total study patients (n=309)*				
No. of patients with dyspepsia symptoms	53	17.2 [13.1–21.8]	7.1 ± 5.6[b]	3.5 ± 1.7
Dyspepsia	23	7.4 [4.8–11.0]	6.3 ± 4.1	3.3 ± 1.4
Upper abdominal pain	5	1.6 [0.5–3.7]	4.8 ± 5.7	4.0 ± 2.6
Abdominal pain	1	0.3 [0.0–1.8]	4.0	6.0
Abdominal discomfort	15	4.9 [2.7–7.9]	9.5 ± 6.8	3.3 ± 1.6
Epigastric discomfort	17	5.5 [3.2–8.7]	7.1 ± 5.8	3.8 ± 1.6
(b) *Patients on continuous drug treatment for gastritis and gastric ulcer (n=50)*				
No. of patients with dyspepsia symptoms	9	18.0 [8.6–31.4]	11.4 ± 5.4[b]	4.2 ± 2.2
Dyspepsia	2	4.0 [0.5–13.7]	8.0	4.0 ± 0.0
Upper abdominal pain	1	2.0 [0.1–10.6]	15.0	2.0
Abdominal pain	0	–	–	–
Abdominal discomfort	5	10.0 [3.3–21.8]	11.5 ± 7.1	3.8 ± 2.3
Epigastric discomfort	2	4.0 [0.5–13.7]	11.0	6.5 ± 0.7

Abbreviations: GOS, global overall severity; 95% CI, 95% confidence intervals.

[a] including patients in whom "Days to reporting" could not be identified.
[b] Mean ± SD.

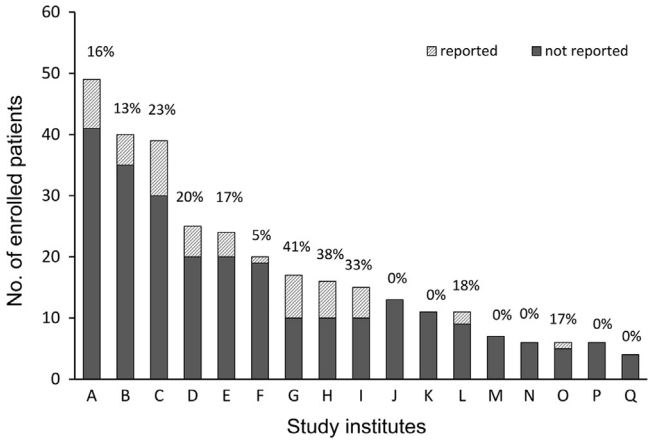

Fig. 3. Part 1: Incidences of dyspepsia symptoms by study institute (*n*=309). Proportion (%) of patients with dyspepsia symptoms in enrolled study patients. Two institutes were excluded as no participants were enrolled in the study.

3.1.5. Developments of stroke, systemic embolism, and bleeding events

To evaluate the safety of dabigatran, key events including stroke, systemic embolism, and bleeding were investigated. No stroke or systemic embolism was reported during the Part 1 period of the study. However, bleeding events occurred in six patients (1.9%), including one case of gastrointestinal bleeding (severe, interrupted), three cases of epistaxis (mild to moderate, interrupted), two cases of hematuria (mild to moderate, discontinued), and one case of ulorrhagia (mild to moderate, interrupted). The outcome for all of these patients was that they all recovered or symptoms improved.

3.1.6. Odds ratios per patients' background factors on dyspepsia

To investigate the influence of patient baseline characteristics on the incidence or severity of dyspepsia symptoms, odds ratios and their 95% CIs were calculated for each of nine baseline characteristics, and the results are summarized in forest plots (Fig. 4).

Multivariate stepwise regression analysis found that none of the nine recorded patient characteristics (age, sex, body mass index (BMI), creatinine clearance, use of concomitant antiplatelet agents, previous use of warfarin, history of peptic ulcers, previous use of drugs for gastric ulcer or gastritis, or daily dose of dabigatran) was significantly associated with the incidence or severity of dyspepsia symptoms (Fig. 4).

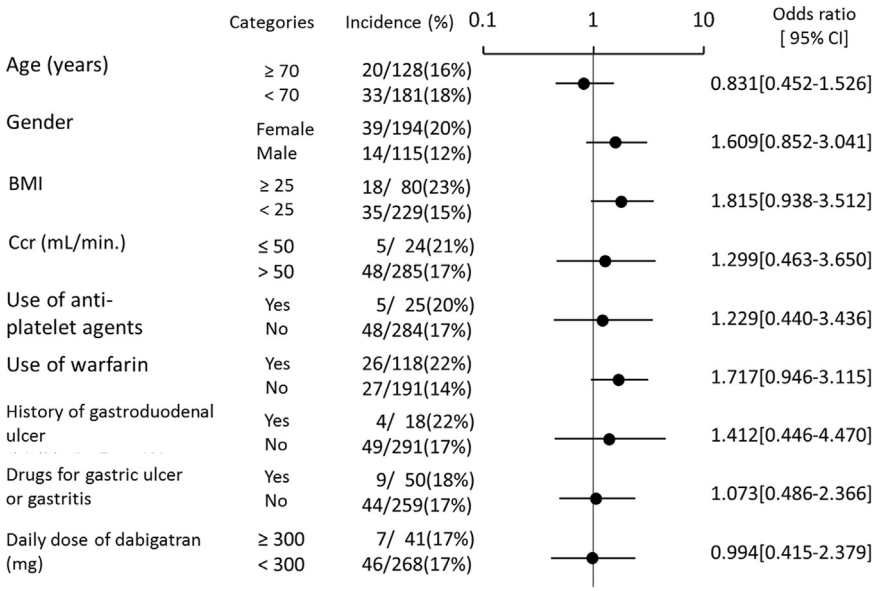

Fig. 4. Part 1: Odds ratios of the impact of patients' background factors on dyspepsia symptoms and its variables ($n=309$). In a Forest plot, the closed dot (•) indicates the odds ratio, and horizontal bar represents the 95% confidence intervals (95% CI). A vertical line at 1 indicates that there is no difference between categories. If the 95% CI does not cross or touch the vertical line at 1, it means that there is a statistically significant difference between the categories ($\alpha=0.05$). BMI, body mass index and Ccr: creatinine clearance.

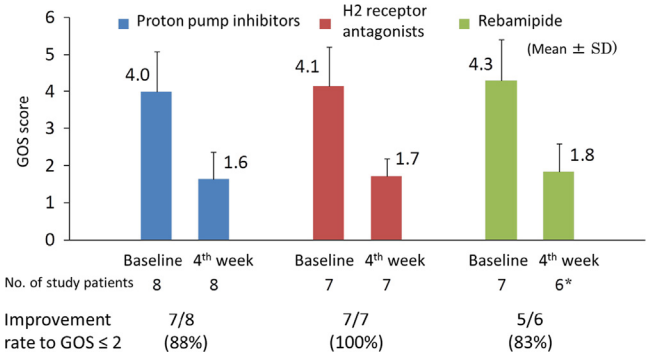

Fig. 5. Part 2: influence of pharmacologic treatment on dyspepsia symptoms. *One patient in the rebamipide group dropped out having withdrawn informed consent. GOS, Global overall severity.

3.2. *Part 2 of the study: therapeutic effect of peptic ulcer treatments on dyspepsia*

In Part 2 of the study, we evaluated any improvement from administering drugs for gastric ulcer or gastritis in patients with severity of dyspepsia symptoms of GOS scores ≥ 3 at the end of Part 1 (Fig. 5). Out of 35 patients with dyspepsia of ≥ 3 of GOS score, 11 patients discontinued the study, and 2 patients could not be randomized according to the attending physician's decision. As a result, because the number of the enrolled patients was smaller than expected, we suggest that these results should be considered to be exploratory.

Dyspepsia symptoms improved within 4 weeks in all treatment groups (Fig. 5): the mean extent of improvement in GOS score from baseline in each group was similar (proton pump inhibitor group improved from 4.0 to 1.6, H2-receptor antagonist group from 4.1 to 1.7 and rebamipide group from 4.3 to 1.8). Almost all patients (83–100%) improved, i.e. GOS scores changed to ≤ 2 at Week 4 (end of Part 2) from ≥ 3 at baseline (end of Part 1). No stroke, systemic embolism, or bleeding event was reported during the Part 2 period of the study.

4. Discussion

We evaluated and determined the incidence and severity of subjective reports of dyspepsia symptoms due to dabigatran. Based on the results of the RE-LY trial [4], the AE that was significantly more common with dabigatran than with warfarin was dyspepsia. In the sub-group (326 Japanese patients) analysis of the RE-LY trial [5], the incidence of dyspepsia symptoms in Japanese patients increased to approximately 25%. Therefore, based on this information regarding dyspepsia, care for gastrointestinal symptoms should be required to use dabigatran for stroke prevention in daily clinical practice in Japan.

Sobieraj et al. [11] reported on the mechanisms that might be responsible for GI symptoms attributable to antithrombotic agents used for stroke prevention in AF. Aspirin directly irritates the gastric mucosa and impairs the ability of prostaglandins to provide mucosal protection [12]. Dabigatran is formulated in pellets containing a tartaric acid core as a low pH is required to enhance absorption, which may lead to higher rates of dyspepsia and the increased risk of GI bleeding with the 150 mg dose [4]. Generally, drug-induced esophageal or upper GI ulcers develop because of contact of drugs with the upper GI mucosa and their subsequent retention there [13]. The mechanism of injury resulting from bisphosphonates includes destruction of the phospholipid layer [14]. Okada et al. [15] found exfoliative esophagitis or esophageal ulcers in the middle-lower esophagus with white membraniform attachments in the endoscopic examination of patients with AF who complained of symptoms suggestive of GI irritation. This finding supports a role for dabigatran's galenic formulation, and, therefore, the incidence of dyspepsia does not differ with differing doses of dabigatran.

The observed incidence of dyspepsia symptoms was 17.2% (95% CI: 13.1–21.8%) and this incidence was considerably lower than the approximately 25% reported in the sub-group analysis of Japanese patients in the RE-LY study. Nonetheless, in the original analysis of the RE-LY study, dyspepsia occurred in 707 patients (11.8%) and 688 patients (11.3%) in the 110-mg and 150-mg dabigatran groups, respectively ($P<0.001$ for both comparisons), and these incidences were lower than our result of 17.2%. Therefore, the incidence of dyspepsia symptoms due to dabigatran may vary from 10% to 20%.

We were not able to identify any risk factors for the development of dyspepsia symptoms from the nine characteristics that we recorded. Although there were trends to suggest that sex, BMI, and previous use of warfarin might be influential, these did not reach statistical significance. We were surprised that a history of upper gastrointestinal ulcer proved not to be a significant risk factor for dyspepsia. The reasons are unclear, but our finding may be explained by differences in the mechanisms of mucosal injury caused by non-steroidal anti-inflammatory drugs and dabigatran.

There were very large differences in the incidences of dyspepsia symptoms reported from our study institutes, which ranged from 0% to 41%. This could be explained by the observation that most institutes that reported no incidence only enrolled a smaller number of patients (≤ 15 patients), or that explanations or guidance about potential adverse reactions given to patients initiated on dabigatran may have differed between investigators.

In Part 2 of the study, the number of patients with GOS scores ≥ 3 at the end of Part 1 (7 or 8 patients for each treatment group) was considerably lower than preliminary planned estimation (40 patients for each treatment group). Consequently, the number of patients in Part 2 was too small to evaluate and compare the improvement effects among drugs for gastric ulcer or gastritis on dabigatran-related dyspepsia, other than that each class of drug appeared to be effective within 4 weeks of starting treatment. These findings might indicate that the mechanisms underlying dyspepsia are totally different between other gastrointestinal-toxic drugs and dabigatran.

In general, dabigatran was well tolerated by patients in this observational study. Dyspepsia occurred in 17.2% of patients at initiation of therapy, but was mild or moderate in intensity. When dyspepsia symptoms were more intrusive in patients, it responded well to treatment with proton pump inhibitors, H2-receptor antagonists, or rebamipide.

5. Conclusions

This prospective observational study was conducted to evaluate the incidence and degree of severity of subjectively reported patient symptoms of dyspepsia due to dabigatran treatment. The incidence of dyspepsia symptoms (GOS scale $>=3$) was 17.2%. We found no significant factors in patient characteristics that could predict dyspepsia symptoms, although the incidence was significantly different among the different study institutes that participated in the study. Proton pump inhibitors, H2-receptor antagonists, and rebamipide improved the dyspepsia symptoms due to dabigatran treatment.

Conflict of interest

T. Yamashita has received research grants from Boehringer-Ingelheim and Daiichi-Sankyo, and honoraria from Boehringer-Ingelheim, Bayer, Bristol-Myers Squibb, Pfizer, and Daiichi-Sankyo.

E. Watanabe is on the advisory panel of Biotronik Japan and received honoraria for lecture fees from Bayer and Boehringer-Ingelheim.

T. Ikeda is on the advisory panel of Boehringer-Ingelheim, Bayer, Bristol-Myers Squibb, and Pfizer. and received research support from Boehringer-Ingelheim, Bayer, and Bristol-Myers Squibb, and honoraria for lecture fees from Boehringer-Ingelheim, Bayer, Bristol-Myers Squibb, and Pfizer.

T. Shiga received research support from Daiichi-Sankyo and honoraria for lecture fees from Daiichi-Sankyo, Boehringer-Ingelheim, Bayer, and Bristol-Myers Squibb.

K.F. Kusano is an advisory panel of Bayer and received honoraria for lecture fees from Bayer, Pfizer, Daiichi-Sankyo, Boehringer-Ingelheim, and Bristol-Myers Squibb.

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