Burden of upper gastrointestinal symptoms in patients prescribed dabigatran for stroke prevention

Pak-Hei Chan[1], Jo-Jo Hai[1], Duo Huang[1], Mei-Han Ho[1], Esther W Chan[2], Bernard Man-Yung Cheung[3], Annie On-On Chan[4], Ian Chi-Kei Wong[2], Hung-Fat Tse[1], Ivan Fan-Ngai Hung[4] and Chung-Wah Siu[1]

Abstract

Background: Dabigatran, a non-vitamin K antagonist oral anticoagulant, has been shown to prevent stroke in patients with non-valvular atrial fibrillation. Nonetheless, studies show that 10%–30% of those prescribed dabigatran experience dyspepsia that may eventually lead to discontinuation of therapy and loss of clinical benefit.

Aim: To evaluate the gastrointestinal tolerability of dabigatran utilizing a validated questionnaire, as well as determining subsequent non-compliance and drug discontinuation.

Method: This is an observational study. All patients were assessed by a validated questionnaire, Hong Kong dyspepsia index, prior to drug prescription and again 4 weeks later.

Results: In this study, 115 patients with non-valvular atrial fibrillation (mean age: 74.6 ± 11.4 years; mean CHA_2DS_2-VASc score was 3.39 ± 1.59) were prescribed dabigatran. At baseline, the mean Hong Kong dyspepsia index was 12.9 ± 1.6 and nine patients had significant dyspepsia (Hong Kong dyspepsia index $\geqslant 16$). After 4 weeks, the mean Hong Kong dyspepsia index was similar at 12.6 ± 1.9 ($p = 0.23$). There was no change in Hong Kong dyspepsia index after initiation of dabigatran in 59 (51.3%) patients, and improvement in 37 (32.2%). Only 19 (16.5%) patients had worsening of Hong Kong dyspepsia index, and among these 19 patients, only 1 patient (0.9%) discontinued dabigatran due to significant dyspepsia.

Conclusion: Worsening of dyspepsia with dabigatran 110 mg twice daily was uncommon with correct drug administration and clear instructions provided. Systematic assessment of dyspeptic symptoms using a validated questionnaire (i.e. Hong Kong dyspepsia index) before and after treatment initiation allows a more objective comparison of dyspeptic symptoms.

Keywords

Dabigatran, atrial fibrillation, upper gastrointestinal symptoms

Introduction

Atrial fibrillation (AF) confers a five-fold increased risk of ischemic stroke.[1–4] A vitamin K antagonist (VKA) oral anticoagulant (OAC) has been shown to be effective in preventing ischemic stroke in patients with AF.[5] International guidelines recommend the use of oral anticoagulation to prevent stroke in such patients, except in those with a CHA_2DS_2-VASc score = 0.[6,7] Nevertheless, studies have shown that VKA-OACs are overtly underused in clinical practice due to the difficulty in maintaining good anticoagulation control, as well as the fear of life-threatening bleeding complications.[8–10]

Dabigatran, the first commercially available non-vitamin K antagonist oral anticoagulant (NOAC), has revolutionized

[1]Division of Cardiology, Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[3]Division of Clinical Pharmacology, Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[4]Division of Gastroenterology and Hepatology, Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

Corresponding author:
Chung-Wah Siu, Division of Cardiology, Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong.
Email: cwdsiu@hku.hk

the management of stroke prevention in AF. In the RE-LY (Randomized Evaluation of Long-term anticoagulation therapY) study, dabigatran 110 mg twice daily was shown to be comparable to an adjusted dose of VKA in reducing stroke and systemic embolism, but associated with a lower risk of major bleeding, in particular intracranial hemorrhage.[11,12] Dabigatran 150 mg twice daily has been shown to be superior to VKA in reducing thromboembolic events, without an increased risk of major bleeding.[11,13,14] Nonetheless, in the RE-LY study, 1 in 10 patients prescribed dabigatran developed dyspepsia that was twice as prevalent compared with those prescribed VKA and led to non-compliance and drug discontinuation.[11]

It has been reported that dyspepsia accounted for 30% of all dabigatran discontinuation in a "real-world" clinical setting,[15] but there is a paucity of prospective data concerning the occurrence of upper gastrointestinal symptoms. Appropriate advice and pre-emptive measures such as advising patients to take the drug with meals may reduce the incidence of upper gastrointestinal symptoms and consequent discontinuation rate. In this study, we sought to assess the gastrointestinal tolerability of dabigatran, as well as the consequent non-compliance and drug termination in order to identify clinical parameters that could predict dabigatran intolerance.

Methods

Patients

Dabigatran-naïve patients who were ≥ 18 years old, had documented non-valvular AF, a $CHA_2DS_2\text{-}VAS_c$ score ≥ 1, and preferred dabigatran to other available OACs were recruited to this study. Those who had significant valvular disease, previous valvular replacement, life expectancy <1 year, creatinine clearance or estimated glomerular filtration rate <30 mL/min, pregnancy or pregnancy plan during the trial period, or any other medical condition that rendered the patient unsuitable for dabigatran were excluded.

Study design

This was a single-center, observational study conducted at Queen Mary Hospital, Hong Kong, between 1 January 2014 and 31 December 2014 that evaluated the upper gastrointestinal symptoms upon initiation of dabigatran in patients with AF. The study complied with the Declaration of Helsinki and was approved by the locally appointed ethics committee. After enrollment, all patients were prescribed dabigatran 110 mg twice per day. They were instructed to take doses 12 h apart, with a meal, and then remain upright for at least 30 min. Demographic data including cardiovascular risk factors, medications, and prior history of gastrointestinal pathologies were recorded at baseline. Individual ischemic stroke risk was calculated at baseline using the $CHA_2DS_2\text{-}VASc$ score (C: congestive heart failure (1 point); H: hypertension (1 point); A_2:

age 65–74 years (1 point) and age ≥ 75 years (2 points); D: diabetes mellitus (1 point); S: prior stroke or transient ischemic attack (2 points); VA: vascular disease (1 point); and Sc: sex category - female (1 point) scores as described in recent guidelines).[6,7] Symptoms of dyspepsia were quantified before and 4 weeks after initiation of dabigatran using a previously validated questionnaire, the Hong Kong dyspepsia index (HKDI).[16,17] Briefly, the index comprises questions about 12 symptoms (epigastric pain, upper abdominal bloating, upper abdominal dull ache, epigastric pain before meals, epigastric pain when anxious, vomiting, nausea, belching, acid regurgitation, heartburn, feeling of acidity in the stomach, and loss of appetite) that are graded on a five-point Likert scale: 1 (none), no symptoms; 2 (mild), symptoms can be easily ignored; 3 (moderate), awareness of symptoms but easily tolerated; 4 (severe), symptoms sufficient to cause interference with normal activity; and 5 (incapacitating), incapacitating symptoms with an inability to perform daily activities and/or require days off work. The index has been previously demonstrated to be discriminative between dyspeptic patients and controls (HKDI ≥ 16).[16] The serial change in HKDI correlated well with improvement and worsening of dyspepsia symptoms after therapeutic intervention (Kendall's $\tau = 0.21$, $p = 0.02$). The primary endpoint of this study was the change in HKDI before and 4 weeks after initiation of dabigatran. The secondary endpoint was dabigatran discontinuation within 4 weeks.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Categorical variables are presented in frequency tables. Statistical comparisons were performed using Student's t-test or Fisher's exact test, as appropriate. The change in HKDI scores from immediately before to 4 weeks after initiation of dabigatran was assessed by paired-sample t-test. Calculations were performed using SPSS software (version 21.0). A p-value <0.05 was considered statistically significant.

Result

A total of 115 patients with non-valvular AF were recruited in this study. Table 1 summarizes their clinical characteristics. The mean age was 74.6 ± 11.4 years, and more than 50% of patients were ≥ 75 years. The mean $CHA_2DS_2\text{-}VASc$ score was 3.39 ± 1.59. Hypertension was present in 80 (69.6%) patients, diabetes mellitus in 30 patients (26.1%), and history of ischemic stroke or transient ischemic attack in 26 (14.8%). Approximately one-third of patients were prescribed warfarin and another third were on aspirin prior to initiation of dabigatran. In addition, five patients had a past history of peptic ulcer (4.3%), four patients had gastritis (3.5%), one had a gastric polyp (0.9%), and one had a gastrointestinal stromal tumor (0.9%).

Table 1. Baseline characteristics of the entire study population.

	All (n = 115)
Age (years)	
Mean age	74.6 ± 11.4
65–74	34 (29.6)
⩾75	62 (53.9)
Female, n (%)	55 (47.8)
Hypertension, n (%)	80 (69.6)
Diabetes mellitus, n (%)	30 (26.1)
Coronary artery disease, n (%)	13 (11.3)
Prior myocardial infarction, n (%)	6 (5.2)
Hypertrophic cardiomyopathy, n (%)	5 (4.3)
Heart failure, n (%)	26 (22.6)
Peripheral artery disease, n (%)	1 (0.9)
Stroke/transient ischemic attack (TIA), n (%)	17 (14.8)
Prior gastrointestinal bleeding, n (%)	2 (1.7)
Mean CHA$_2$DS$_2$-VASc	3.39 ± 1.59
Estimated glomerular filtration rate, n (%)	66.3 ± 15.2 mL/min
Previous warfarin use, n (%)	39 (33.9)
Previous aspirin use, n (%)	37 (32.2)
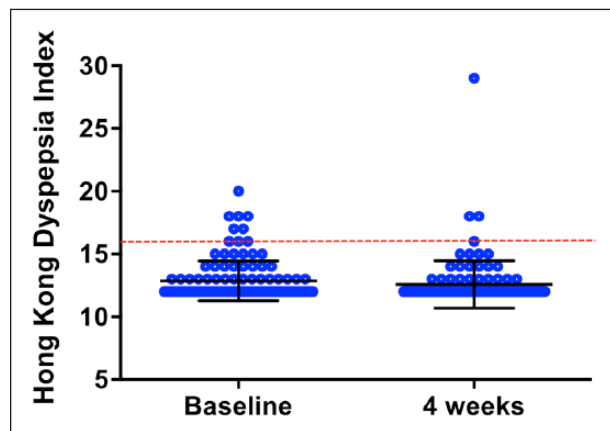
Figure 1. Scatter plot of Hong Kong dyspepsia index at baseline and 4 weeks after initiation of dabigatran. The red dashed line dented the cutoff (⩾16) for significant dyspepsia.[16]

At baseline, the mean HKDI was 12.9 ± 1.6 with a high level ⩾16 present in nine patients (7.8%), that is, significant dyspepsia. A concomitant proton pump inhibitor was prescribed for 47 (40.9%) patients and a histamine-2 (H2) antagonist for 28 (24.3%) patients. No patient was newly commenced on either proton pump inhibitor or H2 antagonist in between these two HKDI questionnaires. After 4 weeks of dabigatran therapy, the mean HKDI was 12.6 ± 1.9, not significantly different to the baseline (p = 0.23, Figure 1). There was no change in HKDI in 59 (51.3%) patients, improvement in 37 (32.2%), and worsening of HKDI in only 19 (16.5%) patients. Of note, the number of patients with significant dyspepsia, that is, HKDI ⩾16, reduced from 9 (7.8%) to 4 (3.5%) after initiation of dabigatran. Only 1

patient (0.9%) who had a past history of duodenal ulcer discontinued dabigatran due to significant dyspepsia despite concomitant use of a proton pump inhibitor. During the 4-week study period, there was no gastrointestinal bleeding or other bleeding episode in our study population.

Table 2 compares the baseline characteristics between patients with and without worsening of HKDI after initiation of dabigatran. Compared with those without worsening of HKDI, patients with worsening HKDI score were more likely to be female (43.8% vs 68.4%, p = 0.05). There was no significant difference in the age, renal function, co-morbidities, baseline HKDI, past history of gastrointestinal disease, or concomitant prescription of a proton pump inhibitor or H$_2$ blocker between the two groups of patients (all with p ⩾ 0.05).

Discussion

In this study, we evaluated the gastrointestinal tolerance of dabigatran in patients who were naïve to dabigatran. Most patients were prescribed either a proton pump inhibitor (40.9%) or a H2 antagonist (24.3%). The HKDI was administered to enable an objective evaluation of dyspeptic symptoms prior to and 4 weeks after the use of dabigatran. Our study showed that when systematically assessed by the HKDI, worsening of dyspepsia with dabigatran 110 mg twice daily was not common, and drug discontinuation due to gastrointestinal symptoms was infrequently encountered. Although previous studies including the RE-LY trial and real-world cohorts showed a high incidence of "dyspepsia,"[11,15,18] this phenomenon was not observed in this study. Of note, the definition of "dyspepsia" employed in these previous studies was less clear and none systematically assessed the occurrence and severity of dyspeptic symptoms before and after initiation of dabigatran therapy.[11,15,18] Patients are generally referred with the description of chronic or recurrent pain or discomfort centered in the upper abdomen,[19] thus assessment of dyspepsia is largely based on patient reports, rather than physiological or laboratory parameters.[16] In this study, we employed a validated questionnaire that comprised the ratings of 12 relevant dyspeptic symptoms to quantify the presence and severity of dyspepsia before and after initiation of dabigatran therapy.[16] Interestingly, with the use of a validated questionnaire, we found that fewer patients reported a worsening of dyspeptic symptoms after initiation of dabigatran. This is in line with the results of a recently published Danish cohort that showed that dabigatran was not associated with increased hospitalization for dyspepsia-like diagnosis, an objective outcome measure.[20] Of note, only one patient (0.9%) in this study discontinued dabigatran due to significant dyspepsia despite concomitant use of a proton pump inhibitor. The previous findings of a high incidence of dyspepsia associated with the use of dabigatran may be related to the lack of systematic symptom assessment. Pre-existing dyspepsia was not recognized or documented with consequent injudicious attribution of dyspeptic symptoms to the use of

Table 2. Baseline characteristics of patients with and without worsening HKDI 4 weeks after initiation of dabigatran.

	Patients without worsening HKDI ($n = 96$)	Patients with worsening HKDI ($n = 19$)	*p*-value
Mean age, (years)	74.1 ± 11.8	76.9 ± 8.8	0.33
Female, *n* (%)	42 (43.8)	13 (68.4)	0.05*
Hypertension, *n* (%)	63 (65.6)	17 (89.5)	0.05
Diabetes mellitus, *n* (%)	24 (25.0)	6 (31.6)	0.55
Prior myocardial infarction, *n* (%)	5 (5.2)	1 (5.3)	1.00
Hypertrophic cardiomyopathy, *n* (%)	4 (4.2)	1 (5.3)	1.00
Heart failure, *n* (%)	21 (21.9)	5 (26.3)	0.67
Stroke/transient ischemic attack (TIA), *n* (%)	15 (15.6)	2 (10.5)	0.73
Prior gastrointestinal bleeding, *n* (%)	1 (1.0)	1 (5.3)	0.30
Prior upper gastrointestinal pathology, *n* (%)	9 (9.4)	3 (15.8)	0.42
Baseline HKDI $\geqslant$ 16	9 (9.4)	0 (0)	0.35
Mean CHA_2DS_2-VASc	3.28 ± 1.63	3.95 ± 1.22	0.10
Estimated glomerular filtration rate (mL/min)	66.8 ± 15.0	63.3 ± 16.0	0.37
Previous warfarin use, *n* (%)	34 (35.4)	5 (26.3)	0.44
Previous aspirin use, *n* (%)	30 (31.3)	7 (36.8)	0.63
Concomitant proton pump inhibitor, *n* (%)	37 (38.5)	10 (52.6)	0.25
Concomitant H2 blocker, *n* (%)	24 (25.0)	4 (21.1)	0.71

dabigatran, rather than a true increase in the incidence or severity of dyspepsia with dabigatran itself.

Another explanation of our results is the focused education of patients about correct administration of dabigatran. Although there is no evidence regarding clinical management of upper gastrointestinal symptoms related to dabigatran, data from the RE-LY study have shown that taking dabigatran with two glasses of water or with food and remaining upright for at least 30 min afterwards are reasonable measures to reduce drug-related dyspepsia.[21] The duration of our study lasted only 4 weeks. Although data from previous studies have suggested that dyspepsia is more likely to occur early after initiation of dabigatran,[20,22] it remains possible that more patients will develop worsening of dyspepsia with time. In addition, the impact of routine use of a proton pump inhibitor or H2 antagonist for patients prescribed dabigatran could not be assessed from this study, and since such practice is becoming more common, it is possible that fewer patients will experience dyspepsia. Finally, we only studied dabigatran at a lower dose of 110 mg twice daily. Previous studies have reported no increase in non-bleeding gastrointestinal adverse events when dabigatran dose was increased to 150 mg twice daily.[20,21]

Limitations

First, this was a single-center study in an Asian population. Due to differences in genetic and environmental factors that may contribute to dyspeptic symptoms, our results may not be generalized to patients of the other ethnicities. Second, we studied a single dose of dabigatran, 110 mg twice daily. The gastrointestinal effects associated with dabigatran 150 mg twice daily remain uncertain. Third, our study lasted for 4 weeks. Longer follow up will be needed to identify those who develop worsening of dyspeptic symptoms late after initiation of dabigatran therapy. Finally, the prescription of a proton pump inhibitor or H2 antagonist was the individual decision of the physician and not randomized.

Conclusion

Our study showed that with correct administration, worsening of dyspepsia with dabigatran 110 mg twice daily was uncommon. Patients should be given instructions regarding administration of dabigatran at the time of treatment initiation and with regular reinforcement thereafter. Systematic assessment of dyspeptic symptoms using a validated questionnaire before and after treatment initiation enables a more objective comparison of symptoms and may prevent unnecessary drug discontinuation.

Informed consent

Written informed consent was waived by the institutional ethics review board for all subjects due to the retrospective nature of this study and the fact that all patients' identity was anonymized.

Trial registration

This trial is not registered in the clinical trial registry due to its observational nature of the study.

References

1. Gladstone DJ, Bui E, Fang J, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke* 2009; 40: 235–240.
2. Huang D, Anguo L, Yue WS, et al. Refinement of ischemic stroke risk in patients with atrial fibrillation and CHA2 DS2 -VASc score of 1. *Pacing Clin Electrophysiol* 2014; 37: 1442–1447.
3. Siu CW, Lip GY, Lam KF, et al. Risk of stroke and intracranial hemorrhage in 9727 Chinese with atrial fibrillation in Hong Kong. *Heart Rhythm* 2014; 11: 1401–1408.
4. Siu CW and Tse HF. Net clinical benefit of warfarin therapy in elderly Chinese patients with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2014; 7: 300–306.
5. Hart RG, Pearce LA and Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; 146: 857–867.
6. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012; 33: 2719–2747.
7. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014; 64: e1–76.
8. Bungard TJ, Ackman ML, Ho G, et al. Adequacy of anticoagulation in patients with atrial fibrillation coming to a hospital. *Pharmacotherapy* 2000; 20: 1060–1065.
9. Hylek EM and Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med* 1994; 120: 897–902.
10. Hylek EM, Skates SJ, Sheehan MA, et al. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1996; 335: 540–546.
11. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361: 1139–1151.
12. Ho CW, Ho MH, Chan PH, et al. Ischemic stroke and intracranial hemorrhage with aspirin dabigatran, and warfarin: impact of quality of anticoagulation control. *Stroke* 2015; 46: 23–30.
13. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365: 883–891.
14. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365: 981–992.
15. Ho MH, Ho CW, Cheung E, et al. Continuation of dabigatran therapy in "real-world" practice in Hong Kong. *PLoS ONE* 2014; 9: e101245.
16. Hu WH, Lam KF, Wong YH, et al. The Hong Kong index of dyspepsia: a validated symptom severity questionnaire for patients with dyspepsia. *J Gastroenterol Hepatol* 2002; 17: 545–551.
17. Tan VP, Cheung TK, Wong WM, et al. Treatment of functional dyspepsia with sertraline: a double-blind randomized placebo-controlled pilot study. *World J Gastroenterol* 2012; 18: 6127–6133.
18. Schulman S, Shortt B, Robinson M, et al. Adherence to anticoagulant treatment with dabigatran in a real-world setting. *J Thromb Haemost* 2013; 11: 1295–1299.
19. Talley NJ and Vakil N. Practice parameters committee of the American College of G. Guidelines for the management of dyspepsia. *Am J Gastroenterol* 2005; 100: 2324–2337.
20. Staerk L, Gislason GH, Lip GY, et al. Risk of gastrointestinal adverse effects of dabigatran compared with warfarin among patients with atrial fibrillation: a nationwide cohort study. *Europace* 2015; 17: 1215–1222.
21. Bytzer P, Connolly SJ, Yang S, et al. Analysis of upper gastrointestinal adverse events among patients given dabigatran in the RE-LY trial. *Clin Gastroenterol Hepatol* 2013; 11: 246–252.e1–5.
22. Huisman MV, Lip GY, Diener HC, et al. Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: resolving uncertainties in routine practice. *Thromb Haemost* 2012; 107: 838–847.