Analysis of Upper Gastrointestinal Adverse Events Among Patients Given Dabigatran in the RE-LY Trial

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BACKGROUND & AIMS: **Dabigatran is an oral and direct inhibitor of thrombin. In a study of patients with atrial fibrillation (the RE-LY trial), twice as many subjects given dabigatran reported dyspepsia-like symptoms compared with those given warfarin (controls). We analyzed data from this trial to quantify upper gastrointestinal nonbleeding adverse events (NB-UGI AEs).**

METHODS: **We analyzed the AE database from the RE-LY trial (18,113 subjects) and assigned NB-UGI AEs to 4 groups: those associated with gastroesophageal reflux (GERD), upper abdominal pain and dyspepsia, dysmotility, or gastroduodenal injury. We analyzed frequency, timing, and severity, and clinical variables associated with NB-UGI AEs.**

RESULTS: **NB-UGI AEs occurred in 16.9% of subjects given dabigatran and in 9.4% of controls (relative risk [RR], 1.81; 95% confidence interval [CI], 1.66%–1.97%; $P < .001$). Rates of AEs were not associated with the dose of dabigatran. Among subjects with any UGI symptom who were given dabigatran (n = 2045), symptoms were rated as mild in 46.3%, moderate in 44.8%, and severe in 8.9%; these values were similar to those of controls. GERD-associated NB-UGI AEs were most frequent among the 4 groups (compared with controls, RR, 3.71; 95% CI, 2.98%–4.62%; $P < .001$). Four percent of subjects stopped taking dabigatran because of NB-UGI AEs (most within 3 months of starting therapy), compared with 1.7% of controls (RR, 2.34; 95% CI, 1.90%–2.88%; $P < .001$). NB-UGI AEs slightly increased risk of major GI bleeding among subjects given dabigatran and controls (6.8% vs 2.3%, $P < .001$).**

CONCLUSIONS: **Among patients given dabigatran for atrial fibrillation, NB-UGI AEs are generally mild or moderate; 4% stopped taking the drug over a median of 21.7 months. The greatest increase was in GERD-type NB-UGI AEs. These observations should guide management and prevention strategies. ClinicalTrials.gov number, NCT00262600.**

Keywords: Upset Stomach; Clinical Trial; Post Hoc Analysis; Side Effect; Toxicity.

Dabigatran is a potent, direct, reversible, and competitive inhibitor of thrombin, and is newly approved for the prevention of stroke/systemic emboli and venous thromboembolic events. In the pivotal global trial comparing dabigatran with warfarin in patients with atrial fibrillation (the RE-LY trial, N = 18,113), dabigatran 110 mg twice daily carried a similar risk of stroke and a lower risk of bleeding, including intracranial bleeding, than warfarin, whereas dabigatran 150 mg twice daily carried a lower risk of stroke (ischemic and/or hemorrhagic), intracranial hemorrhage, or life-threatening bleeding, and a similar risk of major bleeding.[1] Dabigatran is administered orally as a prodrug (dabigatran etexilate) and is converted to active dabigatran after absorption across the small intestinal mucosa.[2] In the initial RE-LY report,[1] the only adverse effects that were increased in dabigatran-treated patients relative to controls were "dyspepsia-like symptoms" (11.3%–11.8% compared with 5.8%), and (at the higher dabigatran dose) major gastrointestinal (GI) bleeding (1.51%/y vs 1.02%/y). GI adverse events (AEs) also previously were reported in atrial fibrillation patients in phase II and noted in the phase 3 studies of dabigatran for the treatment and prevention of deep venous thrombosis.[3–5]

In the RE-LY trial, nonbleeding GI AEs were reported subjectively by patients as part of general AE reporting and were

Abbreviations used in this paper: AE, adverse event; CI, confidence interval; FDA, Food and Drug Administration; GERD, gastroesophageal reflux disease; GI, gastrointestinal; H2RA, histamine-2 receptor-antagonist; MedDRA, Medical Dictionary for Regulatory Activities; NB, nonbleeding; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; RR, relative risk; UGI, upper gastrointestinal.

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interpreted by the physician-investigator at the study site.[1] Major outcome events, such as major GI bleeding, underwent central adjudication. In the initial reports from RE-LY, the category of dyspepsia-like symptoms included upper abdominal pain, abdominal pain, abdominal discomfort, epigastric discomfort, and dyspepsia.[1] The GI AEs not included in this category were reported in the Food and Drug Administration (FDA) briefing document and are contained in the product label.[6,7]

The RE-LY database also contains specific data regarding each adverse GI event, such as timing of onset, location, quality, and severity. In addition, the RE-LY database captured demographic and general clinical data. Thus, the database contains information regarding GI signs and symptoms that potentially may help guide prevention and management strategies. In the present study, we analyzed the RE-LY database to describe the clinical characteristics of dabigatran-related nonbleeding upper gastrointestinal adverse events (NB-UGI AEs).

Methods

RE-LY Trial Design

All analyses were performed using the database from the RE-LY trial (N = 18,113).[1,8] Briefly, the RE-LY trial compared double-blind doses of dabigatran etexilate 110 mg twice daily and 150 mg twice daily with open-label warfarin (target international normalized ratio, 2.0–3.0) in patients with atrial fibrillation. The median follow-up period was 2 years, the primary efficacy outcome was prevention of stroke or systemic embolism, and the main safety outcome was major bleeding. Because the present study represents a safety analysis, we used the RE-LY safety data set, which includes all data for the interval starting with the first administration of study drug through 6 days after permanent stop of the study drug.

Definitions

In the RE-LY trial, all AEs were associated with general coding terms (preferred terms) based on the Medical Dictionary for Regulatory Activities (MedDRA, version 10.0). In the original report of RE-LY, AEs coded within 5 MedDRA (version 10.0) preferred terms (*dyspepsia*, *abdominal pain upper*, *abdominal pain*, *abdominal discomfort*, *epigastric discomfort*) were collapsed and reported as dyspepsia-like symptoms. Other GI AEs during RE-LY were captured in the RE-LY AE database and were reported in the FDA briefing document. This approach explains some differences regarding reporting GI event numbers in the public domain.

Each AE in RE-LY also was associated with the more specific MedDRA lower level term codes, which reflect clinical details such as symptom quality and location. To better understand GI AEs occurring during RE-LY, we therefore reviewed the MedDRA gastroenterological lower level terms in detail and subsequently organized them into clinically relevant categories (Supplementary Table 1). In an initial step, we noted that AEs coded as the nonlocalizing MedDRA preferred term "abdominal pain" were not associated with dabigatran-related side effects (2.6% and 2.7%, respectively; relative risk [RR], 0.95; 95% confidence interval [CI], 0.79–1.14; $P = .57$). We therefore focused our efforts on AEs related to the upper GI tract.

To analyze NB-UGI AEs in detail, 2 experienced gastroenterologists (P.B. and J.A.) classified all relevant lower level terms into 4 predefined, clinically relevant categories.

Gastroesophageal reflux. This subgroup included 33 lower level terms that are suggestive of NB-UGI AEs related to gastroesophageal reflux disease (GERD) and/or an esophageal origin, such as *heartburn*, *retrosternal burning*, and *esophagitis*, and excluded nonspecific NB-UGI AEs.

Upper abdominal pain/classic dyspepsia. This subgroup included 55 lower level terms classically associated with dyspepsia, such as *epigastric burning*, *epigastric pain*, and *epigastric discomfort*.[9,10]

Dysmotility-related symptoms. This subgroup included 42 lower level terms classically associated with motility disorders, such as *nausea*, *vomiting*, *eructation*, and *gastroparesis*.

Gastroduodenal mucosal injury. This subgroup included 127 lower level terms that reflected endoscopic signs of gastroduodenal mucosal injury, such as *gastritis*, *duodenitis*, and *peptic ulcer*.

All GI-related lower level terms were classified into 1 of these 4 subgroups for analysis (Supplementary Table 1). The classification scheme was created by consensus of the 2 gastroenterologists. At the time the classification was created, the gastroenterologists were blinded to the number of AEs occurring during RE-LY per lower level term, both according to treatment arm and overall.

Analyses

The frequencies of NB-UGI AEs occurring at any time during the trial (as opposed to events per year) were compared between dabigatran-treated subjects and warfarin-treated controls. In addition, we assessed the timing of onset of NB-UGI AEs relative to drug initiation, and the severity of symptoms (mild, moderate, or severe as assessed by the investigator). For an analysis of regional variation in the reporting of NB-UGI AEs, the 951 trial sites were classified into 4 regions: North America (total number of patients: N = 6533), western Europe (N = 2700), eastern and central Europe (N = 2098), and the rest of the world (N = 6782).

To test the relationship between patients' baseline demographic or clinical characteristics and the development of NB-UGI AEs, we performed a univariate regression analysis. Variables included in this analysis were as follows: age; sex; ethnicity; geographic region of origin; body mass index; concurrent prescription medication use (including proton pump inhibitor [PPI], histamine-2 receptor-antagonist [H2RA], aspirin, nonsteroidal anti-inflammatory drug [NSAID]/coxib); comorbidity (including diabetes mellitus, hypertension, congestive heart failure); and the use of alcohol and tobacco. Kaplan–Meier curves were constructed to describe the timing of permanent study drug discontinuation owing to UGI NB-UGI AEs.

To test the association of NB UGI symptoms with GI bleeding, we used the definitions of bleeding types used in RE-LY. Specifically, major GI bleeding was defined as bleeding localized to the GI tract and associated with a reduction in hemoglobin level of 2.0 g/dL or more on consecutive measurements over any time period, transfusion of 2 or more units of blood, or symptomatic bleeding into a critical area or organ; life-threatening GI bleeding was a subset of major GI bleeding defined as bleeding associated with a reduction in hemoglobin level of 5.0 g/dL or more, transfusion of 4 or more units of blood or the use