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Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study

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BACKGROUND & AIMS: Use of dabigatran, an inhibitor of thrombin, increases the risk of gastrointestinal bleeding (GIB). However, it is not clear whether gastroprotective agents (GPAs) prevent GIB in dabigatran users. We investigated the risk of GIB and the role of gastroprotective agents (including proton pump inhibitors and histamine type-2–receptor antagonists) in patients using dabigatran. **METHODS:** We performed a retrospective cohort study using a population-wide database managed by the Hong Kong Hospital Authority. Patients newly prescribed dabigatran from 2010 through 2013 were included in the analysis. Poisson regression was used to assess the risk of GIB in dabigatran users by incidence rate ratio (IRR), adjusted for patient characteristics, comorbidities, and concurrent medications. **RESULTS:** Among the 5041 patients newly prescribed dabigatran, 124 (2.5%) developed GIB during follow-up evaluation (4.2/100 patient-years). The risk of GIB in this population increased among patients 75 years and older (IRR, 2.47; 95% confidence interval [CI], 1.66–3.68), patients with a history of peptic ulcers or GIB (IRR, 2.31; 95% CI, 1.54–3.46), and patients who used aspirin (IRR, 1.52; 95% CI, 1.03–2.24). Concomitant use of gastroprotective agents was associated with a reduced risk of GIB (IRR, 0.52; 95% CI, 0.35–0.77). Subcategory analysis showed that use of proton pump inhibitors (IRR, 0.53; 95% CI, 0.31–0.91) or histamine type-2–receptor antagonists (IRR, 0.61; 95% CI, 0.40–0.94) were associated with a lower risk of GIB. Further analysis showed that the risk reduction by gastroprotective agents was significant for only upper GIB (IRR, 0.29; 95% CI, 0.15–0.54), and only for patients with a prior history of peptic ulcers or GIB (IRR, 0.14; 95% CI, 0.06–0.30). **CONCLUSIONS:** In the Hong Kong population, use of gastroprotective agents was associated with a reduced risk of GIB in patients taking dabigatran. The association was stronger for upper GIB than lower GIB, and in patients with a prior history of peptic ulcers or GIB.

Keywords: Anticoagulant; Drug Side Effect; PPI; H2RA.

Dabigatran, an oral direct thrombin inhibitor,[1] is a novel oral anticoagulant (NOAC) approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). Unlike the traditional oral anticoagulant warfarin, dabigatran has a predictable pharmacokinetic profile and does not require frequent blood monitoring. In the Randomized Evaluation of the Long-Term Anticoagulation Therapy (RE-LY) trial, dabigatran 150 mg twice daily was superior to warfarin in the prevention of stroke and systemic embolism in AF patients and noninferior to warfarin at 110 mg twice daily.[2]

Despite its comparable efficacy and relative convenience, several randomized controlled trials and reports have shown that the risk of gastrointestinal bleeding (GIB) is higher with the use of dabigatran than traditional therapies across different indications.[2–5] A recent systematic review on previous clinical trials showed that the pooled odds ratio of GIB associated with dabigatran use was 1.6 when compared with traditional therapies including warfarin.[6] Recently, the US Food and Drug Administration released a safety announcement that dabigatran is associated with a higher rate of gastrointestinal bleeding compared with warfarin in patients with nonvalvular AF, based on their latest analysis of the Mini-Sentinel database.[7] However, the actual bleeding risk of dabigatran use for various indications in daily clinical practice outside a restrictive clinical trial setting is less well described.

Although current guidelines recommend that proton pump inhibitors (PPIs) should be considered in patients at high risk of GIB receiving antithrombotic therapy,[6,8–10] the role of gastroprotective agents including PPIs and histamine type-2–receptor antagonists (H2RAs) in the prevention of GIB associated with dabigatran remains undefined.

This study determined the risk of GIB in patients with newly prescribed dabigatran in a large population-based retrospective cohort study from Hong Kong. We also identified the risk factors and the effects of gastroprotective agents in dabigatran-associated GIB in this cohort.

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Abbreviations used in this paper: **AF, atrial fibrillation; CDARS, Hong Kong Clinical Data Analysis and Reporting System; CI, confidence interval; CMS, Clinical Management System; GIB, gastrointestinal bleeding; HA, Hospital Authority; HKW, Hong Kong West; HR, hazard ratio; H2RA, histamine type 2–receptor antagonist; IRR, incidence rate ratio; NOAC, novel oral anticoagulant; NPV, negative predictive value; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; PPV, positive predictive value; RE-LY, Randomized Evaluation of the Long-Term Anticoagulation Therapy.**

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Materials and Methods

Data Source

This study used the electronic medical records of the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority (HA), which is the sole public-funded health care provider of Hong Kong. The HA currently serves a population of more than 7 million, managing 42 hospitals, 47 Specialist Out-patient Clinics, and 73 General Out-patient Clinics organized into 7 hospital clusters according to geographic location.[11] The HA uses the Clinical Management System (CMS), a computerized clinical management system, to record all key clinical information such as treatment, diagnoses, prescriptions, laboratory results, and procedure information; and to write consultation and discharge summaries.[12] It also allows clinicians and health care specialists to order and review care in their daily practice.[13] Electronic patient records in the HA, including demographics, date of consultation, date of hospital admission and discharge, diagnoses, procedures, drug prescriptions, and laboratory tests were transferred from CMS to CDARS for audit and research proposes.[13] CDARS has been used for conducting high-quality, population-based studies.[13–17] A local study showed high coding accuracy in CDARS with a positive predictive value (PPV) of 90%.[18] Nonetheless, we conducted further validation on a sample of patients in this cohort to ensure the validity of our data set.

All patient records in CDARS are anonymized to protect patient confidentiality. A unique reference number is allocated for each individual patient to facilitate data retrieval and further analysis. The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW 13-468). Informed consent from patients was not required because the data used in this study were anonymized.

Study Design

This was a retrospective cohort study. We identified all patients who were newly prescribed dabigatran between January 1, 2010, and December 31, 2013, from CDARS. The index date was defined as the date of the first dabigatran prescription. The follow-up evaluation of each patient was commenced from the index date until the development of GIB, death, the prescription of an alternative anticoagulant (warfarin, rivaroxaban, or apixaban), the end of the study period (December 31, 2013), or 30 days after discontinuation (defined as >30 days of interval between prescription refills) of dabigatran, whichever came first. Another 30-day follow-up period was added after the final prescription of dabigatran to account for noncompliance and to capture any GIB that may have led to treatment discontinuation. Patients who received dabigatran in the 12 months before the index date and patients who were prescribed other anticoagulants on the index date were excluded Patients'. co-existing medical illnesses before the index date and drugs concurrently prescribed in the follow-up period were retrieved from the CDARS (Figure 1).

Outcome and Covariates

The primary outcome was the development of GIB after the commencement of dabigatran. Patients who developed GIB were identified in CDARS with the physician-assigned International Classification of Diseases codes (Clinical Modification, 9th revision) (Supplementary Table 1). We included possible diagnoses of GIB including peptic ulcer hemorrhage (531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, and 534.6), bleeding gastritis and/or duodenitis (535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, and 535.71), intestinal hemorrhage (562.02, 562.03, 562.12, 562.13, 569.3, 569.85, and 569.86), and gastrointestinal hemorrhage (578). Upper GIB and non-upper GIB were classified by the diagnostic codes and free text information in CDARS (Supplementary Table 1).

The use of the following medications during the follow-up period was included as a covariate in terms of dichotomous variables (present/absent) in the analysis (Figure 1): use of aspirin, clopidogrel, nonsteroidal anti-inflammatory drugs (NSAIDs), PPIs, H2RAs, and selective serotonin reuptake inhibitors.[19–23] Baseline medical conditions including prior ischemic stroke/transient ischemic attack/systemic embolism, renal disease, and prior history of peptic ulcer/GIB also were counted as dichotomous covariates in the analysis.[20–22] For each patient, all diagnosis records dated before the individual index date were retrieved using International Classification of Diseases, Clinical Modification, 9th revision codes (Supplementary Table 1) from CDARS for the identification of the baseline medical conditions.

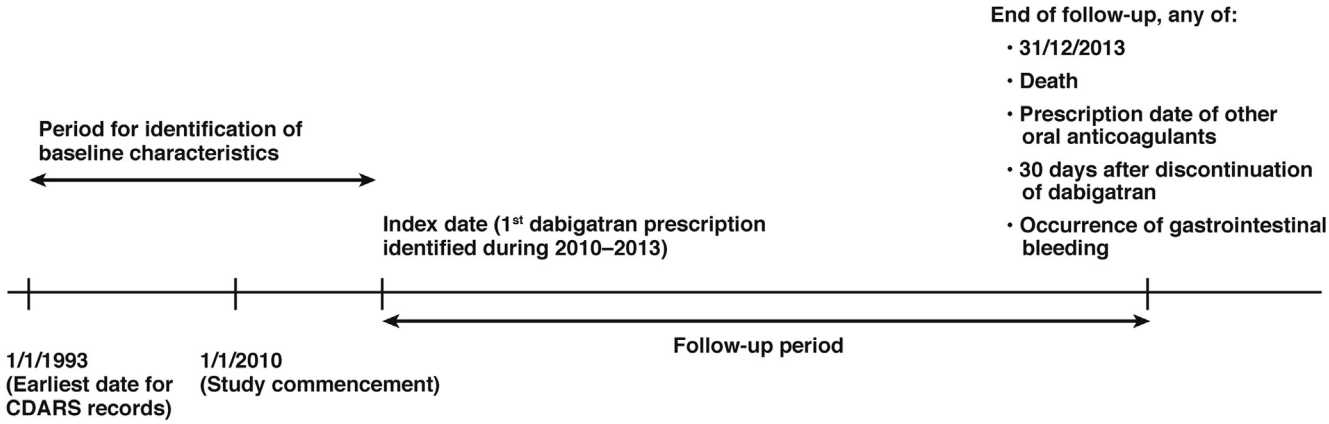

Figure 1. Study design.