Risk of gastrointestinal adverse effects of dabigatran compared with warfarin among patients with atrial fibrillation: a nationwide cohort study

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Aims

To examine the risk of gastrointestinal adverse effects associated with dabigatran use compared with warfarin among patients with atrial fibrillation (AF).

Methods and results

Patients with AF and no history of gastrointestinal diseases initiating dabigatran or warfarin were identified from Danish nationwide registries from 22 August 2011 until 31 December 2012. Patients were classified as naive or experienced users, according to prior use of oral anticoagulant (OAC) therapy. The risk of subsequent proton pump inhibitor (PPI) use, upper dyspepsia-like diagnoses (gastroesophageal reflux, gastritis, gastric, and duodenal ulcer) and gastrointestinal bleeding requiring hospitalization, gastroscopy, and discontinuation of dabigatran and warfarin was examined by cumulative incidence rates and multivariable adjusted Cox regression models. We identified five groups: OAC-naive warfarin (n = 4534); OAC-naive dabigatran 110 mg b.i.d. (dabigatran 110) (n = 1168); OAC-naive dabigatran 150 mg b.i.d. (dabigatran 150) (n = 1844); OAC-experienced dabigatran 110 (n = 1143); and OAC-experienced dabigatran 150 (n = 1748). Compared with OAC-naive warfarin, the rate of initiating PPIs was significantly increased for OAC-naive dabigatran 110 mg users, and the risk of discontinuation was increased for OAC-experienced dabigatran 150 mg users, but not for the other dabigatran-treated groups, relative to OAC-naive warfarin.

Conclusion

Dabigatran was not associated with upper dyspepsia-like diagnoses or gastrointestinal bleeding requiring hospitalization, and gastroscopy. The risk of discontinuation was increased for OAC-experienced dabigatran 150 mg users, and the risk of discontinuation was increased for OAC-naive dabigatran 110 mg users.

Keywords

Oral anticoagulation • Non-vitamin K antagonist oral anticoagulant • Proton pump inhibitors • Dyspepsia • Gastrointestinal bleeding • Discontinuation

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What’s new?

- The use of dabigatran for non-valvular AF has been linked to increased concerns of gastrointestinal complications.
- In patients with non-valvular AF and no history of gastrointestinal diseases, initiation of dabigatran is not associated with an increased risk of upper dyspepsia-like diagnoses, gastrointestinal bleeding, or gastroscopy compared with warfarin.
- Oral anticoagulation-naive patients treated with dabigatran 110 mg have a higher risk of initiating subsequently proton pump inhibitors than warfarin-treated patients.
- The risk of discontinuation is increased for oral anticoagulation-experienced dabigatran 150 mg users.

Introduction

Dabigatran etexilate was the first of the non-vitamin K antagonist oral anticoagulants approved for stroke prevention in patients with atrial fibrillation (AF). The use of dabigatran is increasing, but dabigatran has been linked to gastrointestinal adverse effects that may be severe and even fatal in case of gastrointestinal bleeding. Gastrointestinal adverse effects may also cause non-adherence to treatment, which may increase the risk of stroke and thromboembolism.

Dabigatran was compared with warfarin in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, leading to its regulatory approval and recommendation in guidelines. The RE-LY trial reported a significantly higher rate of major gastrointestinal bleeding and dyspepsia with dabigatran than that with warfarin. Other studies have reported varying association between dabigatran and gastrointestinal bleeding. On that notion, clarification is needed. Additionally, no studies have previously examined the association between dabigatran and the use of proton pump inhibitors (PPIs). The Danish nationwide registries provide access to investigate these kinds of subjects in ‘real-world’ patients.

The primary aim of this nationwide cohort study was to examine the extent of upper dyspepsia-like diagnoses and gastrointestinal bleeding requiring hospitalization, and subsequently PPI use, of dabigatran compared with warfarin among patients with AF and no history of gastrointestinal diseases in a real-world setting. Secondly, we assessed adherence and discontinuation of dabigatran compared with warfarin and whether treatment discontinuation was associated with adverse gastrointestinal events and PPI use.

Methods

Data sources

In Denmark, all residents are, at birth or immigration, provided with a unique and permanent civil registration number that allows linkage between nationwide registries on the individual level. We obtained data from the following registries: (i) The Danish National Patient Registry that holds information about all hospital admissions since 1978 and at discharge; each hospitalization is coded with one primary and if appropriate one or more secondary diagnoses, in accordance with the International Classification of Diseases. In addition, the registry contains information about all procedures and surgical operations since 1996 (The Nordic Medical Statistics Committees Classification of Surgical Procedures). The Danish National Prescription Registry has kept record of all drug prescriptions dispensed, Anatomical Therapeutic Chemical classification code (ATC), and package size from pharmacies in Denmark since 1993. (iii) The Danish Civil Registration System contains information about an individual’s vital status and cause of death.

Study population

The study period was between 22 August 2011 (the day dabigatran became available in Denmark) and 31 December 2012. Throughout this period, we included patients with AF if one of two situations occurred: (i) an oral anticoagulation (OAC) naïve AF patient initiated first-time OAC treatment or (ii) a warfarin-experienced AF patient (warfarin prior to 22 August 2011) initiated dabigatran treatment. Patients were included at the day of treatment initiation, defined as the date of the first claimed prescription. According to the OAC treatment regime, patients were stratified into five groups: (i) warfarin-naive warfarin initiators (called OAC-naive warfarin), (ii) warfarin-naive dabigatran 110 mg twice daily initiators (called OAC-naive dabigatran 110), (iii) warfarin-naive dabigatran 150 mg twice daily initiators (called OAC-naive dabigatran 150), (iv) warfarin-experienced dabigatran 110 mg twice daily initiators (called OAC-experienced dabigatran 110), and (v) warfarin-experienced dabigatran 150 mg twice daily initiators (called OAC-experienced dabigatran 150).

We excluded patients aged <30 or >100, or with valvular disease, total hip or knee replacement surgery up to 8 weeks before baseline, and deep venous thrombosis or pulmonary embolism up to 6 months before baseline. In addition, we excluded patients with prior gastrointestinal bleeding, gastroesophageal reflux, gastritis, gastric and duodenal ulcer, gastroscopy, and PPI use 180 days before baseline.

Concomitant medical therapy and comorbidities

Using prescriptions filled from 0 to 180 days prior to the baseline stratification, we recorded the concomitant medical therapy listed in Table 1. Comorbidities were determined from diagnosis codes and validated methods corresponding to the baseline stratification.

CHADS2 [congestive heart failure, hypertension, age ≥75 (double weight), diabetes mellitus, stroke/transient ischaemic attack], CHA2DS2-VASc (CHA2DS2 added with vascular disease, age 65–74, female sex), and an HAS-BLED (hypertension, abnormal renal/liver function, stroke, previous bleeding, labile international normalized ratio (left out because data are unfilled), elderly (age >65), drug/alcohol abuse) scores were calculated for each patient at baseline stratification, as done in previous studies.

Outcomes

Outcomes were initiating PPIs (ATC: A02BC), admission to a hospital with upper dyspepsia-like diagnoses (gastroesophageal reflux, gastritis, gastric and duodenal ulcer), gastrointestinal bleeding, and gastroscopy. In addition, we determined a combined outcome that consisted of all the outcomes added together. Proton pump inhibitor use included all types of PPIs available on the market during the study period (esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole). Proton pump inhibitors are a mainstay in medical therapy for stomach discomfort, including gastroesophageal reflux, ulcer, and acid peptic diseases. Gastroesophageal reflux, gastritis, gastric and duodenal ulcer, and gastrointestinal bleeding were defined from the corresponding primary or secondary diagnostic codes. Gastroscopy was identified from procedural codes.
The secondary outcome was defined by cessation or switch of OAC treatment during follow-up. It was identified by the end of a prescription of the baseline-initial OAC treatment regime without a new prescription of the same OAC was claimed within 30 days.

All the definitions are provided in Supplementary material online, Table S1.

**Statistics**

Baseline characteristics of the five groups (OAC-naive warfarin, OAC-naive dabigatran 110, OAC-naive dabigatran 150, OAC-experienced dabigatran 110, and OAC-experienced dabigatran 150) were presented as numbers and percentages, or as means and standard deviations (SD).

We used the Aalen–Johansen method to estimate the risk of the outcomes taking into account the risk of death from other causes (competing risks). Risk time was constituted of time since baseline until an outcome occurred. Crude cumulative incidences were fitted into plots.

Cox proportional hazard models were used to examine outcomes with OAC-naive warfarin as reference. The hazard ratios (HRs) of the different outcomes were estimated, and for the gastrointestinal outcomes, we adjusted for factors in the CHA2DS2-VASc score, and treatment with aspirin or non-steroidal anti-inflammatory drugs. A two-sided significance level of 0.05 was used. Model check was performed: the Cox models all fulfilled the proportional hazard assumption, and linearity of continuous covariates (age). Additionally, we explored for relevant interactions without any significant findings including no gender-based differences, unless otherwise reported.

Data management and statistical analyses were performed using SAS (version 9.2 for Windows, SAS Institute, NC) and R (version 3.0.2 for Windows, R Foundation for Statistical Computing, Vienna).

**Ethics**

Retrospective registry-based studies do not require approval from the Health Research Ethics Committee System; data were structured with no possibility for patient identification. The Danish Data Protection Agency had approved the use of data for the study (journal number: 2007-58-0015/GEH-2014-012 I-Suite number: 02720).

**Results**

**Study population characteristics**

Figure 1 illustrates the flow chart of inclusion of the study population from 22 August 2011 to 31 December 2012. We identified 10 437

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### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>OAC-naive warfarin</th>
<th>OAC-naive dabigatran 110</th>
<th>OAC-naive dabigatran 150</th>
<th>OAC-experienced dabigatran 110</th>
<th>OAC-experienced dabigatran 150</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4534 (43.4)</td>
<td>1168 (11.2)</td>
<td>1844 (17.7)</td>
<td>1143 (11.0)</td>
<td>1748 (16.8)</td>
</tr>
<tr>
<td>Female</td>
<td>1903 (42.0)</td>
<td>638 (54.6)</td>
<td>708 (38.4)</td>
<td>583 (51.0)</td>
<td>563 (32.2)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>70.3 (11.3)</td>
<td>80.0 (8.7)</td>
<td>65.9 (8.7)</td>
<td>79.6 (8.1)</td>
<td>67.7 (8.5)</td>
</tr>
<tr>
<td>CHADS2 score*, mean (SD)</td>
<td>1.4 (1.2)</td>
<td>2.0 (1.2)</td>
<td>1.1 (1.1)</td>
<td>2.3 (1.3)</td>
<td>1.5 (1.2)</td>
</tr>
<tr>
<td>CHA2DS2-VASc score*, mean (SD)</td>
<td>2.6 (1.6)</td>
<td>3.6 (1.4)</td>
<td>2.2 (1.4)</td>
<td>3.9 (1.5)</td>
<td>2.6 (1.5)</td>
</tr>
<tr>
<td>HAS-BLED score*, mean (SD)</td>
<td>1.9 (1.1)</td>
<td>2.3 (1.0)</td>
<td>1.8 (1.1)</td>
<td>2.4 (1.0)</td>
<td>1.9 (1.0)</td>
</tr>
<tr>
<td>Concomitant medical therapy (180 days before baseline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA (aspirin)</td>
<td>1969 (43.4)</td>
<td>538 (46.1)</td>
<td>727 (39.4)</td>
<td>383 (33.5)</td>
<td>537 (30.7)</td>
</tr>
<tr>
<td>Dipyridamole (persantin)</td>
<td>163 (3.6)</td>
<td>53 (4.5)</td>
<td>113 (6.1)</td>
<td>49 (4.3)</td>
<td>53 (3.0)</td>
</tr>
<tr>
<td>ADP-receptor inhibitors</td>
<td>316 (7.0)</td>
<td>110 (9.4)</td>
<td>54 (3.0)</td>
<td>8 (0.7)</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>Heparin</td>
<td>12 (0.3)</td>
<td>5 (0.4)</td>
<td>3 (0.2)</td>
<td>2 (0.7)</td>
<td>7 (0.3)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>674 (14.9)</td>
<td>137 (11.7)</td>
<td>255 (13.8)</td>
<td>95 (8.3)</td>
<td>176 (10.1)</td>
</tr>
<tr>
<td>H2-receptor-antagonist</td>
<td>8 (0.2)</td>
<td>4 (0.3)</td>
<td>1 (0.1)</td>
<td>3 (0.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>896 (19.8)</td>
<td>220 (18.8)</td>
<td>247 (13.4)</td>
<td>302 (22.0)</td>
<td>366 (20.9)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>443 (9.8)</td>
<td>107 (9.2)</td>
<td>97 (5.3)</td>
<td>120 (10.5)</td>
<td>124 (7.1)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>693 (15.3)</td>
<td>169 (14.5)</td>
<td>169 (9.2)</td>
<td>284 (24.9)</td>
<td>319 (18.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2032 (44.8)</td>
<td>542 (46.4)</td>
<td>768 (41.7)</td>
<td>687 (60.1)</td>
<td>1083 (62.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>520 (11.5)</td>
<td>121 (10.4)</td>
<td>189 (10.3)</td>
<td>172 (15.1)</td>
<td>250 (14.3)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>644 (14.2)</td>
<td>293 (25.1)</td>
<td>293 (15.9)</td>
<td>291 (25.5)</td>
<td>279 (16.0)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>178 (3.9)</td>
<td>80 (6.9)</td>
<td>62 (3.4)</td>
<td>131 (11.5)</td>
<td>97 (5.6)</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>24 (0.5)</td>
<td>8 (0.7)</td>
<td>9 (0.5)</td>
<td>9 (0.8)</td>
<td>14 (0.8)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>125 (2.8)</td>
<td>17 (1.5)</td>
<td>13 (0.7)</td>
<td>25 (2.2)</td>
<td>14 (0.8)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>123 (2.7)</td>
<td>35 (3.0)</td>
<td>62 (3.4)</td>
<td>40 (3.5)</td>
<td>63 (3.6)</td>
</tr>
<tr>
<td>Surgery</td>
<td>859 (19.0)</td>
<td>195 (16.7)</td>
<td>310 (16.8)</td>
<td>234 (20.5)</td>
<td>337 (19.3)</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%).
ASA, acetylsalicylic acid; NSAIDs, non-steroidal anti-inflammatory drugs; OAC, oral anticoagulation; RAS, renin-angiotensin system; TIA, transient ischaemic attack.
*The CHADS2 score is a measure of risk of stroke based on congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, stroke/TIA (double weight).
*CHA2DS2-VASc: adding age ≥ 75 (double weight), vascular disease, age 65–74, and female sex to CHADS2.
*HAS-BLED: hypertension, abnormal renal/liver function, stroke, previous bleeding, labile international ratio (left out because data are unfilled), elderly (age ≥ 65), drug/alcohol abuse.
patients among whom 5903 (56.7%) were dabigatran-treated patients. Baseline characteristics with concomitant medical therapy, comorbidities, and previous surgical procedures for the population are given in Table 1. Overall mean age was 71.2 (SD, 11.0) and 4395 (42.1%) were female. Oral anticoagulant-naive dabigatran 150 and OAC-experienced dabigatran 150 were younger, more often males, and had lower estimated risk of stroke and bleeding compared with the other groups.

**Risk of adverse gastrointestinal events**

The median duration of follow-up was 244.0 (interquartile range, 105.0–377.0) days. Of the included patients, 461 (4.4%) died during follow-up.

Figures 2 and 3 present crude cumulative incidences of the combined gastrointestinal outcome and initiation of PPIs, respectively. Oral anticoagulant-naive dabigatran 110 had an increased crude cumulative incidence of a combined gastrointestinal outcome and initiation of PPIs compared with the other groups. The initiation of PPIs was most frequent in the first 3 months. Similar figures for each of the other outcomes are available in the Supplementary material online, Figures S1–S3.

Figure 4 shows the adjusted HRs of the gastrointestinal outcomes; OAC-naive warfarin was used as the reference. Oral anticoagulant-naive dabigatran 110 was associated with a significant increased risk of initiating PPIs (HR, 1.24; 95% confidence interval (CI), 1.02–1.50); however, for this group there was no tendency of increased risk of the other outcomes observed. Oral anticoagulant-naive dabigatran 150, OAC-experienced dabigatran 110, and OAC-experienced dabigatran 150 were not associated with a higher risk of initiating PPIs, admissions with upper dyspepsia-like diagnoses, gastrointestinal bleeding, and gastroscopy.

**Discontinuation of dabigatran during follow-up**

Figure 5 shows the discontinuation of OAC treatment after baseline. Oral anticoagulant-experienced dabigatran 150 was the only...
group with a statistically significant higher risk of discontinuation (HR, 1.13; 95% CI, 1.02–1.25). For interactions, we found age-based differences with \( P < 0.0001 \). A subgroup analysis stratifying for age 75 is available in the Supplementary material online, Figure S4.

**Figure 4** Main outcome measures. Adjusted HRs of the gastrointestinal outcomes of dabigatran compared with warfarin (Cox proportional hazard model with 95% CI). Adjusted for congestive heart failure, hypertension, diabetes mellitus, stroke/transient ischaemic attack, vascular disease, age, sex, and treatment with acetylsalicylic acid or non-steroidal anti-inflammatory drugs. CI, confidence interval; OAC, oral anticoagulation; PPI, proton pump inhibitor.

**Sensitivity analyses**

A subgroup analysis was performed reporting the results for dabigatran 110 and 150 as a whole compared with OAC-naive warfarin, Table 2. For purposes of sensitivity analyses, we included chronic kidney disease, alcohol abuse, bleeding, and previous gastrointestinal surgery, as potential confounders in the Cox models. The results were unaffected (data not shown). Similarly, patients with previous gastrointestinal surgery and \( H_2 \)-receptor-antagonists were excluded in the model without any changes in results (data not shown).

Supplementary material online, Table S2 shows that for the gastrointestinal outcomes exclusion of all PPI-users within 1 year before baseline did not alter the results markedly, while excluding all PPI-users within 2 years before baseline brought similar, but insignificant, results. For the gastrointestinal outcomes, further subgroup analyses were performed according to gender and age <75 or \( \geq 75 \) without any changes in the findings (data not shown).
agreement with Huisman et al. started on lower dose dabigatran to avoid symptoms. In addition, patients more prone to gastrointestinal adverse effects were treated patients, which may indicate selection bias towards that ally significant higher risk of initiating PPIs compared with warfarin-found a statistically significant increase in the prescribing rates for investigated the PPI use before and after prescribing dabigatran. They more likely to occur early after starting dabigatran treatment. Patients with dyspepsia related to dabigatran are recommended by the European Society of Cardiology to reduce symptoms with a PPI.21 Our results showed that subsequent initiation of PPI was most common in the first 3 months after initiation of dabigatran therapy for the OAC-naive dabigatran 110 (Figure 4). This was in agreement with Huisman et al.,22 who reported that dyspepsia is more likely to occur early after starting dabigatran treatment. Studies of dabigatran and PPI use are scarce, but Carley et al.20 investigated the PPI use before and after prescribing dabigatran. They found a statistically significant increase in the prescribing rates for PPIs after initiation of dabigatran therapy. In our study, OAC-naive dabigatran 110, as the only dabigatran-treated patients, had a statistically significant higher risk of initiating PPIs compared with warfarin-treated patients, which may indicate selection bias towards that patients more prone to gastrointestinal adverse effects were started on lower dose dabigatran to avoid symptoms. In addition, OAC-naive dabigatran 110 had a high mean age (80.0, SD 8.7), CHA2DS2-VASc score (3.6, SD 1.4), and an HAS-BLED score (2.3, SD 1.0) compared with the other groups in the present study, and this could indicate that the patients are in a poorer condition than the other groups leading to a higher risk of initiation of a PPI.

Upper dyspepsia-like diagnoses
In the RE-LY trial, dyspepsia was the only significantly more common adverse effect seen with dabigatran vs. warfarin; dabigatran 110 mg had the highest frequency. A more itemized table of frequencies of patients with dyspepsia-like and gastritis-like symptoms from the RE-LY trial showed that dyspepsia (12.7, 12.2, and 5.9%), upper abdominal pain (3.0, 2.8, and 1.3%), and gastritis (2.5, 2.1, and 1.5%) were the most frequent symptoms for dabigatran 110 mg, dabigatran 150 mg, and warfarin, respectively.23 We did not find increased associated risk of upper dyspepsia-like diagnoses requiring admission to a hospital in our data. Difficulties can be encountered, when trying to examine dyspepsia. Choi et al.18 attempted to identify dyspepsia by reviewed questionnaire, and found significant differences in the frequencies of indigestion, regurgitation, nausea, and stomach pain, with the highest score among dabigatran-treated patients compared with the warfarin-treated patients.

Gastrointestinal bleeding
In a meta-analysis by Holster et al.,9 based on three studies, they showed that gastrointestinal bleeding was associated with dabigatran use with an odds ratio of 1.58 (95% CI, 1.29–1.93). Another meta-analysis by Sipahi et al.,11 supported the results from Holster et al. with a risk ratio of 1.41 (95% CI, 1.28–1.55). The RE-LY trial and the Random Evaluation of RE-COVER24 trial were included in both meta-analyses, which would lead to the similar findings. In contrast, the present study was based on real-world patients, where physicians have a more free choice of selecting an OAC fitting the patients’ profile. However, if physicians fit dabigatan use for patients with a non-increased potential for adverse gastrointestinal events, this may lead to a possible underestimation of our results.

Another recently published observational study,25 from Denmark found similar results as to our results except for OAC-naive dabigatran 110, who had a HR, 0.50 (95% CI, 0.27–0.94) of major gastrointestinal bleeding compared with warfarin; one of the differences between the studies was the adjustments in the Cox proportional model. Moreover, our results were based on diagnosis codes of all major and non-major gastrointestinal bleeding, whereas the other study only used diagnosis codes of major gastrointestinal bleeding.

We would assume that in clinical practice, many physicians would probably not start dabigatran treatment on patients with a history of gastrointestinal diseases (especially dyspepsia or gastrointestinal bleeding) given the association with this drug in the RE-LY trial. In our study, we selected patients with no history of gastrointestinal diseases or PPI use 180 days before baseline to reduce selection bias and to answer the question whether this group of patients has a higher

### Table 2 Subgroup analysis

<table>
<thead>
<tr>
<th>Initiating PPIs</th>
<th>Adjusted HR (95% CI)</th>
<th>Dabigatran 110</th>
<th>Dabigatran 150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>1.09 (0.93–1.27)</td>
<td>1.07 (0.93–1.27)</td>
<td></td>
</tr>
<tr>
<td>Upper dyspepsia-like diagnoses</td>
<td>Reference</td>
<td>0.66 (0.28–1.55)</td>
<td>1.09 (0.49–2.43)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>Reference</td>
<td>0.92 (0.42–2.01)</td>
<td>1.13 (0.55–2.34)</td>
</tr>
<tr>
<td>Gastroscopy</td>
<td>Reference</td>
<td>0.89 (0.66–1.21)</td>
<td>0.93 (0.70–1.25)</td>
</tr>
<tr>
<td>Combined gastrointestinal outcome</td>
<td>Reference</td>
<td>1.09 (0.94–1.27)</td>
<td>1.07 (0.93–1.23)</td>
</tr>
</tbody>
</table>

Adjusted HRs for dabigatran 110 (OAC-naive dabigatran 110 plus OAC-experienced dabigatran 110) and dabigatran 150 (OAC-naive dabigatran 150 plus OAC-experienced dabigatran 150) vs. OAC-naive warfarin.
risk of gastrointestinal adverse events when treated with dabigatran compared with warfarin. The difference in the inclusion and exclusion criteria between our study, the RE-LY trial, and other studies can also explain our finding that patients on dabigatran did not have a higher risk of gastrointestinal adverse effects.

**Discontinuation of dabigatran**

The RE-LY trial and another observational study reported higher rates of discontinuation for dabigatran 110 mg and dabigatran 150 mg compared with warfarin. In our study, OAC-experienced dabigatran 150 patients were the ones to discontinue with treatment. Patients changing OAC treatment, also called ‘swappers’, can appear to have unexpected outcomes, and this has previously been shown by Sørensen et al. Furthermore, this result can be explained by residual confounding. We could not extract information about whether a physician stopped the dabigatran treatment or it was due to non-adherence for the OAC-experienced dabigatran 150. Additionally, we could not point out an association between a gastrointestinal outcome and discontinuation with dabigatran. However, it is still possible that discontinuation of dabigatran is due to gastrointestinal adverse effects, if the patient decided to stop treatment due to an adverse gastrointestinal event without consulting a physician. The RE-COVER trial showed that discontinuation was primarily due to adverse events, and dyspepsia was the only significantly more common adverse event among dabigatran-treated patients relative to the warfarin-treated patients ($P < 0.001$).

In an everyday clinical setting, our results can offer an improved safety of dabigatran. Relative to OAC-naive warfarin: (i) patients initiating dabigatran 110 mg showed a greater need for PPIs; (ii) patients initiating dabigatran 150 mg had the same risk of admission due to upper dyspepsia-like diagnoses, gastrointestinal bleeding, and subsequently PPI use; (iii) patients with warfarin experience treated with dabigatran, independent of dose, had the same risk of admission due to upper dyspepsia-like diagnoses, gastrointestinal bleeding, and subsequent PPI use; (iv) only patients with warfarin experience treated with dabigatran 150 mg had an increased risk of discontinuation of treatment. Alternately, physicians could consider another OAC agent.

**Strengths and limitations**

Danish registry studies have strengths and limitations: the nationwide data based on ‘real-life’ patients gave strength to this study, but the limitations lied in the observational study design, the quality of the data, and the possibility of selection bias compared with randomized clinical trials. However, the Danish registries are well validated. We were able to identify PPIs, NSAIDs, aspirin, and H$_2$-receptor-antagonists claimed by prescriptions, but in addition, some of the drugs were sold over the counter. Owing to the financial reimbursement with prescriptions, we could maintain the persistence of drug use and then minimize the limitations. Moreover, we presumed that the majority of patients initiating OAC with subsequently adverse gastrointestinal events would contact a physician, who would prescribe a PPI. It was a limitation that we were not able to distinguish between if PPI was prescribed as prophylaxis or as treatment for gastrointestinal adverse effects. The drug reimbursement regime in Denmark reduced the differences in drug costs between dabigatran and warfarin. Therefore, a selection bias due to the difference in drug cost would be minimal.

By using major and non-major diagnosis codes of gastrointestinal bleeding, gastroesophageal reflux, gastritis, gastric, and duodenal ulcer, we entailed a high sensitivity, but it was a limitation that the outcomes only were based on diagnosis codes without clinical information. Furthermore, the sensitivity of the outcomes had not been validated in previous studies. Our results could underestimate the association between dabigatran and the gastrointestinal outcomes, because we were unable to include patients with dyspepsia without diagnosis codes from an admission and because of confounding by indication. To overcome this limitation, we looked into PPI use and discontinuation of treatment.

We chose not to include dabigatran-experienced warfarin initiators in this study, since only 59 patients were identified in this group, and this would not qualify for adequate power. Furthermore, warfarin-experienced warfarin patients were not included, because we wanted to compare patients initiated on dabigatran with patients initiated on warfarin. When a physician plans to initiate oral anticoagulation, this study design could help him to choose initiation of dabigatran or warfarin. Our study was not divided into time periods, and therefore, a part of the included patients could potentially switch OAC therapy during follow-up, leading to an underestimation of the true association. Labile international normalized ratio, body mass index, and other potential confounders, which cannot be identified in the registries, could have influenced our results. We made an effort to minimize this by making a sensitivity analysis with adjustments of chronic kidney diseases and by using methods from previous parallel studies. Finally, another limitation was the observational study design, the relatively short study period, and the low number of events of dyspepsia-like diagnoses and bleeding. Nonetheless, the results from this study were comparable with previous studies.

**Conclusion**

In conclusion, treatment with dabigatran was not associated with subsequent PPI use, upper dyspepsia-like diagnoses, or gastrointestinal bleeding requiring hospitalization compared with warfarin among patients with AF and no history of gastrointestinal diseases or PPI use 180 days before dabigatran or warfarin treatment was started. However, patients dosed with dabigatran 110 b.i.d. without prior warfarin experience were more often prescribed PPI subsequently. Discontinuation of dabigatran was more common among patients with a prior warfarin experience treated with dabigatran 150 mg b.i.d. Our study did not support an association between dabigatran and subsequent PPI use, upper dyspepsia-like diagnoses, or gastrointestinal bleeding requiring hospitalization, or cessation of dabigatran.

**Supplementary material**

Supplementary material is available at Europace online.

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