Revaprazan is the first acid pump antagonist with a function similar to that of proton pump inhibitors (PPIs). It has a dual action, active suppression of gastric acid secretion and gastric mucosa protection. While PPIs are known to enhance the prolongation of prothrombin time by warfarin, no research has been done on the drug interaction between revaprazan and warfarin. This study was conducted in order to verify the potential drug interaction between revaprazan and warfarin. Omeprazole, a representative PPI, was used as the control for revaprazan. We searched for patients who were given either revaprazan or omeprazole along with warfarin using the medical record database of Seoul National University Hospital between July 2007 and June 2010. Among the 15 patients who took revaprazan and warfarin together, 73.3% (11/15) showed more than 30% reduction of anticoagulation effect by warfarin after revaprazan was added. The revaprazan group showed a significant shortening of prothrombin time during revaprazan administration compared to pre- and post-revaprazan medication ($P < 0.05$) while the omeprazole group did not show such difference. Revaprazan seems to have cumulative dose-dependent anti-warfarin or anti-coagulation effect, as judged from the fact that the longer medication with revaprazan showed correlation with the shortening of prothrombin time ($R = -0.632$, $P < 0.05$). This study shows a possible interaction between revaprazan and warfarin and suggests that revaprazan can cause shortening of prothrombin time. Therefore, when revaprazan is prescribed to patients on warfarin therapy, prothrombin time should be frequently monitored.

**Keywords:** drug interactions; omeprazole; prothrombin time; proton pump inhibitors; warfarin

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Revaprazan, 5,6-dimethyl-2-(4-fluorophenylamino)-4-[(1-methyl-1,2,3,4-tetrahydroisoquinoline-2-yl) pyrimidine hydrochloride, is an acid pump antagonist (APAs) that efficiently controls acid secretion by inhibiting the acid pump, the final step in gastric acid secretion (Maton 1991; McTavish et al. 1991). It is a new medicine recently approved by the Korean Food and Drug Administration (KFDA) for the treatment of gastric diseases including peptic ulcer (Chung et al. 2005; Choi et al. 2006; Chang et al. 2007). It is a new medicine recently approved by the Korean Food and Drug Administration (KFDA) for the treatment of gastric diseases including peptic ulcer (Chung et al. 2005; Choi et al. 2006; Chang et al. 2007). While proton pump inhibitors (PPIs) reduce acid secretion by irreversibly suppressing H⁺/K⁺-ATPase enzyme, the last step in gastric acid secretion, revaprazan reversibly inhibits the exchange of H⁺-ion by competitively adhering to the K⁺-ion binding area in acid pump, thereby reducing acid secretion without hypergastrinemia. With these pharmacological differences, revaprazan has advantages such as rapid onset of action independent of gastric acid secretion as well as ability to control physiological gastric acid secretion (Yu et al. 2004). Owing to these advantages, Revaprazan is being prescribed more frequently in clinical settings as a substitute for PPIs in Asian countries.

Warfarin is the most widely used anticoagulant in the world. However, this drug should be used with caution due to its narrow target range. A close monitoring of the clotting level is required in order to maintain the balance between bleeding and thrombosis. Therefore, when other drugs are co-prescribed with warfarin, they should be checked to see whether or not they affect the anti-coagulative effect of warfarin (Ansell et al. 1997).

In contrast to warfarin, revaprazan is a relatively new medicine and its effect on warfarin metabolism or action has not yet been fully investigated. Recently, the indications for the gastric acid suppression therapy were expanded to include; prophylactic acid suppression treatment for post-cardiac surgery gastrointestinal bleeding to reduce the pro-
J.W. Jung et al.

procedure’s high mortality rate (Hata et al. 2005), use of acid suppressant to control gastric acidity to prevent stress ulcers in conjunction with the use of mechanical ventilators in the intensive care unit (Yang and Lewis 2003). With the increase in the number of patients who need these types of care or procedures like endoscopic mucosal dissection (Ono 2005), the use of medicines such as PPIs and APAs is steadily increasing.

The current study was conducted to verify drug interaction between revaprazan and warfarin. Omeprazole, a representative PPI, was used as the control because it is prescribed for the same indications as revaprazan in many clinical settings.

Materials

Study subject

The current study screened patients over 18 years old who had received revaprazan or omeprazole during their warfarinization at Seoul National University Hospital between July 2007 and June 2010 by reviewing Electronic Medical Records (EMR) retrospectively. The initial number of screened patients was 41 in revaprazan group and 55 in omeprazole group. Among screened patients, we narrowed our search to the ones who satisfied the following criteria; i) warfarin was started at least six months before adding the target medicines (revaprazan or omeprazole), ii) the target medicine was co-administered with warfarin at least for 7 consecutive days, iii) dose of warfarin was maintained constant during the administration of the target medicine, iv) prothrombin time (PT) was checked during or within 10 days after initiation of the target medicine. In order to exclude patients under unstable warfarinization independent of co-medication, patients were excluded if their average International Normalized Ratio (INR) values 3 months prior to starting the target medicine were not maintained within mean ± one standard deviation of their previous 1-year INR values. The administered therapeutic dose of revaprazan was 200 mg a day in all the study patients. For those patients selected in this study, two drug adverse reaction experts performed the WHO-UMC causality assessment system (Edwards and Biriell 1994; Meyboom et al. 1997).

Grouping Method

We grouped the patients into ‘INR-decreased cases’ whose INR changed 30% or more after revaprazan medication compared to the average INR value 3 months before revaprazan and the other ‘INR-unchanged cases’.

Statistical Analyses

We used SPSS (version 17.0, SPSS inc., Chicago, IL, USA) for statistical analyses. We indicated the median value to the continuous variable and range. To compare the revaprazan group and the omeprazole group, Chi-square test and Fisher’s exact test as well as Mann-Whitney test were performed. The paired t-test was carried out to evaluate the difference in the INR values before and after the target medication. We also performed a multivariate linear regression test to compare the dose of warfarin consumed by the two groups, and calculated a linear regression as well as the Pearson correlation efficiency to assess the percentage change in INR and correlation of each variable. We concluded that all the results were statistically meaningful when $P < 0.05$.

Results

Selection of study patients

There were 32 patients who started warfarin at least six months before adding the revaprazan medication during the study period. Among them, 28 satisfied criteria for stable INR for 3 months before revaprazan. And 23 of 28 were medicated with revaprazan for more than 7 days. Fifteen out of these 23 maintained the same dose of warfarin during revaprazan medication and also had PT-INR results tested during or within 10 days after discontinuation of revaprazan medication (Fig. 1). For omeprazole, 12 patients were included in the study based on the same selection criteria as the revaprazan group.

The indications for warfarin treatment of 27 patients (15 in revaprazan group and 12 in omeprazole group) were

Maintain warfarin ≥ 6 months before revaprazan medication

N=32

Maintain stable PT-INR before revaprazan medication

N=28

Coadministrate warfarin and revaprazan ≥ 7 days

N=23

Maintain the same dose of warfarin pre- and post-revaprazan medication

N=20

PT-INR value was available within 10 days after initiation of revaprazan

N=15

Fig. 1. Selection of study patients with revaprazan. PT-INR, prothrombin time-international normalized ratio.
valve replacement \((n = 16)\), atrial fibrillation \((5)\), renal infarction \((2)\), pulmonary embolism \((1)\), deep vein thrombosis \((1)\), nephrotic syndrome \((1)\), and paroxysmal nocturnal hemoglobinuria \((1)\). Among the patients who showed INR changes, revaprazan or omeprazole was evaluated as having probable causality for the change of INRs based on WHO-UMC criteria.

**Comparison of clinical aspects between the revaprazan group and the omeprazole group**

There was no significant difference in age, sex, hepatic or renal function between the revaprazan group and the omeprazole group (Table 1). There was one patient each in revaprazan group and with omeprazole group who had cardiac cirrhosis. However, there was no significant difference in parameters of liver function tests between two groups. The revaprazan group was heavier \((P = 0.041)\) and had higher warfarin dosage than the omeprazole group \((3.43 \text{ mg vs. } 2 \text{ mg}, P = 0.041)\). However, when adjusted for age, sex, and weight, the warfarin dosage did not show any significant difference \((P > 0.05)\). Average INR values either 3 months or 1 year prior to the target medication did not show any significant difference between two groups. In revaprazan group, one patient took cefuroxime axetil that may enhance the anticoagulation effect of warfarin. However, no significant change in INR was demonstrated with cefuroxime in addition to revaprazan and warfarin.

The median time from initiation of target medication to the first post-medication INR test was 14 days in the revaprazan group and 14.5 days in the omeprazole group. However, the INR values showed significant difference between the two groups \((1.2 \text{ vs. } 2.16 \text{ in the revaprazan group and the omeprazole group, respectively. } P = 0.010)\).

In the revaprazan group, 12 out of 15 patients showed INR decrease of more than 30%, and the remaining 3 patients did not show any significant change. In contrast, none of the patients in the omeprazole group showed any significant shortening of INR.

Comparing the average INR value during 3 months before co-medication and the first post-target medication INR, the revaprazan group showed a 39.5% sequential decrease \((1.99 \text{ vs. } 1.2, P < 0.001)\), while the omeprazole group did not show any statistically significant sequential difference \((1.96 \text{ vs. } 2.16, P > 0.05)\) (Fig. 2). Additionally, we saw a similar pattern when the first post-target medication INR value was compared to the average INR value during 1 year prior to target medication \((2.24 \text{ vs. } 1.2, P < 0.001 \text{ in the revaprazan group, } 2.07 \text{ vs. } 2.16, P > 0.05 \text{ in the omeprazole group})\).

**Analysis of clinical characteristics of the revaprazan group**

In the revaprazan group, 12 patients showed INR decrease of more than 30%, while the remaining 3 did not show any significant change (Table 2). Between these two sets of patients, we did not find any significant difference in age, sex, hepatic or renal function, and daily warfarin dose. However, INR-decreased cases had a longer duration of revaprazan medication than the INR-unchanged cases \((21.5 \text{ days vs. } 7 \text{ days}, P = 0.009)\). Interestingly, there was a correlation between duration of revaprazan medication and the degree of INR shortening within the revaprazan group. The longer the revaprazan was maintained, the larger was the INR decrease \((K = −0.632, P = 0.012)\) (Fig. 3).

The clinical aspects of the 12 INR-decreased patients are described in Table 3. Eight of them were taking warfarin after cardiac valve replacement surgery due to valvular heart disease and the other four were treated with warfarin for atrial fibrillation, deep vein thrombosis, or paroxysmal nocturnal hemoglobinuria. As for other combined medications, six patients were prescribed with non-steroidal anti-

### Table 1. Characteristics of patients with warfarin medicated with revaprazan or omeprazole.

<table>
<thead>
<tr>
<th></th>
<th>Revaprazan (N = 15)</th>
<th>Omeprazole (N = 12)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57 (48-93)</td>
<td>61 (46-83)</td>
<td>NS</td>
</tr>
<tr>
<td>Male (%)</td>
<td>6 (40.0%)</td>
<td>1 (8.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, Kg</td>
<td>62.62 (42.85-89.60)</td>
<td>50.30 (44.55-84.00)</td>
<td>0.041</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>22 (11-53)</td>
<td>15 (11-46)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>1.1 (0.8-1.4)</td>
<td>0.9 (0.7-1.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Daily warfarin dose, mg</td>
<td>3.43 (2-8)</td>
<td>2 (1-5.86)</td>
<td>0.041</td>
</tr>
<tr>
<td>Duration of target medication, days*</td>
<td>14 (7-30)</td>
<td>14.5 (11-89)</td>
<td>NS</td>
</tr>
<tr>
<td>INR in previous 3 months</td>
<td>1.99 (1.5-2.72)</td>
<td>1.96 (1.29-2.87)</td>
<td>NS</td>
</tr>
<tr>
<td>INR in previous 1 year</td>
<td>2.24 (1.59-2.81)</td>
<td>2.07 (1.26-2.85)</td>
<td>NS</td>
</tr>
<tr>
<td>INR after target medication</td>
<td>1.2 (0.98-2.42)</td>
<td>2.16 (1.26-4.02)</td>
<td>0.010</td>
</tr>
<tr>
<td>INR change compared with INR of previous 3 months, %</td>
<td>−39.5 (−58.48-21.61)</td>
<td>10.19 (−15.23-72.29)</td>
<td>0.001</td>
</tr>
<tr>
<td>INR change compared with INR of previous 1 year, %</td>
<td>−36.81 (−61.24-3.53)</td>
<td>5.05 (−14.78-83.73)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Duration of target medication until the first post-target medication INR test was done.

INR, international normalized ratio; ALT, alanine aminotransferase; NS, not significant.

Age and all the laboratory values were depicted as mean and range in the bracket.
inflammatory drugs (NSAIDs) or histamine H2 receptor antagonist (H2-blockers), which are known to enhance INR prolongation by warfarin. Other than these, there were no combined medications that could interfere with anti-coagulation by warfarin. There was no recognizable thrombotic event among 12 INR-decreased patients.

The effect of revaprazan medication was delineated well in Patient 4, shown in Table 3. A 76-year-old male had been taking warfarin for 3 years to manage atrial fibrillation and maintain stable INR with warfarin (3 mg/day). Before revaprazan medication, his INR value had been remained stable as 2.48 ± 0.38 (mean ± standard deviation) in the previous year and the last INR measured at 25 days before revaprazan medication was 2.12. He began to take revaprazan prescribed by his otolaryngologist for globus symptom and his INR decreased to 0.98 on the 15th day of revaprazan medication. Even after his daily warfarin dose was raised to 4 mg/day, his INR remained around 1-1.5. Eventually, his Warfarin dose was escalated and maintained at 6 mg/day. He finished his revaprazan medication on the 167th day and his INR followed up on the 235th day was prolonged to 4.3. Subsequently, his Warfarin dose was reduced to 5 mg/day. However, after two months, a large hematoma developed in his right thigh and his INR was still remarkably prolonged to 8.62. During the period of INR fluctuation, there were no newly introduced or discontinued

Table 2. Comparison of characteristics of patients medicated with revaprazan according to INR change after revaprazan medication.

<table>
<thead>
<tr>
<th></th>
<th>INR-decreased cases N=12</th>
<th>INR-unchanged cases N=3</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>59 (48-93)</td>
<td>55 (53-63)</td>
<td>NS</td>
</tr>
<tr>
<td>Male (%)</td>
<td>5 (41.7%)</td>
<td>1 (33.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, Kg</td>
<td>63.30 (42.85-81.45)</td>
<td>57.20 (47.50-89.60)</td>
<td>NS</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>20 (11-53)</td>
<td>29 (23-32)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>1.1 (0.8-1.4)</td>
<td>1.1 (0.8-1.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Daily warfarin dose, mg</td>
<td>30.5 (14.0-62.0)</td>
<td>21 (14-13)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of revaprazan, days*</td>
<td>21.5 (10.0-30.0)</td>
<td>7 (7-13)</td>
<td>0.009</td>
</tr>
<tr>
<td>PT-INR in previous 3 months</td>
<td>2.12 (1.78-2.72)</td>
<td>1.94 (1.50-1.99)</td>
<td>NS</td>
</tr>
<tr>
<td>PT-INR in previous 1 year</td>
<td>2.25 (1.70-2.81)</td>
<td>2.11 (1.59-2.34)</td>
<td>NS</td>
</tr>
<tr>
<td>PT-INR after revaprazan</td>
<td>1.19 (0.98-1.50)</td>
<td>1.84 (1.45-2.42)</td>
<td>0.009</td>
</tr>
<tr>
<td>PT-INR change compared with INR of previous 3 months, %</td>
<td>−44.89 (−58.48-−29.02)</td>
<td>−3.33 (−5.15-21.61)</td>
<td>0.004</td>
</tr>
<tr>
<td>PT-INR change compared with INR of previous 1 year, %</td>
<td>−45.70 (−61.24-−32.31)</td>
<td>−8.81 (−12.83-3.53)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Duration of revaprazan until the first post-revaprazan medication INR test was done.

INR, international normalized ratio; ALT, alanine aminotransferase; NS, not significant.
Age and all the laboratory values were depicted as mean and range in the bracket.

Fig. 2. Changes in the prothrombin time-international normalized ratio (PT-INR).
A. 15 patients with revaprazan, B. 12 patients with omeprazole. Before treatment values represent 3 months-average before the target medication. The revaprazan group showed a significant shortening of INR after medicated with revaprazan while the omeprazole group did not show any statistically significant sequential difference by omeprazole medication.

A

B

$P < 0.0001$

$P > 0.05$
Discussion

In the current study, revaprazan co-administration revealed a potential inhibitory effect on the anticoagulation effect of warfarin. Eighty percent of the patients who took revaprazan showed significant decrease in INR, and this finding was markedly different from omeprazole, the PPIs drug. This inhibitory effect appears to have a correlation with the duration of revaprazan treatment.

Table 3. Detailed characteristics of 12 patients who showed shortening of INR after revaprazan medication.

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Indication for warfarin</th>
<th>Duration*</th>
<th>PT-INR</th>
<th>Other drugs which can affect INR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Previous 1 year**</td>
<td>Previous 3 months**</td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>57</td>
<td>VR</td>
<td>22</td>
<td>2.26</td>
<td>2.62</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>61</td>
<td>VR</td>
<td>28</td>
<td>2.81</td>
<td>2.13</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>53</td>
<td>VR</td>
<td>14</td>
<td>2.73</td>
<td>2.72</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>76</td>
<td>Af</td>
<td>25</td>
<td>2.48</td>
<td>2.36</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>48</td>
<td>PNH</td>
<td>14</td>
<td>1.70</td>
<td>1.78</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>77</td>
<td>VR</td>
<td>30</td>
<td>1.87</td>
<td>1.92</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>56</td>
<td>VR</td>
<td>14</td>
<td>2.27</td>
<td>2.35</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>55</td>
<td>VR</td>
<td>23</td>
<td>2.19</td>
<td>2.11</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>93</td>
<td>DVT</td>
<td>21</td>
<td>1.81</td>
<td>1.98</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>62</td>
<td>VR</td>
<td>26</td>
<td>2.2</td>
<td>2.46</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>70</td>
<td>Af</td>
<td>10</td>
<td>2.24</td>
<td>1.98</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>56</td>
<td>VR</td>
<td>14</td>
<td>2.13</td>
<td>2.00</td>
</tr>
</tbody>
</table>

*Duration of revaprazan medication until the first post-revaprazan INR test was done.

**Mean INR values before medication of revaprazan.

†Post-revaprazan INR was checked during or within 10 days after initiation of revaprazan.

INR, international normalized ratio; VR, valve replacement; Af, atrial fibrillation; PNH, paroxysmal nocturnal hemoglobinuria; DVT, deep vein thrombosis.

Revaprazan is the first APAs (Yu et al. 2004) featuring suppression of acid secretion and protection of gastric membrane, and displayed a quick and powerful suppression of gastric acid secretion in clinical tests. This is especially apparent when observing the pH change in the stomach over a 24 hour period. Its pharmacological action begins very rapidly compared to existing irreversible PPIs (Yu et al. 2004). In clinical tests, it was effective with a once daily dose in maintaining gastric pH at 3 and higher for 24 hours in the treatment of peptic ulcer and its safety and effectiveness were proven by a phase II clinical study. No signifi-

![Fig. 3. Correlation between duration of revaprazan treatment and degree of prothrombin time shortening.](image)

The longer the revaprazan was maintained, the larger the degree of INR decrease in 15 patients who maintained the same dose of warfarin ($R = −0.632, P = 0.012$).
cant difference in its efficacy and adverse event in gastritis, gastric ulcer, and duodenal ulcer in revaprazan users was found when compared to omeprazole users (Chung et al. 2005; Choi et al. 2006; Chang et al. 2007). Also, the chronic toxicity test showed no evidence of direct damage to the liver by revaprazan (Chung et al. 2005; Choi et al. 2006; Chang et al. 2007).

Recently, revaprazan was found to control the mitogen-activated protein kinase (MAPK) extracellular signal regulated protein kinases (ERK1/2) signaling in gastric mucosa in addition to suppressive effect of gastric acid secretion. It was also found to be effective in protecting gastric mucosa by increasing protective proteins such as cyclooxygenase-2 resulting in production of prostaglandin as well as vascular endothelial growth factor (VEGF), interleukin (IL)-8 (Yeo et al. 2006). In addition to having a protective function in stomach membrane, revaprazan can control inflammation that occurs when the cultured gastric mucosa is infected with *Helicobactor pylori* (Yeo et al. 2006). Compared to rabeprazole, another PPIs, revaprazan showed almost identical results in the post-treatment of endoscopic submucosal dissection, and no additional adverse drug reaction was reported thus far (Kim et al. 2010). However, until now, there has been no study that specifically looked into the drug interaction between warfarin and revaprazan.

Despite its narrow therapeutic window, warfarin requires close and constant monitoring because of its wide dosing range. Even though it may be cumbersome to check a patient’s INR regularly in order to properly adjust the dose, warfarin is certainly a lifesaving medicine (Ansell et al. 1997). While the appropriate individual warfarin dose is affected by weight, age, and sex as well as the genetic polymorphism like cytochrome (CYC) P450 isoenzyme and vitamin K epoxide reductase complex subunit 1 (Wadelius et al. 2005; Aquilante et al. 2006), the major factors that induce unexpected change of INR are usually other co-administered medications, food, alcohol, and dietary supplements. As polypharmacy is more common nowadays, other medications coadministered with warfarin can become more problematic in maintaining a stable INR in warfarin users (Greenblatt and von Moltke 2005). According to one research, 84% of the patients on warfarin were found to be also taking the medicines that can affect the INR (Kotirum et al. 2007). Therefore a more detailed evaluation and sufficient information for drug interaction with warfarin are required for all drugs available in the market.

Similar to revaprazan, PPIs act on H⁺/K⁺-ATPase, the last step in gastric acid secretion, and have been used worldwide for acid-related diseases such as peptic ulcer, gastroesophageal reflux disease, and Zollinger-Ellison syndrome (Sachs 1997). However unlike revaprazan, PPIs are known to affect metabolism or pharmacokinetics of some co-administered medicine by interrupting CYP enzyme system or inhibiting the absorption of other drugs (Andersson 1991, 1996). PPIs are mainly catalyzed by CYP450 isoenzyme, CYP2C19, and CYP2C19 enzyme interferes with the metabolism of warfarin. Therefore if PPIs and warfarin are taken together, they can inhibit each other competitively (Andersson et al. 1993). Among PPIs, omeprazole and lansoprazole are known to suppress CYP2C19 substrate very efficiently (Ko et al. 2007). On the other hand, PPI like rabeprazole are not affected by the genetic polymorphism of CYP2C19 and so it would have little interaction with other medicines such as warfarin (Thjodleifsson and Cockburn 1999). In the current study, while three patients (3/12) in the omeprazole group showed increases in INR of 38.87%, 54.03%, and 72.29% respectively compared to past 3 months average INR, the remaining patients (9/12) did not reveal significant INR change with omeprazole medication. The metabolism of warfarin might have been
suppressed by the above-mentioned CYP450 isoenzyme in those 3 INR increased patients.

We found a negative correlation between duration of revaprazan treatment and degree of INR change. Based on this finding, revaprazan is strongly suspected to inhibit warfarin action or clotting system in a cumulative dose-dependent manner. The mechanisms, which can affect warfarin metabolism, such as induction of warfarin breaking enzymes, alteration of vitamin K metabolism, or action as an antagonist of warfarin, should be considered. The other possible mechanism is direct effect on the clotting factors by revaprazan itself. Unlike in the omeprazole group, simultaneous medication of revaprazan and warfarin caused INR shortening of more than 30% from the baseline in 80% of the medicated patients. There was a difference in baseline warfarin doses between the revaprazan group and the omeprazole group, but this difference disappeared once data were corrected for age, sex, and weight. Hence, we assumed the difference in weight attributed to the difference in warfarin dose between the two groups. There were no known combined drugs that would reduce the effect of warfarin in the revaprazan group. There were, however, 6 patients in the revaprazan group who were actually co-medicated with H2-blockers and NSAIDs, both of which have a potential to promote INR prolongation but only one patient showed 21.6% increase of INR. Although there was no thrombotic event, a couple of complicated cases were found such as hematoma and unexpected excessive prolongation of INR after discontinuation of revaprazan.

In cases of newly introduced drugs, interactions with warfarin had been overlooked in pre-marketing clinical studies but were often found during post-marketing surveillance. The typical example is the celecoxib-warfarin interaction. The manufacturer had concluded no interaction with warfarin by performing open-label, multi-dose, placebo-controlled randomized study performed on 24 healthy volunteers (Karim et al. 2000). However, after its introduction to market, a few case reports began to emerge about clinically significant delays in INR (Mersfelder and Stewart 1997; Haase et al. 2000). In the celecoxib-warfarin case, we see that a drug interaction study for warfarin performed on a small number of normal volunteers cannot represent various clinical situations such as polymorphism, comorbid conditions, polypharmacy, and extreme age of patients (Holbrook et al. 2005).

We believe that revaprazan-warfarin interaction may develop via one of the mechanisms previously described but it is still unknown how revaprazan influences the anti-coagulation effect of warfarin. We expect revaprazan may have some effects on CYP isoenzyme, vitamin K pathway, and absorption process of warfarin. The correlation between the % change in INR and the duration of revaprazan medication suggests revaprazan may have a cumulative effect on inhibiting anti-coagulation by warfarin.

Our study has some limitations in that it is a retrospective analysis and that the number of co-medicated patients was not large. However, despite these limitations, we could find some meaningful evidence of revaprazan and warfarin interaction. Since its recent launch, revaprazan has been used more commonly in many Asian countries and due to its advantages over PPIs it has a potential for even wider use. Therefore, precise information on its drug interaction is needed for accurate precautions and proper contra indication before its use becomes more prevalent. To achieve this, future clinical trials are needed to provide further evidence of the effect of revaprazan on anti-coagulation effect of warfarin conducted on a large number of normal volunteers. A pharmacological assessment for the mechanisms of their interaction should also be performed. At the same time, more active post-marketing surveillance should be followed. Based on the results of these studies, a new guideline for the use of revaprazan in warfarinized patients should be established and introduced to physicians and patients before the use of revaprazan.

The current study suggests a possible drug interaction between revaprazan and warfarin; revaprazan could induce shortening of INR in well-controlled warfarinized patients. Therefore, when revaprazan use is considered for patients who are already on warfarin or have a higher risk of thrombotic events, physicians should pay extra attention on coagulation and need to check INR more frequently. Prospective studies for INR monitoring in patients who use revaprazan with warfarin are needed to clarify the association between these two drugs.

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Conflict of Interest

The authors report no conflicts of interest.

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