Impact of *Helicobacter pylori* eradication timing on the risk of thromboembolism events in patients with peptic ulcer disease: a population-based cohort study

Jung-Nien Lai,1 Yi-Jun Liao,2,3 Cheng-Li Lin,4 Chi-Sen Chang,5 Yen-Chun Peng2,5,6

**ABSTRACT**

**Objectives** To evaluate the impact of *Helicobacter pylori* eradication on venous thromboembolism (VTE) events, and the differences between early and late treatment timing.

**Design** A population-based cohort study.

**Setting** Taiwan’s National Health Insurance Research Database.

**Participants** A total of 6736 patients who received *H. pylori* eradication therapy from 2000 to 2010 were identified. We randomly selected 26,944 subjects matching in gender, age and baseline year as comparison cohort.

**Primary and secondary outcome measures** The incidence rate ratios of VTE in the *H. pylori* eradication cohorts to that of the control cohort were examined. Multivariable Cox proportional hazard regression analysis was used to estimate the relative HRs and 95% CI of VTE development.

**Results** The total incidence rate of VTE was observed in the late *H. pylori* eradication cohort, the early *H. pylori* eradication cohort and the control cohort (15.2, 3.04 and 2.91 per 1000 person-years, respectively). An age-specific trend was found in the late *H. pylori* eradication cohort, with a greater rate of VTE in the 50–65 years and more than 65 years age groups (adjusted HR 5.44; 95% CI 4.21 to 7.03 and 3.13; 95% CI 2.46 to 3.99). With comorbidities, the late *H. pylori* eradication cohort seemed to have the highest VTE incidence rate and adjusted HR (4.48; 95% CI 3.78 to 5.30).

**Conclusions** Late *H. pylori* eradication was associated with a significantly increased risk of VTE, and there was a significantly greater risk of VTE in patients with female gender, age more than 50 years and with comorbidities.

**INTRODUCTION**

*Helicobacter pylori* infection is one of the most important infections in humans. Chronic *H. pylori* infection causes chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia and gastric cancer.1 Besides gastric diseases, non-gastric events are also associated with *H. pylori* infection, including cardiovascular diseases, lung diseases, haematological diseases, eye and skin diseases, hepatobiliary diseases, diabetes mellitus and neurological disorders.2 3 *H. pylori* eradication treatment for diagnosed *H. pylori* infection is the standard of care. In recent decades, the clinical guidelines have seen significant scientific advances regarding the management of *H. pylori* infection.4

The issue of post-*H. pylori* eradication requires further investigation. *H. pylori* eradication could improve gastric mucosa atrophy and intestinal metaplasia, decrease peptic ulcer and lower gastric cancer risk, but it exacerbates gastro-oesophageal reflux due to acid.5 The most promising long-term effect of *H. pylori* eradication could decrease the risk of gastric cancer.6 *H. pylori* eradication could trigger an inflammatory state and induce molecular mechanisms by expressing virulence peptides. Moreover, *H. pylori* infection interferes with the host absorbance of different nutrients, and potentially influences the host’s health outside the gastrointestinal tract. Growing evidence has shown that a variety of conditions and disorders are caused by *H. pylori* infection, such as idiopathic diseases.
infection. It has been clearly established that eradication when compared with patients with persistent improvements in gastric histology following 99% of Taiwan’s 23 launched on 1 March 1995 and currently covers almost The National Health Insurance (NHI) programme was Data source MATERIALS AND METHODS Data source The National Health Insurance (NHI) programme was launched on 1 March 1995 and currently covers almost 99% of Taiwan’s 23 million residents. Data from the Longitudinal Health Insurance Database 2000 were provided by Taiwan’s National Health Research Institutes, and included information on outpatient and ambulatory visits, hospital inpatient care and dental services. The diagnostic codes in the current study were based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Sampled participants Recruited patients were aged 20 years or above with a history of peptic ulcer disease (ICD-9-CM codes 531, 532 and 533), which was subsequently treated with H. pylori eradication therapy. According to the insurance payment rules of the NHI system, the diagnosis of most patients who received H. pylori-related treatment was confirmed by upper gastrointestinal endoscopy examination. The treatment of H. pylori eradication by triple or quadruple therapy was defined as involving multiple medications as follows: a proton pump inhibitor or H2 receptor blocker, clarithromycin or metronidazole, and amoxicillin or tetracycline, with or without bismuth (details of all eligible H. pylori eradication regimens were reported previously). These drug combinations were prescribed in the same order, and the duration of therapy was from 7 to 14 days. The early H. pylori eradication cohort was defined as patients receiving H. pylori eradication therapy within 1 year of diagnosis of peptic ulcer disease, and the late H. pylori eradication cohort was defined as patients receiving H. pylori eradication therapy more than 1 year after peptic ulcer diseases were diagnosed. The index date for patients was set as the date that they first received H. pylori eradication therapy. The exclusion criteria were missing data regarding date of birth, sex or history of VTE (ICD-9-CM 415.1, 415.8 except 415.11) prior to the index date. For comparison, controls were randomly selected from the pool of participants without peptic ulcer disease who did not receive H. pylori eradication therapy. According to age (every 5-year span), sex and year of receiving H. pylori eradication therapy, controls were 1:4 frequency matched to each H. pylori eradication case.

Patient and public involvement Taiwan NHI programme is a general population health-care insurance system covering more than 99% population. NHI was initiated on 1 March 1995 in Taiwan, and is still working well now. The de-identified database included medical records of enrollees registered in the National Health Insurance Research Database (NHIRD). A subset of the NHIRD contains data of 1 million randomly selected enrollees from the NHI programme and was used in this study. The claims data were totally encrypted identification information. The disease codes of the database were identified according to the ICD-9-CM. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Variables of interest The general diagnostic process of the NHI programme was based on physical examination and quantitative ultrasound. All patients were followed up until a diagnosis of VTE was made or they were censored for loss to follow-up, withdrawal from the NHI programme or 31 December 2011, whichever occurred first. Hypertension, diabetes, hyperlipidaemia, coronary artery disease (CAD), heart failure, cancer, stroke, and lower leg fracture or surgery were considered as covariates.

Statistical analysis The X2 test and Student’s t-test were used to determine differences in categorical and continuous variables between H. pylori eradication (including early and late H.
pylori eradication therapy) and control cohorts. The incidence density rate of VTE was calculated for each instance of early H. pylori eradication therapy, late H. pylori eradication therapy and for the control cohort. The incidence rate ratios of VTE in the H. pylori eradication cohorts to that of the control cohort and the 95% CI were estimated using a Poisson regression model. The relative HRs and 95% CIs of VTE development for the H. pylori eradication cohorts were estimated with multivariable Cox proportional hazard regression analysis adjusted for age, sex, and comorbidities of hypertension, diabetes, hyperlipidaemia, CAD, heart failure, cancer, stroke, and lower leg fracture or surgery. All data analyses were performed using the SAS statistical package (V.9.4 for Windows; SAS Institute). A two-tailed p<0.05 indicated statistical significance.

RESULTS

Demographic data
From 2000 to 2010, a total of 6736 subjects received H. pylori eradication treatment, including 3062 patients who received early H. pylori eradication (early eradication cohort), and 3674 patients who received late H. pylori eradication (late eradication cohort). There were 26944 subjects who served as the control cohort for comparison. The demographic data are shown in table 1. There were differences in age among the three cohorts: early eradication, late eradication and control (49.5±14.1, 56.0±14.3, 52.6±14.9; p=0.01). There were no differences in gender ratios among the three cohorts. The late H. pylori eradication cohort had more comorbidities compared with the early eradication and control cohorts.

HR and incidence rate of VTE
In table 2, it can be seen that there was no significant difference in risk of VTE between the early H. pylori eradication cohort and control cohort. The total incidence rates of VTE were determined for the late H. pylori eradication cohort, the early H. pylori eradication cohort and the control cohort (15.2, 3.04 and 2.91 per 1000 person-years, respectively). With respect to gender, VTE incidence was higher in the late H. pylori eradication cohort in men and women, and female gender in the late H. pylori eradication cohort had the highest incidence rate (20.5 per 1000 person-years). The age-specific trend in the late H. pylori eradication cohort was found to be greater in the 50–65 years and more than 65 years age groups (adjusted HR 5.44; 95% CI 4.21 to 7.03 and 3.13; 95% CI 2.46 to 3.99). The VTE incidence was lower in the early eradication cohort with more than 65 years old (adjusted HR 0.21; 95% CI 0.08 to 0.56). The early H. pylori eradication cohort seemed to have a lower risk of VTE compared with the late H. pylori eradication cohort. Regarding comorbidities, the late H. pylori eradication cohort seemed to have the highest VTE incidence rate (4.48, 95% CI 3.78 to 5.30).

HRs of late and early H. pylori eradication
Table 3 shows that the risk of VTE was significantly higher in the late H. pylori eradication cohort than in the early
Table 2  HRs of venous thromboembolism between control subjects and early or late *Helicobacter pylori* eradication

<table>
<thead>
<tr>
<th></th>
<th>Control (N=26944)</th>
<th>Early eradication (N=3062)</th>
<th>Adjusted HR (95% CI)</th>
<th>Late eradication (N=3674)</th>
<th>Adjusted HR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event</td>
<td>Rate*</td>
<td>Event</td>
<td>Rate*</td>
<td>IRR (95% CI)</td>
</tr>
<tr>
<td>All</td>
<td>414</td>
<td>2.91</td>
<td>54</td>
<td>3.04</td>
<td>1.04 (0.93 to 1.18)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>220</td>
<td>3.46</td>
<td>23</td>
<td>3.14</td>
<td>0.91 (0.75 to 1.10)</td>
</tr>
<tr>
<td>Male</td>
<td>194</td>
<td>2.47</td>
<td>31</td>
<td>2.97</td>
<td>1.20 (1.04 to 1.39)‡</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤49</td>
<td>83</td>
<td>1.27</td>
<td>28</td>
<td>2.82</td>
<td>2.23 (1.96 to 2.53)‡</td>
</tr>
<tr>
<td>50–65</td>
<td>138</td>
<td>2.83</td>
<td>22</td>
<td>4.10</td>
<td>1.45 (1.19 to 1.76)‡</td>
</tr>
<tr>
<td>≥65</td>
<td>193</td>
<td>6.92</td>
<td>4</td>
<td>1.62</td>
<td>0.23 (0.14 to 0.40)‡</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>133</td>
<td>1.51</td>
<td>26</td>
<td>2.42</td>
<td>1.61 (1.42 to 1.82)‡</td>
</tr>
<tr>
<td>Yes</td>
<td>281</td>
<td>5.20</td>
<td>28</td>
<td>3.98</td>
<td>0.77 (0.63 to 0.94)§</td>
</tr>
</tbody>
</table>

*Incidence rate per 1000 person-years.
†Multiple analyses including age, sex, and comorbidities of hypertension, diabetes, hyperlipidaemia, coronary artery disease, heart failure, cancer, stroke, and lower leg fracture or surgery.
‡P<0.001.
§P<0.01.
IRR, incidence rate ratio.
H. pylori eradication cohort (adjusted HR 3.56, 95% CI 2.63 to 4.81). The risk of VTE was significantly greater for both genders, and women had a significantly higher risk compared with men. The age-specific adjusted HR of VTE in the late H. pylori eradication cohort compared with the early H. pylori eradication cohort was not significant for the younger group (adjusted HR 0.84; 95% CI 0.43 to 1.67). Without comorbidities, the difference of adjusted HR between the late H. pylori eradication cohort and the early eradication cohort was not significant (0.83, 95% CI 0.42 to 1.62).

**Incidences and adjusted HRs of DVT and PE, according to follow-up period, in the H. pylori eradication patients compared with the control patients**

Furthermore, we compared incidence densities and HRs of VTE among three cohorts by follow-up duration (table 4). The incidence of VTE was greater in the late H. pylori eradication cohort when follow-up duration ≤5 years (25.4 per 1000 person-years). The highest risk occurred during the >5 years of follow-up period (adjusted HR 7.92, 95% CI 4.27 to 14.7) in the late H. pylori eradication cohort compared with the early eradication cohort.

**DISCUSSION**

Our results showed that the timing of H. pylori eradication significantly affected risk of VTE. There was a significantly greater risk of late H. pylori eradication for VTE for female gender, age over 50 years and with comorbidities.

It is possible that H. pylori initiates an inflammatory process in the stomach and may even generate a systemic response throughout the host. H. pylori eradication therapy could effectively prevent the progression of the pathological process in the gastric mucosa. The patient may also experience systemic effects, beyond the stomach, from H. pylori eradication. The association between H. pylori and VTE may not be strong, which would explain why our results showed no significant difference in risk of VTE between the early H. pylori eradication and control cohorts. However, late H. pylori eradication, particularly with comorbidities, showed a significantly increased risk of VTE compared with early H. pylori eradication. The timely eradication of the infection would likely lead to better health status in an H. pylori-infected population, not only with respect to prevention of peptic ulcers and gastric cancer, but also in terms of risk of VTE, as shown in the present study.

**H. pylori** may be an independent risk factor for atherothrombotic events in animals and humans. Infection with H. pylori did not appear to be associated with DVT in a specific disease. H. pylori eradication therapy could cause more extensive beneficial effects, regardless of any relationship with H. pylori. Eradicating H. pylori infection is currently the standard of care, and could ultimately cause more good than harm. Beyond peptic ulcer recurrence and cancer occurrence, H. pylori eradication could cause systemic effects, such as metabolic and inflammatory processes. While the association of H. pylori and clinical conditions is not directly correlated, H. pylori eradication may cause systemic changes within the host that are not immediately apparent. Previous studies were primarily concerned with how H. pylori could affect systems within the body, including cardiovascular diseases, neurological disorders, diabetes mellitus, ear and eye diseases, immunological and haematological disorders, liver and bile tract diseases, and gynaecological and respiratory diseases.

### Table 3 HRs of venous thromboembolism between early and later Helicobacter pylori eradication

<table>
<thead>
<tr>
<th></th>
<th>Early eradication</th>
<th>Late eradication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR (95% CI)</td>
<td>Adjusted HR* (95% CI)</td>
</tr>
<tr>
<td>All</td>
<td>1 (reference)</td>
<td>5.00 (4.25 to 5.90)†</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1 (reference)</td>
<td>6.52 (4.98 to 8.54)†</td>
</tr>
<tr>
<td>Male</td>
<td>1 (reference)</td>
<td>3.57 (2.91 to 4.38)†</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤49</td>
<td>1 (reference)</td>
<td>0.65 (0.51 to 0.82)†</td>
</tr>
<tr>
<td>50–65</td>
<td>1 (reference)</td>
<td>5.37 (4.03 to 7.17)†</td>
</tr>
<tr>
<td>≥65</td>
<td>1 (reference)</td>
<td>14.9 (7.77 to 28.7)†</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (reference)</td>
<td>0.83 (0.66 to 1.05)</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (reference)</td>
<td>5.70 (4.41 to 7.37)†</td>
</tr>
</tbody>
</table>

*Multiple analyses including age, sex, and comorbidities of hypertension, diabetes, hyperlipidaemia, coronary artery disease, heart failure, cancer, stroke, and lower leg fracture or surgery.
†P<0.00.

IRR, incidence rate ratio.
Late *H. pylori* eradication was associated with a significantly increased risk of VTE. The risk of VTE was significantly greater in patients with female gender, age more than 50 years and with comorbidities. Therefore, we recommended administering *H. pylori* eradication therapy early.

**Table 4** Trends of venous thromboembolism risks by stratified follow-up years

<table>
<thead>
<tr>
<th>Follow-up time, years</th>
<th>Control (N=26944)</th>
<th>Early eradication (N=3062)</th>
<th>Adjusted HR†</th>
<th>Late eradication (N=3674)</th>
<th>Adjusted HR†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case</td>
<td>Rate*</td>
<td>IRR (95% CI)</td>
<td>Case</td>
<td>Rate*</td>
</tr>
<tr>
<td>≤5</td>
<td>216</td>
<td>2.08</td>
<td>1.64 (1.46 to 1.84)†</td>
<td>198</td>
<td>5.19</td>
</tr>
<tr>
<td>&gt;5</td>
<td>42</td>
<td>3.41</td>
<td>1.92 (1.38 to 2.68)‡</td>
<td>12</td>
<td>2.21</td>
</tr>
<tr>
<td>≤5</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>3.54 (3.00 to 4.18)‡</td>
<td>11.5 (8.43 to 15.8)‡</td>
<td>7.92 (4.27 to 14.7)‡</td>
</tr>
<tr>
<td>&gt;5</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>4.21 (1.38 to 2.68)‡</td>
<td>2.41 (1.70 to 3.41)‡</td>
<td></td>
</tr>
</tbody>
</table>

*Incidence rate per 1000 person-years.
†Multiple analyses including age, sex, and comorbidities of hypertension, diabetes, hyperlipidaemia, coronary artery disease, heart failure, cancer, stroke, and lower leg fracture or surgery.
‡P<0.001.
IRR, incidence rate ratio.

**CONCLUSIONS**

Late *H. pylori* eradication was associated with a significantly increased risk of VTE. The risk of VTE was significantly greater in patients with female gender, age more than 50 years and with comorbidities. Therefore, we recommended administering *H. pylori* eradication therapy early. Further study is needed to gain a more comprehensive understanding of the systemic insults and molecular mechanisms involved in *H. pylori* eradication. Besides gastric diseases and cancers, *H. pylori* infection may not directly cause VTE events, but late *H. pylori* eradication could be a risk factor for VTE. The processes underlying this phenomenon are unclear, but several possible mechanisms have been suggested. *H. pylori* eradication therapy could have beneficial systemic effects. In addition, a recent study reported that *H. pylori* eradication treatment was associated with a risk for VTE. Further study is needed to gain a more comprehensive understanding of the systemic insults and molecular mechanisms involved in *H. pylori* eradication.
Author affiliations

1Department of Chinese Medicine, China Medical University, Taichung, Taiwan
2Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan
3School of Medicine, National Chung Hsin University, Taichung, Taiwan
4Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
5School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
6School of Medicine, National Chung Hsin University, Taichung, Taiwan
7Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan
8Department of Chinese Medicine, China Medical University, Taichung, Taiwan


Funding The work was supported in part by Taiwan’s Ministry of Health and Welfare Clinical Trial Center (MOHW109-TDU-B-212-114004) and the MOST Clinical Trial Consortium for Stroke (MOST 108-2321-B-009-003).

Disclaimer The funders had no role in the study design, data collection and analysis, the decision to publish or preparation of the manuscript.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of China Medical University Hospital and (CMUH104-REC2-115). The need for informed consent was waived by the IRB of China Medical University.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD

Yen-Chun Peng http://orcid.org/0000-0002-8993-3039

REFERENCES
