Received: 4 April 2023 | Revised: 13 April 2023 | Accepted: 12 May 2023

DOI: 10.1111/hel.12990

ORIGINAL ARTICLE

Helicobacter WILEY

Risk of hospitalization for upper gastrointestinal bleeding in *Helicobacter pylori* eradicated patients newly started on warfarin or direct oral anticoagulants: A population-based cohort study

Fang Jiang[1] | Chengsheng Ju[2] | Chuan-Guo Guo[1,3] | Ka Shing Cheung[1] | Bofei Li[4,5] | Simon Y. K. Law[4] | Wallis C. Y. Lau[2] | Wai K. Leung[1]

[1]Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China

[2]Research Department of Practice and Policy, School of Pharmacy, University College London, London, UK

[3]Department of Gastroenterology, Beijing Friendship Hospital, Capital Medical University, Beijing, China

[4]Department of Surgery, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China

[5]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China

Correspondence
Wai K. Leung, Department of Medicine, Queen Mary Hospital, University of Hong Kong, 102 Pokfulam Road, Hong Kong.
Email: waikleung@hku.hk

Abstract

Background: To investigate risks of hospitalization for upper gastrointestinal bleeding (UGIB) in *H. pylori*-eradicated patients newly started on warfarin or direct oral anticoagulants (DOACs).

Methods: We identified all patients who had previously received *H. pylori* eradication therapy or were found to have no *H. pylori* on endoscopy and were then newly started on warfarin or DOACs from a population-based electronic healthcare database. Primary analysis was the risk of UGIB between warfarin and DOACs users in *H. pylori*-eradicated patients. Secondary analysis included the UGIB risk between *H. pylori*-eradicated and *H. pylori*-negative patients who were newly started on warfarin or DOACs. The hazard ratio (HR) of UGIB was approximated by pooled logistic regression model incorporating the inverse propensity of treatment weightings with time-varying covariables.

Results: Among *H. pylori*-eradicated patients, DOACs had a significantly lower risk of UGIB (HR: 0.26, 95% CI 0.09–0.71) compared with warfarin. In particular, lower UGIB risks with DOACs were observed among older (≥65 years) patients, female, those without a history of UGIB or peptic ulcer, or ischemic heart disease, and non-users of acid-suppressive agents or aspirin. Secondary analysis showed no significant difference in UGIB risk between *H. pylori*-eradicated and *H. pylori*-negative patients newly started on warfarin (HR: 0.63,95% CI 0.33–1.19) or DOACs (HR: 1.37, 95% CI 0.45–4.22).

Conclusions: In *H. pylori*-eradicated patients, new users of DOACs had a significantly lower risk of UGIB than new warfarin users. Furthermore, the risk of UGIB in new warfarin or DOACs users was comparable between *H. pylori*-eradicated and *H. pylori*-negative patients.

KEYWORDS
direct thrombin inhibitor, factor Xa inhibitor, gastrointestinal bleeding

1 | INTRODUCTION

Gastrointestinal bleeding (GIB) is a common cause of hospital admission. In the United States, GIB was responsible for 530,855 hospital admissions, 8180 (2.4%) hospital deaths and more than $300 million of total expenditure in 2018.[1] While *H. pylori* is an important cause of GIB and peptic ulcer bleeding, eradication of *H. pylori* has been shown to reduce the risk of subsequent upper GIB (UGIB).[2] Apart from *H. pylori*, concurrent medication use is another major cause of GIB, including the use of aspirin, non-steroidal anti-inflammatory drugs, and anti-coagulants.[3–7]

Anticoagulants, vitamin K antagonists (warfarin) and direct oral anticoagulants (DOACs), are increasingly used for the prevention of thromboembolism. DOACs, which include the direct thrombin inhibitor and factor Xa inhibitors, have the advantage of more rapid onset and spare the need for frequent blood monitoring for dose titration. However, both warfarin and DOACs could lead to major clinical bleeding complications including GIB.[5–7] Nonetheless, past studies showed an inconsistent association between the use of DOACs and warfarin with GIB. While a meta-analysis[8] including randomized controlled trials (RCTs) showed that DOACs significantly increased GIB by 25% compared with warfarin, another meta-analysis[9] showed no significant difference in the risk of GIB between DOACs and warfarin use. Some observational studies[7,10] reported that warfarin had a higher GIB risk compared with DOACs. Other studies suggested a difference in GIB risk with different DOACs,[11–15] with dabigatran and rivaroxaban associated with a higher risk of GIB and apixaban associated with a lower risk of GIB compared with warfarin. In addition, some studies[16,17] showed that either dabigatran or rivaroxaban was not associated with GIB risk than warfarin. These conflicting results could be due to the failure to consider the confounding role of *H. pylori* infection.

While *H. pylori* infection and oral anticoagulants are both risk factors for GIB, this study aimed to eliminate the role of *H. pylori* on UGIB by including only *H. pylori*-eradicated and *H. pylori*-negative patients. In this study, we first determined the risk of hospitalization for UGIB in a large cohort of *H. pylori*-eradicated patients from Hong Kong who were newly started on warfarin or DOACs. We further determined the UGIB risks of individual DOACs, including apixaban, dabigatran, and rivaroxaban, compared with warfarin in this cohort. To further characterize the role of *H. pylori* eradication on risk of UGIB in warfarin or DOACs users, we also compared the risks of UGIB in another cohort of *H. pylori*-negative patients who were newly started on warfarin or DOACs.

2 | METHODS

2.1 | Data sources

This was a territory-wide retrospective cohort study, which was based on data retrieved from the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority. The CDARS is an electronic healthcare database that captures medical information of all patients attending public hospitals and clinics in Hong Kong, and the details for patients' information have been described in our previous studies.[2,3,18–21] To ensure patients' confidentiality, data were anonymized and a unique reference key was used to represent each de-identified patient in the CDARS.

This study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (reference number: UW 21–431). Since data were anonymized in the database, informed consent from patients was not required by the Institutional Review Board.

2.2 | Study subjects

We included all adult patients who had previously received *H. pylori* eradication therapy between January 1, 2003, and December 31, 2017, in Hong Kong.[18,22] These patients had been prescribed their first course of clarithromycin-containing triple therapy lasting 7–14 days, which was the main eradication regime given in Hong Kong during that period. Patients who required retreatment for *H. pylori* were excluded and the details of various retreatment regimes were described previously.[18,22] The accuracy of retreatment inferred eradication failure had been verified in our previous study.[18]

From the *H. pylori*-eradicated cohort, we identified all patients who were newly started on warfarin or DOACs from January 1, 2010, as the first approval date for DOACs locally was in 2010. The date of the first prescription of warfarin or DOACs after *H. pylori* eradication was defined as the index date to stratify patients into the two exposure groups. To clarify the risk of individual DOACs, we further divided new DOACs users into users of apixaban, dabigatran, or rivaroxaban. Edoxaban was not included in this analysis due to the very limited sample size. The details of the selection for included and excluded patients in the *H. pylori*-eradicated cohort are presented in Figure S1.

To further clarify the role of *H. pylori* eradication on the risk of UGIB in new warfarin or DOACs users, we included a second cohort of *H. pylori*-negative cohort as the control reference.[2] These patients were found to have no *H. pylori* on their index endoscopy and had no history of prescription for *H. pylori*. The date of the first prescription of warfarin or DOACs after endoscopy was defined as the index date to stratify patients into the exposure groups. The details of the flow chart for patient selection of *H. pylori*-negative cohort are depicted in Figure S2.

2.3 | Exposure of interest

The exposure of interest was the new use of warfarin or DOACs (including apixaban, dabigatran, or rivaroxaban). Upon entry into the cohort, patients were classified according to their first anticoagulant prescription after *H. pylori* eradication or upper endoscopy.

2.4 | Other covariates

Patient's baseline characteristics, the time from *H. pylori* eradication to exposure, medical conditions, and concurrent medication uses were included as covariates. Data on past medical conditions were collected from the index date or earlier. As treatment indications of anticoagulants were not available in the database, treatment indication for atrial fibrillation (AF) was assumed if this diagnosis was made within 180 days of the index date. Concurrent medication uses during the follow-up period included proton pump inhibitors (PPIs), histamine type 2 receptor antagonists (H2RAs), nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, other antiplatelets, selective serotonin reuptake inhibitors, and bisphosphonate, which were treated as time-varying variables during the follow-up period. Considering the potential indication bias, new prescriptions for gastroprotective agents, PPIs, and H2RAs drugs, during the last 6 weeks of the event date or censor date were not included. The International Classification of Diseases, Ninth Revision (ICD-9) codes for the disease diagnosis were presented in Table S1.

2.5 | Outcome of interest

The primary outcome was the risk of hospitalization for UGIB in new warfarin or DOACs users in *H. pylori*-eradicated patients. The secondary outcome was to compare the risk of UGIB among new warfarin or DOACs users between *H. pylori*-eradicated and *H. pylori*-negative patients. The date of UGIB-related hospitalization was defined by the earliest diagnosis date for UGIB after the index medication date. The accuracy of using these ICD-9 codes for GIB had been previously verified in our study.[23]

For new warfarin or DOACs users in *H. pylori*-eradicated or *H. pylori*-negative cohort, patients were followed until the occurrence of the study outcome, treatment discontinuation, a switch from the index medication to another anticoagulant (warfarin or DOACs), death, or end of the study (December 2020). The maximum observation period for all users was 3 years after starting anti-coagulants. The details of the schematic diagram of the study design are depicted in Figure S3.

2.6 | Statistical analysis

Continuous data were presented as median with interquartile range (IQR), and categorical data were expressed as numbers and percentages. To balance the difference in baseline characteristics between warfarin and DOACs users in *H. pylori*-eradicated cohort, propensity score (PS)-based stabilized inverse probability of treatment weights (IPTWs) were applied to create a pseudo-population. A multivariable logistic regression model was used to calculate the probability of receiving warfarin or DOACs treatment based on patient's measured characteristics.

Within the *H. pylori*-eradicated cohort, we estimated the causal effects of DOACs use (as well as the use of apixaban, dabigatran, and rivaroxaban uses separately) versus warfarin on the risks of UGIB. We used a pooled logistic regression model incorporating the IPTWs as the outcome model. As the follow-up interval is relatively short and the outcome is infrequent, weighted pooled logistic regression models were used to approximate Cox proportional hazards models after IPTWs to determine the risks of UGIB in the hazard ratios (HRs).[24] Robust variance estimator was used to estimate the standard errors and the 95% confidence intervals (CIs) for HRs.[25] We additionally adjusted the concurrent medications with at least 7 days in 1-month intervals as time-varying variables in multivariable models after IPTWs as the primary model. We also estimated the standardized probability curves of UGIB by fitting the pooled logistic models with product terms between warfarin or DOACs initiation and follow-up time.[26] The probability curves were standardized to the baseline IPTWs and the time-varying concurrent use of other medications. More detailed statistical analyses were depicted in the supplementary document. A two-sided P value less than 0.05 was considered statistically significant. All statistical analyses were performed by the R statistical software version 4.0.3 (R Foundation for Statistical Computing, 2019) and SAS version 9.4 (SAS Institute).

3 | RESULTS

3.1 | Patient characteristics in *H. pylori*-eradicated cohort

In the *H. pylori*-eradicated cohort, there were 1120 and 1651 patients who were newly started on warfarin and DOACs, respectively. Their baseline characteristics were balanced with all ASD less than 0.1 after IPTWs (Table 1). The median age of receiving eradication therapy for warfarin and DOACs users was 65 and 67 years, respectively.

For the subgroup analysis of UGIB risk among different DOACs users, 3 patients who received more than one DOACs at the index date were excluded. Finally, 695 new apixaban users, 568 new dabigatran users, and 385 rivaroxaban users were identified. The baseline characteristics of patients with new apixaban, dabigatran, and rivaroxaban users are shown in Table S2.

3.2 | Risk of upper gastrointestinal bleeding of warfarin versus direct oral anti-coagulants in *Helicobacter pylori*–eradicated cohort

In the *H. pylori*-eradicated cohort, 14 (1.25%) warfarin users and 8 (0.48%) DOACs users had hospitalization for UGIB during the follow-up period with a weighted incidence rate of 2.02 (95% CI 1.18–3.22) and 0.49 (95% CI 0.22–0.96) per 100 person-years, respectively (Table S3).

The pooled logistic regression model showed that DOACs users were associated with a lower risk of UGIB (HR: 0.26, 95% CI 0.09–0.71) than warfarin users. Sensitivity analyses using different

TABLE 1 Baseline characteristics of *Helicobacter pylori*–eradicated patients who were newly started warfarin or DOACs (before and after inverse propensity of treatment weightings).

Characteristics	Warfarin ($n=1120$)	DOACs ($n=1651$)	ASD before IPTWs	ASD# after IPTWs
Age (years)*	65 (55–73)	67 (59–74)	0.24	<0.01
Male (*n*, %)	615 (54.9)	820 (49.7)	0.11	<0.01
Medical conditions (*n*, %)				
UGIB or peptic ulcer	268 (23.9)	342 (20.7)	0.08	<0.01
Diabetes mellitus	252 (22.5)	355 (21.5)	0.02	0.03
Hypertension	497 (44.4)	849 (51.4)	0.14	<0.01
Intracranial hemorrhage	30 (2.7)	42 (2.5)	0.01	0.02
Stroke	171 (15.3)	289 (17.5)	0.06	0.02
IHD	279 (24.9)	392 (23.7)	0.03	0.01
Renal disease	154 (13.8)	111 (6.7)	0.23	0.01
Cirrhosis	29 (2.6)	18 (1.1)	0.11	0.01
Treatment indications (*n*, %)				
AF	244 (21.8)	585 (35.4)	–	–
Other	876 (78.2)	1066 (64.6)	–	–
Medications (*n*, %)				
PPIs	380 (33.9)	712 (43.1)	0.19	0.03
H2RAs	319 (28.5)	532 (32.2)	0.08	0.01
NSAIDs	40 (3.6)	65 (3.9)	0.02	<0.01
Aspirin	399 (35.6)	565 (34.2)	0.03	<0.01
Other antiplatelets	52 (4.6)	93 (5.6)	0.05	0.01
SSRIs	43 (3.8)	56 (3.4)	0.02	<0.01
Bisphosphonate	9 (0.8)	20 (1.2)	0.04	0.01
The time from *H. pylori* eradication to exposure (months)*	67 (31–105)	99 (57–141)	0.54	0.01

Note: Treatment indications were defined within 180 days before the index date. Medications were defined as at least 7 days of use in the first 1-month intervals after the index date.

Abbreviations: DOACs, direct oral anticoagulants; ASD, absolute standardized difference; IPTWs, inverse probability of treatment weightings; UGIB, upper gastrointestinal bleeding; IHD, ischemic heart disease; AF, atrial fibrillation; PPIs, proton pump inhibitors; H2RAs, histamine type 2 receptor antagonists; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

#ASD ≥0.1 is considered to be imbalanced.

*Expressed as median and interquartile range.

intervals of concurrent medications use all showed consistent results (Table 2). The standardized probability curve showed that the 3-year absolute risk of UGIB in warfarin users was 5.22%, while in DOACs users, it was 1.32% (Figure S4).

Subgroup analysis showed that DOACs users had a significantly lower risk of UGIB than warfarin users in patients aged ≥65 years (HR: 0.15, 95% CI 0.04–0.51), female (HR: 0.14, 95% CI 0.02–0.95), with no prior history of UGIB or peptic ulcer (HR: 0.17, 95% CI 0.03–0.88) and IHD (HR: 0.07, 95% CI 0.01–0.61), and those not using concurrent PPIs (HR: 0.13,95% CI 0.02–0.73), H2RAs (HR: 0.25, 95% CI 0.08–0.81), or aspirin (HR: 0.14, 95% CI 0.04–0.44) (Table 3).

For the indications of anticoagulants other than AF, there were 876 warfarin users and 1066 DOACs users, and the baseline characteristics were balanced with all ASD less than 0.1 after IPTWs (Table S4). Sensitivity analysis in non-AF patients showed similar results with DOACs users having a lower risk of UGIB (HR: 0.22, 95% CI 0.08–0.60). Pooled logistic regression models with different intervals of concurrent medication use yielded consistent results (Table S5). Sensitivity analysis was also attempted in AF patients, but only one UGIB event was identified and further analysis was not performed.

3.3 | Risks of upper gastrointestinal bleeding of different direct oral anti-coagulants in *H. pylori*-eradicated cohort

Subgroup analysis was performed to determine the risks of UGIB in *H. pylori*-eradicated patients using different DOACs. Overall, there were 14 (1.25%) warfarin, 2 (0.29%) apixaban, 3 (0.53%)

TABLE 2 Risk of UGIB in *Helicobacter pylori*–eradicated patients newly started on warfarin or DOACs.

Models	HR (95% CI)*	*p* value
Multivariable model 1		
Warfarin	1.0	–
DOACs	0.26 (0.09–0.71)	0.01
Multivariable model 2		
Warfarin	1.0	–
DOACs	0.27 (0.10–0.74)	0.01
Multivariable model 3		
Warfarin	1.0	–
DOACs	0.29 (0.11–0.75)	0.01
Multivariable model 4		
Warfarin	1.0	–
DOACs	0.29 (0.11–0.77)	0.01

Note: Multivariable model 1: Concurrent medications were defined as at least 7 days of use in 1-month intervals; Multivariable model 2: Concurrent medications were defined as at least 7 days use in 3-month intervals; Multivariable model 3: Concurrent medications were defined as at least 14 days use in 1-month intervals; Multivariable model 4: Concurrent medications were defined as at least 14 days of use in 3-month intervals.

Abbreviations: UGIB, upper gastrointestinal bleeding; DOACs, direct oral anticoagulants; CI, confidence interval; HR, hazard ratio.

*HR generated by pooled logistic regression, weighted for inverse probability of treatment weightings and adjusted by time-varying medications use.

dabigatran, and 3 (0.78%) rivaroxaban users who had a hospitalization for UGIB during the follow-up period, with a weighted incidence rate of 2.06 (95% CI 1.22–3.27), 0.72 (95% CI 0.22–1.72), 0.54 (95% CI 0.12–1.53), and 0.61 (95% CI 0.09–2.06) per 100 person-years, respectively (Table S6). The pooled logistic regression model, with at least 7 days concurrent medications use in 1-month intervals, showed that there was no significant difference between warfarin and three individual DOACs users (HR for apixaban: 0.34, 95% CI 0.05–2.38; HR for dabigatran: 0.29, 95% CI 0.07–1.24; HR for rivaroxaban: 0.31, 95% CI 0.08–1.20). Sensitivity analyses using different intervals of concurrent medications use yielded consistent results (Table S7).

3.4 | Risks of upper gastrointestinal bleeding among new warfarin users in *Helicobacter pylori*–eradicated versus *Helicobacter pylori*–negative cohort

There were 1120 new warfarin users in the *H. pylori*-eradicated cohort and 2619 new warfarin users in the *H. pylori*-negative group. The baseline characteristics of the two groups were well balanced with all ASD less than 0.1 (Table S8). Fourteen (1.25%) patients in the *H. pylori*-eradicated group and 45 (1.72%) patients in the *H. pylori*-negative group had UGIB during the follow-up period with a weighted incidence rate of 1.49 (95% CI 0.79–2.56) and 2.55 (95% CI 1.84–3.45) per 100 person-years, respectively (Table S9). The pooled

TABLE 3 Stratified HR for UGIB risk in *H. pylori*-eradicated patients newly started warfarin versus DOACs based on multivariable pooled logistic regression model with 1-month intervals.

Subgroups	HR (95% CI)*	*p* value
Age		
<65 years	0.86 (0.21–3.47)	0.83
≥65 years	0.15 (0.04–0.51)	<0.01
Sex		
Male	0.35 (0.10–1.18)	0.09
Female	0.14 (0.02–0.95)	0.04
UGIB or peptic ulcer history		
Yes	0.35 (0.10–1.22)	0.10
No	0.17 (0.03–0.88)	0.04
IHD history		
Yes	0.92 (0.23–3.70)	0.91
No	0.07 (0.01–0.61)	0.02
PPI use		
Yes	0.31 (0.08–1.15)	0.08
No	0.13 (0.02–0.73)	0.02
H2RA use		
Yes	0.26 (0.03–2.28)	0.22
No	0.25 (0.08–0.81)	0.02
Aspirin use		
Yes	0.81 (0.18–3.66)	0.78
No	0.14 (0.04–0.44)	<0.01

Abbreviations: DOACs, direct oral anticoagulants; UGIB, upper gastrointestinal bleeding; IHD, ischemic heart disease; PPI, proton pump inhibitor; H2RA, histamine type 2 receptor antagonist; CI, confidence interval; HR, hazard ratio.

*HR generated by pooled logistic regression, weighted for inverse probability of treatment weightings and adjusted by time-varying medications use.

logistic regression model with concurrent medications of at least 7 days in 1-month intervals showed no significant difference in the risk of UGIB with new warfarin uses between *H. pylori*-eradicated group and *H. pylori*-negative group (HR: 0.63, 95% CI 0.33–1.19). Sensitivity analyses with other concurrent medications use intervals showed similar results (Table 4). The standardized probability curve showed that 3-year absolute risk of UGIB in new warfarin users was 3.11% and 4.87% among *H. pylori*-eradicated and *H. pylori*-negative groups, respectively (Figure S5A).

3.5 | Risks of upper gastrointestinal bleeding among new direct oral anti-coagulant users in *Helicobacter pylori*–eradicated versus *Helicobacter pylori*–negative cohort

There were 1651 new DOACs users in *H. pylori*-eradicated group and 1052 DOACs users in *H. pylori*-negative group, and the baseline

TABLE 4 Risk of UGIB between *H. pylori*-eradicated and *H. pylori*-negative patients newly started warfarin or DOACs.

Models	HR (95% CI)*	Models	HR (95% CI)*
New warfarin users		**New DOACs users**	
Multivariable model 1		Multivariable model 1	
H. pylori-negative cohort	1.0	*H. pylori*-negative cohort	1.0
H. pylori-eradicated cohort	0.63 (0.33–1.19)	*H. pylori*-eradicated cohort	1.37 (0.45–4.22)
Multivariable model 2		Multivariable model 2	
H. pylori-negative cohort	1.0	*H. pylori*-negative cohort	1.0
H. pylori-eradicated cohort	0.63 (0.33–1.19)	*H. pylori*-eradicated cohort	1.36 (0.45–4.16)
Multivariable model 3		Multivariable model 3	
H. pylori-negative cohort	1.0	*H. pylori*-negative cohort	1.0
H. pylori-eradicated cohort	0.64 (0.34–1.21)	*H. pylori*-eradicated cohort	1.46 (0.48–4.47)
Multivariable model 4		Multivariable model 4	
H. pylori-negative cohort	1.0	*H. pylori*-negative cohort	1.0
H. pylori-eradicated cohort	0.62 (0.33–1.18)	*H. pylori*-eradicated cohort	1.47 (0.48–4.49)

Note: Multivariable model 1: Concurrent medications were defined as at least 7 days use in 1-month intervals; Multivariable model 2: Concurrent medications were defined as at least 7 days use in 3-month intervals; Multivariable model 3: Concurrent medications were defined as at least 14 days use in 1-month intervals; Multivariable model 4: Concurrent medications were defined as at least 14 days use in 3-month intervals.

Abbreviations: UGIB, upper gastrointestinal bleeding; HR, hazard ratio; CI, confidence interval.

*HR generated by pooled logistic regression, weighted for inverse probability of treatment weightings and adjusted by time-varying medications use.

characteristics between the two groups were well balanced with all ASD less than 0.1 (Table S10). A total of 8 (0.48%) DOACs users in *H. pylori*-eradicated group and 5 (0.48%) DOACs users in *H. pylori*-negative group had UGIB hospitalization during the follow-up period with a weighted incidence rate of 0.52 (95% CI 0.24–0.99) and 0.50 (95% CI 0.11–1.41) per 100 person-years, respectively (Table S11). The pooled logistic regression model with concurrent medications use of at least 7 days in 1-month interval showed no significant difference in the risk of UGIB in DOACs users between *H. pylori*-eradicated group and *H. pylori*-negative group (HR: 1.37, 95% CI 0.45–4.22). Sensitivity analyses with different intervals of concurrent medication uses showed consistent results (Table 4). The standardized probability curve showed that 3-year absolute risk of UGIB in DOACs users was 1.15% and 0.84% among *H. pylori*-eradicated and *H. pylori*-negative groups, respectively (Figure S5B).

4 | DISCUSSION

In this population-based cohort study of *H. pylori*-eradicated patients from Hong Kong, we determined the risk of hospitalization for UGIB in patients newly started on warfarin or DOACs. After IPTWs, DOACs users were associated with a 74% lower risk of UGIB compared with warfarin use. The difference was more prominent among older patients (≥65 years), female, those without a history of UGIB or peptic ulcer disease, or IHD, and not using PPIs, H2RAs, or aspirin. To further demonstrate the risk of UGIB in this group of *H. pylori*-eradicated patients who were started on warfarin or DOACs, we included another cohort of *H. pylori*-negative patients as the comparison group. There was no significant difference in the risks of UGIB with warfarin or DOACs use between *H. pylori*-eradicated and *H. pylori*-negative patients. To our knowledge, this is the first study that focused on the real-world risk of UGIB among users of different anticoagulants after elimination of the major confounding factor, *H. pylori* infection.

In this study, the weighted incidence rates of UGIB in new users of warfarin and DOACs who had *H. pylori*-eradicated were 2.02 and 0.49 events per 100 person-years, respectively. The incidence rate of UGIB among warfarin users as reported in a previous cohort study[15] ranged from 0.9 to 1.1 events per 100 person-years, which was lower than that of the current report. The discrepancy may be accounted for by different inclusion criteria as we only included *H. pylori*-eradicated patients in our study. Our cohort may also be older with more comorbidities. For individual DOACs users, the weighted incidence rate of UGIB for apixaban, dabigatran, and rivaroxaban was 0.72, 0.54, and 0.61 events per 100

person-years, respectively. Previous studies[6,15] however reported a wide range of UGIB incidence rates among apixaban, dabigatran, and rivaroxaban users ranging between 0.3 and 1.6 events per 100 person-years.

Our subgroup analysis illustrated that there was no significant difference in the risks of UGIB between warfarin and individual DOACs. However, the finding of this subgroup analysis should be interpreted with caution due to the relatively small sample size of each DOACs group. In contrast, previous large-scale observational study[13–15] indicated that apixaban had a reduced risk of overall GIB or UGIB relative to warfarin. Our age-stratified analysis showed that DOACs was associated with 85% lower risk of UGIB compared with warfarin in patients older than 65 years, and 86% lower risk of UGIB in female. It was however interesting to note that DOACs were otherwise associated with lower UGIB risk in low-risk patients like those without a history of UGIB or peptic ulcer disease, IHD, and those not on PPIs, H2RAs, or aspirin.

Importantly, we also showed no significant difference in the risk of UGIB after warfarin or DOACs use between *H. pylori*-eradicated and *H. pylori*-negative patients. While *H. pylori* is an independent risk factor of UGIB, these data could further support the beneficial effects of *H. pylori* eradication by leveling the risk of UGIB between *H. pylori*-eradicated and *H. pylori*-negative patients.

The strength of this study was the involvement of two large cohorts of *H. pylori*-eradicated and *H. pylori*-negative patients who were newly started on warfarin or DOACs. The baseline characteristics of these patients, including PPIs and aspirin uses, were further matched by PS-based stabilized IPTWs. The IPTW analysis was conducted to ensure the baseline exchangeability between warfarin users and DOACs users. Of note, no previous study had compared the risk of UGIB with warfarin or DOACs users after *H. pylori* eradication and in particular, with *H. pylori*-negative patients. The new user design could precisely estimate the risk of UGIB in these *H. pylori*-eradicated or *H. pylori*-negative patients initiating anticoagulants, which is another important cause of UGIB. Moreover, we adjusted time-varying risk factors of concurrent use of other medications by including them as time-varying variables with 1-month or 3-month intervals during the follow-up period in the multivariable pooled logistic regression model.

This study has several limitations. First, the infection status after *H. pylori* eradication was not documented in the electronic healthcare database and was inferred by the need for retreatment for *H. pylori*. This approach has been used and validated in our previous studies.[2,3,18–22] Second, actual medication compliance could not be determined from this electronic healthcare database, we could only ascertain warfarin or DOACs use from prescription and dispensing records, which may cause potential misclassifications of exposure. Third, as the indications for warfarin and DOACs could be different, particularly in patients with underlying valvular heart disease, this finding may be limited to selected patient groups. However, we have attempted to balance the pre-existing diseases with IPTWs. Fourth, although AF is a common indication for oral anticoagulants, there was only one UGIB case identified among AF patients in our study, which makes further subgroup analysis not feasible. However, we have performed sensitivity analysis on non-AF patients, which yielded consistent results. Fifth, due to the relatively low event rates, subgroup analysis of different DOACs may be underpowered. Sixth, it would be more comprehensive if there is a *H. pylori*-infected cohort and newly started on anticoagulants. However, this cohort was difficult to identify as it is the standard clinical practice to eradicate *H. pylori* infection once diagnosed in Hong Kong. We have also attempted to include the *H. pylori*-infected patients who have failed eradication therapy and started on anti-coagulants, but the number of these patients was so few to have a meaningful comparison. Lastly, like all retrospective studies, there could be inherent and confounding bias that may not be completely adjusted in the analysis. Future prospective randomized studies may still be needed to verify this finding.

5 | CONCLUSION

In this real-world population-based study of *H. pylori*-eradicated patients, we found that new DOACs users were associated with a lower risk of UGIB compared with new warfarin users, particularly in older patients. Moreover, there was no significant difference in the risk of UGIB with new warfarin or DOACs use between *H. pylori*-eradicated and *H. pylori*-negative patients. Our findings may help to better inform the choice of optimal oral anticoagulants in these patients.

AUTHOR CONTRIBUTION

WKL was responsible for conception, design, and critical review of the manuscript. WKL, WL, and SL were involved in supervision of the manuscript. FJ, CGG, KSC, and BL were involved in acquisition of data. FJ, CJ, and CGG were involved in the data analysis. FJ and WKL drafted the manuscript and were involved in the data interpretation. All authors critically reviewed the manuscript and approved the final version of the manuscript.

ACKNOWLEDGMENTS

Guarantor of the article: Wai K. Leung.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

No conflict of interest.

REFERENCES

1. Peery AF, Crockett SD, Murphy CC, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2021. *Gastroenterology*. 2022;162(2):621-644.
2. Jiang F, Guo CG, Cheung KS, Leung WK. Long-term risk of upper gastrointestinal bleeding after helicobacter pylori eradication: a population-based cohort study. *Aliment Pharmacol Ther*. 2021;54(9):1162-1169.

3. Guo CG, Cheung KS, Zhang F, et al. Incidences, temporal trends and risks of hospitalisation for gastrointestinal bleeding in new or chronic low-dose aspirin users after treatment for helicobacter pylori: a territory-wide cohort study. *Gut*. 2020;69(3):445-452.
4. Nagasue T, Nakamura S, Kochi S, et al. Time trends of the impact of helicobacter pylori infection and nonsteroidal anti-inflammatory drugs on peptic ulcer bleeding in Japanese patients. *Digestion*. 2015;91(1):37-41.
5. Cheung KS, Leung WK. Gastrointestinal bleeding in patients on novel oral anticoagulants: risk, prevention and management. *World J Gastroenterol*. 2017;23(11):1954-1963.
6. Ingason AB, Hreinsson JP, Agustsson AS, et al. Rivaroxaban is associated with higher rates of gastrointestinal bleeding than other direct Oral anticoagulants : a Nationwide propensity score-weighted study. *Ann Intern Med*. 2021;174(11):1493-1502.
7. Cangemi DJ, Krill T, Weideman R, Cipher DJ, Spechler SJ, Feagins LA. A comparison of the rate of gastrointestinal bleeding in patients taking non-vitamin K antagonist Oral anticoagulants or warfarin. *Am J Gastroenterol*. 2017;112(5):734-739.
8. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383(9921):955-962.
9. Chai-Adisaksopha C, Crowther M, Isayama T, Lim W. The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis. *Blood*. 2014;124(15):2450-2458.
10. Dawwas GK, Dietrich E, Cuker A, Barnes GD, Leonard CE, Lewis JD. Effectiveness and safety of direct Oral anticoagulants versus warfarin in patients with Valvular atrial fibrillation : a population-based cohort study. *Ann Intern Med*. 2021;174(7):910-919.
11. Hernandez I, Baik SH, Pinera A, Zhang Y. Risk of bleeding with dabigatran in atrial fibrillation. *JAMA Intern Med*. 2015;175(1):18-24.
12. Sharma M, Cornelius VR, Patel JP, Davies JG, Molokhia M. Efficacy and harms of direct Oral anticoagulants in the elderly for stroke prevention in atrial fibrillation and secondary prevention of venous thromboembolism: systematic review and meta-analysis. *Circulation*. 2015;132(3):194-204.
13. Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and Apixaban versus warfarin in Nonvalvular atrial fibrillation. *J Am Heart Assoc*. 2016;5(6):e003725.
14. Li XS, Deitelzweig S, Keshishian A, et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in "real-world" clinical practice. A propensity-matched analysis of 76,940 patients. *Thromb Haemost*. 2017;117(6):1072-1082.
15. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. *BMJ*. 2018;362:k2505.
16. Chan YH, Kuo CT, Yeh YH, et al. Thromboembolic, bleeding, and mortality risks of rivaroxaban and dabigatran in Asians with Nonvalvular atrial fibrillation. *J Am Coll Cardiol*. 2016;68(13):1389-1401.
17. Chang HY, Zhou M, Tang W, Alexander GC, Singh S. Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study. *BMJ*. 2015;350:h1585.
18. Guo CG, Jiang F, Cheung KS, Li B, Ooi PH, Leung WK. Timing of prior exposure to antibiotics and failure of helicobacter pylori eradication: a population-based study. *J Antimicrob Chemother*. 2022;77(2):517-523.
19. Guo CG, Cheung KS, Zhang F, et al. Risks of hospitalization for upper gastrointestinal bleeding in users of selective serotonin reuptake inhibitors after helicobacter pylori eradication therapy: a propensity score matching analysis. *Aliment Pharmacol Ther*. 2019;50(9):1001-1008.
20. Guo CG, Cheung KS, Zhang F, et al. Delay in retreatment of helicobacter pylori infection increases risk of upper gastrointestinal bleeding. *Clin Gastroenterol Hepatol*. 2021;19(2):314-322 e312.
21. Leung WK, Wong IOL, Cheung KS, et al. Effects of helicobacter pylori treatment on incidence of gastric cancer in older individuals. *Gastroenterology*. 2018;155(1):67-75.
22. Jiang F, Guo CG, Cheung KS, Li B, Law SYK, Leung WK. Age of eradication and failure rates of clarithromycin-containing triple therapy for helicobacter pylori: a 15-year population-based study. *Helicobacter*. 2022;27(3):e12893.
23. Chan EW, Lau WC, Leung WK, et al. Prevention of dabigatran-related gastrointestinal bleeding with Gastroprotective agents: a population-based study. *Gastroenterology*. 2015;149(3):586-595 e583.
24. Green MS, Symons MJ. A comparison of the logistic risk function and the proportional hazards model in prospective epidemiologic studies. *J Chronic Dis*. 1983;36(10):715-723.
25. Austin PC. Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. *Stat Med*. 2016;35(30):5642-5655.
26. Dickerman BA, Garcia-Albeniz X, Logan RW, Denaxas S, Hernan MA. Avoidable flaws in observational analyses: an application to statins and cancer. *Nat Med*. 2019;25(10):1601-1606.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Jiang F, Ju C, Guo C-G, et al. Risk of hospitalization for upper gastrointestinal bleeding in *Helicobacter pylori* eradicated patients newly started on warfarin or direct oral anticoagulants: A population-based cohort study. *Helicobacter*. 2023;28:e12990. doi:10.1111/hel.12990