ORIGINAL ARTICLE

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

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ABSTRACT

Objective The risk of GI bleeding (GIB) in aspirin users after *Helicobacter pylori* (HP) eradication remains poorly defined. We characterised the incidences and temporal trends of hospitalisations for all GIB in aspirin users after HP eradication therapy.

Design Based on a territory-wide health database, we identified all patients who had received the first course of clarithromycin-based triple therapy between 2003 and 2012. Patients were divided into three cohorts according to aspirin use: new users (commenced after HP eradication), chronic users (commenced before and resumed after HP eradication) and non-users. The primary outcome was to determine the risk of hospitalisation for GIB.

Results We included 6985 new aspirin users, 5545 chronic users and 48 908 non-users. The age-adjusted and sex-adjusted incidence of hospitalisation for all GIB in new, chronic and non-users was 10.4, 7.2 and 4.6 per 1000 person-years, respectively. Upper and lower GIB accounted for 34.7% and 45.3% of all bleeding, respectively. Compared with chronic users, new users had a higher risk of GIB (HR with propensity score matching: 1.89; 95% CI 1.29 to 2.70). Landmark analysis showed that the increased risk in new aspirin users was only observed in the first 6 months for all GIB (HR 2.10, 95% CI 1.41 to 3.13) and upper GIB (HR 2.52, 95% CI 1.38 to 4.60), but not for lower GIB.

Conclusion New aspirin users had a higher risk of GIB than chronic aspirin users, particularly during the initial 6 months. Lower GIB is more frequent than upper GIB in aspirin users who had HP eradicated.

Significance of the study

What is already known on this subject?
- *Helicobacter pylori* eradication has been shown to reduce the risk of upper GI bleeding (GIB) in patients newly started on aspirin.
- Aspirin is also increasingly recognised to be an important cause of lower GIB.
- However, the long-term risks and temporal patterns of GIB, including upper and lower, among new or chronic aspirin users who had *H. pylori* eradicated remain uncertain.

What are the new findings?
- We found that the risk of GIB, both upper and lower, were significantly higher among new or chronic aspirin users when compared with non-users in a territory-wide cohort of *H. pylori*-infected patients who had received eradication therapy.
- New aspirin users had a significantly higher risk of GIB, especially upper GIB, than chronic aspirin users, particularly during the initial 6 months of aspirin therapy.
- Although the incidence of lower GIB was even more frequent than upper GIB after treatment for *H. pylori*, similar decline in the risk of lower GIB between new and chronic aspirin users was not observed.

How might it impact on clinical practice in the foreseeable future?
- New aspirin users still have an increase in risk of GIB even after eradication of *H. pylori*, particularly during the initial 6 months of aspirin therapy.
- Lower GI tract appears to be an important source of bleeding among aspirin users who had *H. pylori* eradicated.

INTRODUCTION

Acute GI bleeding (GIB) is one of the most common causes of hospitalisation and emergency visit, resulting in a substantial economic burden on the healthcare system. In the USA, GIB accounted for >500 000 hospitalisations and consumed US$4.85 billion in 2012.[1] *Helicobacter pylori* infection, non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin uses are generally considered to be the most important risk factors in the pathogenesis of peptic ulcers as well as the causes of non-variceal upper GI bleeding (UGIB).[2 3] With the widespread use of *H. pylori* eradication therapy, the prevalence of *H. pylori* infection had been declining globally.[4] However, with the ageing population, aspirin is increasingly used in the prevention of cardiovascular or cerebrovascular events,[5] giving rise to the increasing proportion of patients with UGIB due to aspirin. While both *H.*

pylori infection and aspirin are risk factors for peptic ulcer and its complications, *H. pylori* eradication has been shown to reduce the risk of GIB in low-dose aspirin users.[6–8] *H. pylori* eradication is therefore recommended in long-term aspirin users, especially high-risk patients.[8–10]

Apart from UGIB, aspirin is increasingly recognised to be associated with lower GI bleeding (LGIB).[11 12] Although *H. pylori* eradication and the use of gastroprotective agents, including proton pump inhibitors (PPI) and histamine type 2 receptor antagonists (H2RA), could reduce the risk of UGIB, the risk of LGIB remains. There is a significant knowledge gap about the natural history of all-cause GIB, including UGIB and LGIB, among aspirin users who had *H. pylori* eradicated. The issue is further complicated by the potential adaptive effects of the gastric mucosa to aspirin, in which aspirin-associated UGIB tends to occur at the early course of treatment.[13 14] As yet, whether there is similar adaptive effect to aspirin in the lower GI tract remains unknown.

Based on a large cohort of *H. pylori*-eradicated patients from Hong Kong, we characterised the incidences, temporal trends and risks of hospitalisations for all-cause GIB, including UGIB and LGIB, in new aspirin users as compared with chronic users and non-users.

METHODS

Data source

All data were retrieved from the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority. The Hospital Authority is the only public healthcare provider of Hong Kong with >7 million residents. The CDARS is a centralised electronic system which records all patients' clinical information including demographics, diagnoses, prescriptions, treatment, hospitalisation and death.[15–17] All records were anonymised to protect patients' confidentiality, and a unique numeric identifier was assigned to each patient. The International Classification of Diseases, Ninth Revision (ICD-9) was used for disease coding and the accuracy of coding for GIB had been previously verified.[16]

Study subjects and study design

We have previously identified a large cohort of *H. pylori*-infected patients who had received clarithromycin-based triple eradication therapy in Hong Kong between 1 January 2003 and 31 December 2012.[17 18] In this study, we analysed the risk of hospitalisation for GIB in this cohort who used aspirin after *H. pylori* eradication. Patients who were newly started on aspirin after *H. pylori* eradication, but who had not used any aspirin within 2 years before the eradication, were classified as new users. Patients who used aspirin both before and after *H. pylori* eradication therapy were classified as chronic users, whereas those who had never used aspirin both before and after *H. pylori* eradication were labelled as non-users (online supplementary figure 1). Patients who used aspirin before *H. pylori* eradication but did not resume on aspirin after the eradication therapy were excluded.

Since posteradication *H. pylori* statuses were not available in the electronic database, we excluded patients who required retreatment for *H. pylori* as described previously.[17] Other exclusion criteria included patients with follow-up <7 days, patients who had GI cancer, IBD, coagulant deficiency, gastroenteritis or colitis due to radiation and excision of GI tract segment.

Outcome and covariates

The primary outcome was to determine the incidences of hospitalisation for GIB in new aspirin users, chronic users and non-users after *H. pylori* eradication therapy, and to compare the risk of GIB in new users with chronic users. The risk factors of GIB among all aspirin users were also evaluated. The start point of the follow-up period for all aspirin users was the date of starting or resuming aspirin after *H. pylori* eradication therapy. The end point was the occurrence of GIB, 30 days after aspirin discontinuation, death or the end of the study at 30 June 2016. The maximum observation period was set as 10 years. Discontinuation of aspirin was defined as an interruption for >30 days between two aspirin prescriptions. Since there was no definite start date for non-users, the start date was arbitrarily set as 60 days after *H. pylori* eradication. The 60 days was chosen to allow for the healing of possible peptic ulcer, which may falsely increase the bleeding rate.[19] A sensitivity analysis was also performed to use 7 days after eradication as start date for non-users.

The primary end point was hospitalisation for non-variceal GIB, which was retrieved using the ICD-9 codes of UGIB, LGIB and unspecified GIB (578.xx, online supplementary table 1). Hematemesis (578.0) and melena or black tarry stool (578.1) were regarded as UGIB, whereas hematochezia from 578.1 was taken as LGIB in this study. For other diagnoses with the code of 578.xx, the specific bleeding site would be used if the description of the diagnosis had mentioned the bleeding location. Moreover, if there were new specific diagnoses within 30 days, the diagnosis of unspecified GIB would be renewed with the original index date unchanged. As a secondary outcome, the risk of in-hospital mortality was also evaluated, which was defined as death during the hospitalisation for GIB.

Baseline characteristics of the patients, their comorbid medical conditions and concurrent medications were included as covariates in binary variables. Pre-existing medical conditions before enrolment were extracted using ICD-9 codes including history of GIB or peptic ulcer, hypertension, ischaemic heart disease, stroke (ischaemic stroke, transient ischaemic attack or systemic embolism), diabetes, renal disease, intracranial haemorrhage and liver cirrhosis. Concurrent medications (online supplementary table 2) used during the follow-up period which could potentially alter the bleeding risk were also included: gastroprotective agents including PPI and H2RA, other antiplatelet drugs, NSAIDs, anticoagulants, corticosteroids, selective serotonin reuptake inhibitors and bisphosphonate. Drug usage was defined as >7 days use during the follow-up period. To reduce potential indication bias for gastroprotective agents, PPI and H2RA prescription records within the last 4 weeks of the event date or censor date were excluded.

Statistical analysis

Continuous variables were expressed as median and IQR, while categorical variables were presented as frequencies and percentages. Mann-Whitney U test was used for continuous variables and X^2 test or Fisher's exact test was used for categorical variables. Incidence rates and relative risks (RR) among new, chronic aspirin users and non-users were calculated. The in-hospital mortality rate of GIB was also determined.

The risks of hospitalisation for GIB among new, chronic users and non-users were illustrated by fitting Kaplan-Meier curves and the differences were tested using the log-rank test. Cox proportional hazards regression model was used and the bleeding risk was expressed in HRs with 95% CIs. When fitting a Cox regression model, the proportional hazards assumption was checked

using Schoenfeld test and graphical diagnostics by plotting the scaled Schoenfeld residuals against the survival times.[20 21] Once violation of this assumption was observed, interactions of time-dependent covariates with time would be introduced into the regression model.[21] In multivariable Cox regression model, concurrent medications were included as time-varying covariates, of which the follow-up period was split into 3-monthly intervals and drug usage was defined in each interval as >7 days use. In all regression models, aspirin use was included as a time-varying variable.

To balance the potential differences in the baseline characteristics between new and chronic users, the propensity score (PS) matching method was performed using the nearest-neighbour algorithm with a ratio of 1:1 and callipers of width equalling to 0.2. In addition, matching weighting (MW), inverse probability of treatment weighting (IPTW) method were also performed.[22 23] Absolute standardised differences (ASD) were used to compare the mean or prevalence of covariates between groups to identify for imbalance.[24] An ASD ≥0.1 denotes imbalance of baseline characteristics. Therefore, Cox regression models were also fitted with the PS matched, and weighted (MW and IPTW) samples. A competing risk analysis was also performed with PS matched samples, in which death was considered to be a competing event for GIB. To better interpret the temporal trend of bleeding risk in new *versus* chronic users, landmark analyses were performed.[25 26] The HRs were calculated separately in each observational interval, adjusting for all other covariates. A two-sided p value <0.05 were regarded as statistically significant. The R V.3.4.2 (R Foundation for Statistical Computing, Vienna, Austria, 2017) was used in all statistical analyses.

RESULTS

Patient characteristics

Of the 74 612 subjects who had received clarithromycin-based triple therapy for *H. pylori* during the study period, we identified 6985 new and 5545 chronic aspirin users, as well as 48 908 non-users (online supplementary figure 2). The characteristics of all eligible patients are shown in table 1. The median follow-up duration of new, chronic and non-users was 1.48 (IQR 0.42–3.74), 4.09 (IQR 1.27–6.99) and 7.68 (IQR 5.29–10) years, respectively (p<0.001). The daily dosage of aspirin, expressed in person-days, was <100 mg in 84.1%.

Incidences of hospitalisation for GIB

During the follow-up period, 261 (3.74%) new aspirin users, 303 (5.46%) chronic users and 1295 (2.65%) non-users had hospitalisations for GIB. The corresponding age-adjusted and sex-adjusted incidence rate of GIB was 10.4 (95% CI 7.9 to 66.4), 7.2 (95% CI 6.3 to 157.7) and 4.6 (95% CI 4.4 to 4.9) per 1000 person-years, respectively. After stratified by bleeding sites, UGIB and LGIB accounted for 34.7% and 45.3% of all GIB, respectively. For all aspirin users, the proportion of UGIB was 37.2% and LGIB was 40.8%. The adjusted incidence rate of UGIB for new, chronic and non-users were 3.0 (95% CI 2.4 to 61.2), 2.6 (95% CI 2.1 to 155.1), 1.7 (95% CI 1.5 to 1.9) per 1000 person-years, respectively. The corresponding figures of LGIB for the three groups was 5.7 (95% CI 3.5 to 63.1), 3.0 (95% CI 2.4 to 155.3) and 1.9 (95% CI 1.7 to 2.1) per 1000 person-years. The detailed sources of GIB in all patients are shown in the online supplementary table 3.

Both new and chronic aspirin users had higher crude incidence rates of hospitalisation for all GIB, UGIB and LGIB as compared with non-users and the difference was significant in

Table 1 Baseline characteristics of new aspirin users, chronic aspirin users and non-users

		Before matching*		After matching*	
Characteristics	Non-users (n=48 908)	New users (n=6985)	Chronic users (n=5545)	New users (n=2801)	Chronic users (n=2801)
Age at start point (year)†	51.0 (43.0–60.0)	67.0 (59.0–77.0)	68.0 (60.0–76.0)	69.0 (59.0–78.0)	68.0 (60.0–76.0)
Gender (male, %)	21 575 (44.1)	3736 (53.5)	3273 (59.0)	1368 (48.8)	1530 (54.6)
Baseline conditions (%)					
GIB or ulcer history	7168 (14.7)	1466 (21.0)	1293 (23.3)	655 (23.4)	589 (21.0)
Ischaemic heart disease	295 (0.6)	304 (4.4)	2036 (36.7)	304 (10.9)	298 (10.6)
Stroke	195 (0.4)	186 (2.7)	1380 (24.9)	186 (6.6)	191 (6.8)
Hypertension	1985 (4.1)	1562 (22.4)	2060 (37.2)	818 (29.2)	749 (26.7)
Diabetes	1488 (3.0)	973 (13.9)	1313 (23.7)	526 (18.8)	506 (18.1)
Renal disease	362 (0.7)	356 (5.1)	276 (5.0)	173 (6.2)	132 (4.7)
Intracranial haemorrhage	156 (0.3)	87 (1.3)	64 (1.2)	30 (1.1)	32 (1.1)
Cirrhosis	297 (0.6)	65 (0.9)	19 (0.3)	15 (0.5)	14 (0.5)
Medications (%)					
Gastroprotective agents	36 208 (74.0)	6285 (90.0)	5173 (93.3)	2585 (92.3)	2579 (92.1)
Other antiplatelet drugs	258 (0.5)	1358 (19.4)	1016 (18.3)	463 (16.5)	438 (15.6)
NSAIDs	19 636 (40.1)	1247 (17.9)	1142 (20.6)	596 (21.3)	574 (20.5)
Anticoagulants	405 (0.8)	301 (4.3)	270 (4.9)	136 (4.9)	146 (5.2)
Corticosteroids	2626 (5.4)	556 (8.0)	419 (7.6)	238 (8.5)	213 (7.6)
SSRI	3020 (6.2)	477 (6.8)	356 (0.6)	217 (7.7)	180 (6.4)
Bisphosphonate	466 (1.0)	96 (1.3)	82 (1.5)	52 (1.9)	44 (1.6)

Gastroprotective agents include proton pump inhibitors and histamine type 2 receptor antagonists.
*Absolute standardised differences between new and chronic users before or after matching are shown in the online supplementary figure 3.
†Variables expressed as median and IQR.
GIB, GI bleeding; NSAIDs, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitors.

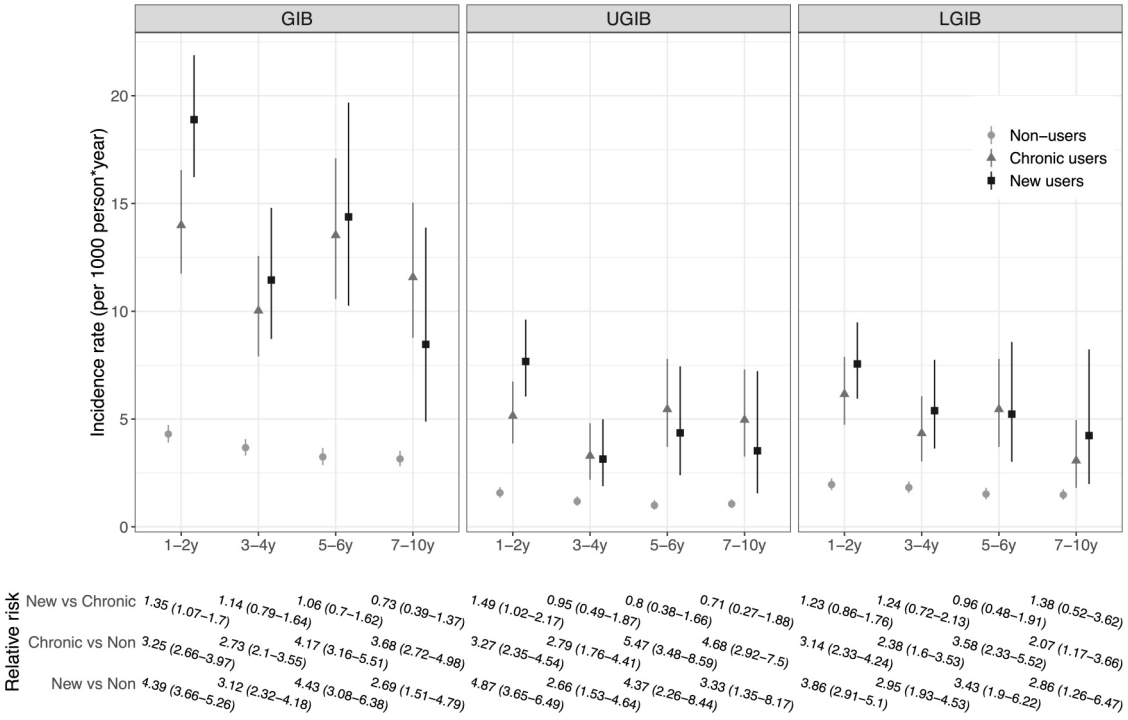

Figure 1 Incidence rates of hospitalisation for all GI bleeding (GIB), upper GI bleeding (UGIB) and lower GI bleeding (LGIB) during the follow-up period in new aspirin users, chronic users and non-users, and the corresponding relative risks between different groups.

each time intervals during follow-up (figure 1). This was consistent in Kaplan-Meier curves for all GIB (log-rank test p<0.001; figure 2A). In the multivariable Cox model, increased risk of GIB was observed in both new (HR 1.92, 95% CI 1.62 to 2.27) and chronic users (HR 1.44, 95% CI 1.19 to 1.74), when compared with non-users. Similar results were obtained when the start date of follow-up of non-users was changed to 7 days after *H. pylori* eradication (new users vs non-users: HR 1.95, 95% CI 1.65 to 2.31; chronic users vs non-users: HR 1.44, 95% CI 1.20 to 1.74).

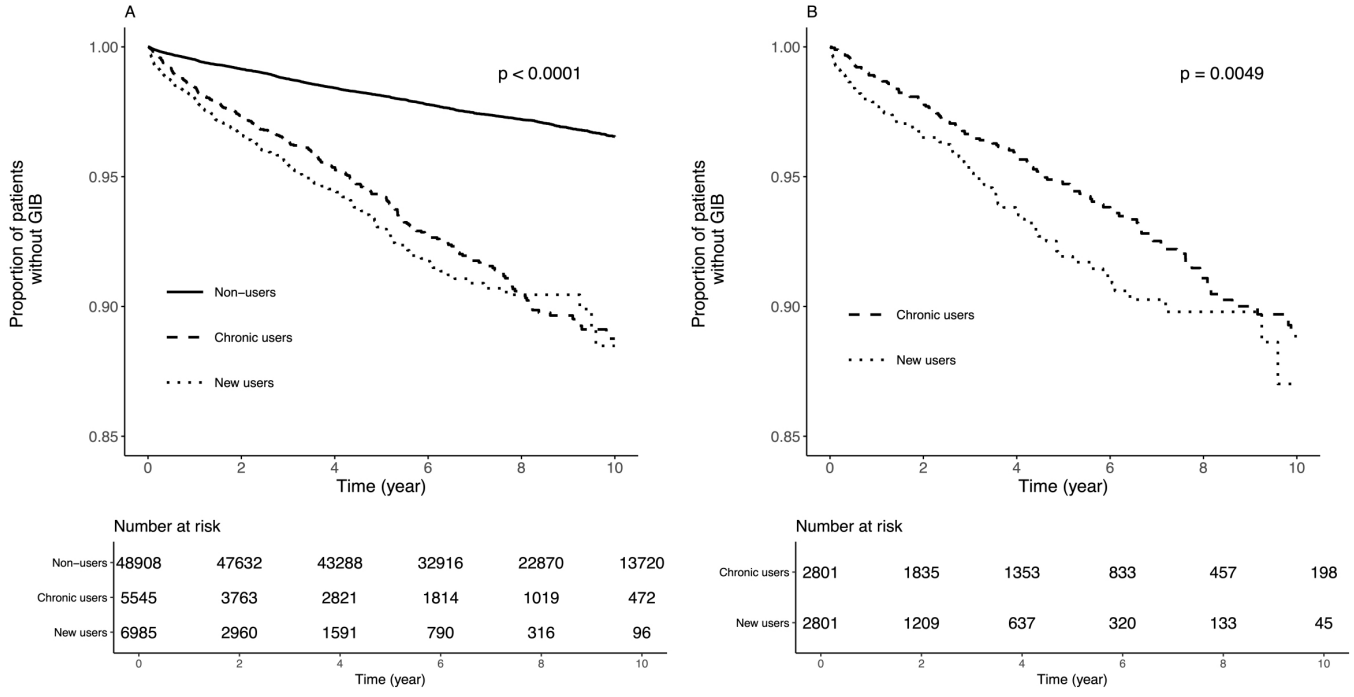

Figure 2 Kaplan-Meier curves for the proportion of patients who were free from GI bleeding (GIB). (A) GIB in all new aspirin users, chronic users and non-users. (B) GIB in matched new aspirin users vs chronic aspirin users.

Table 2 Results of time-dependent regression models comparing new with chronic aspirin users in patients after *Helicobacter pylori* eradication

		GIB		UGIB		LGIB	
Models	Variables	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Univariable Cox regression model with original samples	New users	1.16 (0.98 to 1.38)	0.080	1.12 (0.86 to 1.47)	0.396	1.19 (0.92 to 1.55)	0.187
Including a time-by-covariate interaction	New users	1.41 (1.10 to 1.80)	0.007	-	-	-	-
	New users×time*	0.92 (0.85 to 0.998)	0.04	-	-	-	-
PSM†	New users	1.89 (1.29 to 2.70)	<0.001	1.30 (0.85 to 1.99)	0.234	1.94 (1.29 to 2.91)	0.001
	New users×time	0.89 (0.80 to 1.01)	0.063	-	-	-	-
MW†	New users	1.80 (1.32 to 2.46)	<0.001	2.00 (1.21 to 3.20)	0.007	1.49 (1.07 to 2.07)	0.018
	New users×time	0.87 (0.80 to 0.95)	0.002	0.82 (0.70 to 0.96)	0.015	-	-
IPTW†	New users	1.81 (1.34 to 2.44)	<0.001	1.73 (1.09 to 2.73)	0.019	1.61 (1.15 to 2.25)	0.006
	New users×time	0.87 (0.80 to 0.95)	0.003	0.84 (0.72 to 0.97)	0.018	-	-
Multivariable Cox regression model‡	New users	1.74 (1.32 to 2.29)	<0.001	1.63 (1.08 to 2.46)	0.020	1.53 (1.11 to 2.10)	0.009
	New users×time	0.91 (0.84 to 0.99)	0.025	0.91 (0.79 to 1.04)	0.154	-	-

*Time-by-covariate interactions in regression model, in which time indicates start points of each 3-month interval of the follow-up period, in terms of 0, 0.25, 0.5, 0.75 years, and so forth.
†Propensity scores or weights were calculated based on age, sex, baseline conditions and concomitant medications.
‡Adjusted for age, sex, baseline conditions and concomitant medications which were included as time-varying covariates.
GIB, GI bleeding; IPTW, inverse probability of treatment weighting; LGIB, lower GI bleeding; MW, matching weighting; PSM, propensity score matching; UGIB, upper GI bleeding.

When compared with chronic users, new users had a higher incidence rate of hospitalisation for all GIB (RR 1.25, 95% CI 1.06 to 1.47). Due to the difference in baseline characteristics between the new and chronic users, we have used various models, including PS matching, MW, IPTW and multivariable model to adjust for these differences (online supplementary figure 3), to show that new users still had a higher risk of GIB when compared with chronic users (figure 2B, HR with PS matching: 1.89; 95% CI 1.29 to 2.70 and table 2). The result was also consistent in the competing risk regression (HR 1.79, 95% CI 1.09 to 2.97).

Data validation

To validate the final *H. pylori* statuses of patients who had UGIB after *H. pylori* eradication, we retrieved the final *H. pylori* statuses of 51 patients from our centre. Among them, only two (3.9%) were found to be positive including one patient who was negative by urea breath test post-treatment but became positive on re-examination during GIB.

In-hospital mortality of GIB

The in-hospital mortality rate of GIB for new, chronic and non-users was 9.6% (25/261), 9.6% (29/303) and 5.3% (69/1295), respectively. In multivariable model, new users (HR 2.23, 95% CI 1.18 to 4.22) were associated with a higher risk of in-hospital mortality than non-users. There was no significant difference between chronic users and non-users (HR 1.87, 95% CI 0.97 to 3.60), as well as between new and chronic users (HR 1.47, 95% CI 0.72 to 3.01).

Time trend of hospitalisation for GIB in aspirin users

The crude incidence rates of hospitalisation for GIB in both new and chronic users showed a declining trend with time (figure 1). When comparing new with chronic users, the elevated risk of all GIB decreased over time in all models except for PS matching, where a borderline CI was noted (HR 0.89, 95% CI 0.80 to 1.01; table 2 and online supplementary figure 4). Specifically, the difference in the incidences of GIB between new and chronic users was only significant in the first 2 years for all GIB (RR 1.35, 95% CI 1.07 to 1.7) and UGIB (RR 1.49, 95% CI 1.02 to 2.17; figure 1). In the landmark analysis of all GIB, the risk of GIB associated with new aspirin use was significantly higher in the first 6 months (HR 2.10, 95% CI 1.41 to 3.13; figure 3A), but not in the following period (HR 1.18, 95% CI 0.93 to 1.50). The result was consistent with the landmark analysis of UGIB (0–6 months: HR 2.52, 95% CI 1.38 to 4.60; >6 months: HR 0.96, 95% CI 0.64 to 1.45; figure 3B). Similar decline in LGIB risk between new and chronic aspirin users was not detected (Schoenfeld test in multivariable Cox model, p=0.934).

Factors associated with hospitalisation for GIB among aspirin users

In multivariable model with all aspirin users, we confirmed that new aspirin users had higher risk of GIB than chronic users (HR 1.74, 95% CI 1.32 to 2.29, figure 4). Other risk factors of GIB included history of GIB or ulcer (HR 2.78, 95% CI 2.15 to 3.60), renal disease (HR 2.25, 95% CI 1.65 to 3.08), stroke (HR 1.50, 95% CI 1.07 to 2.12), use of other antiplatelet drugs (HR 1.49, 95% CI 1.11 to 2.00), NSAIDs (HR 1.64, 95% CI 1.14 to 2.35), corticosteroids (HR 1.91, 95% CI 1.29 to 2.35) and older age (HR 1.05, 95% CI 1.03 to 1.06). Subgroup analysis further showed that new aspirin users had higher risk of GIB both in patients with (HR 1.93, 95% CI 1.27 to 2.94) or without history of GIB or ulcer (HR 1.58, 95% CI 1.09 to 2.28).

On the other hand, the use of gastroprotective agents was associated with a lower risk of GIB (HR 0.34, 95% CI 0.25 to 0.46) in aspirin users, including the use of PPI (HR 0.46, 95% CI 0.36 to 0.58) and H2RA (HR 0.43, 95% CI 0.32 to 0.56). Benefits of gastroprotective agents on lowering risk of GIB were also found in other subgroups including elderly (≥60 years), those who had concurrent use of aspirin with NSAIDs or other antiplatelet therapies (online supplementary table 4).

DISCUSSION

While *H. pylori* infection and aspirin are both important risk factors for UGIB,[27] elimination of *H. pylori* infection would leave aspirin and/or NSAIDs to be the major risk factor(s) for UGIB.[4 12] Hence, study on *H. pylori*-eradicated subjects could possibly delineate the natural history of aspirin-related GIB. This is the first study to characterise the incidences, temporal

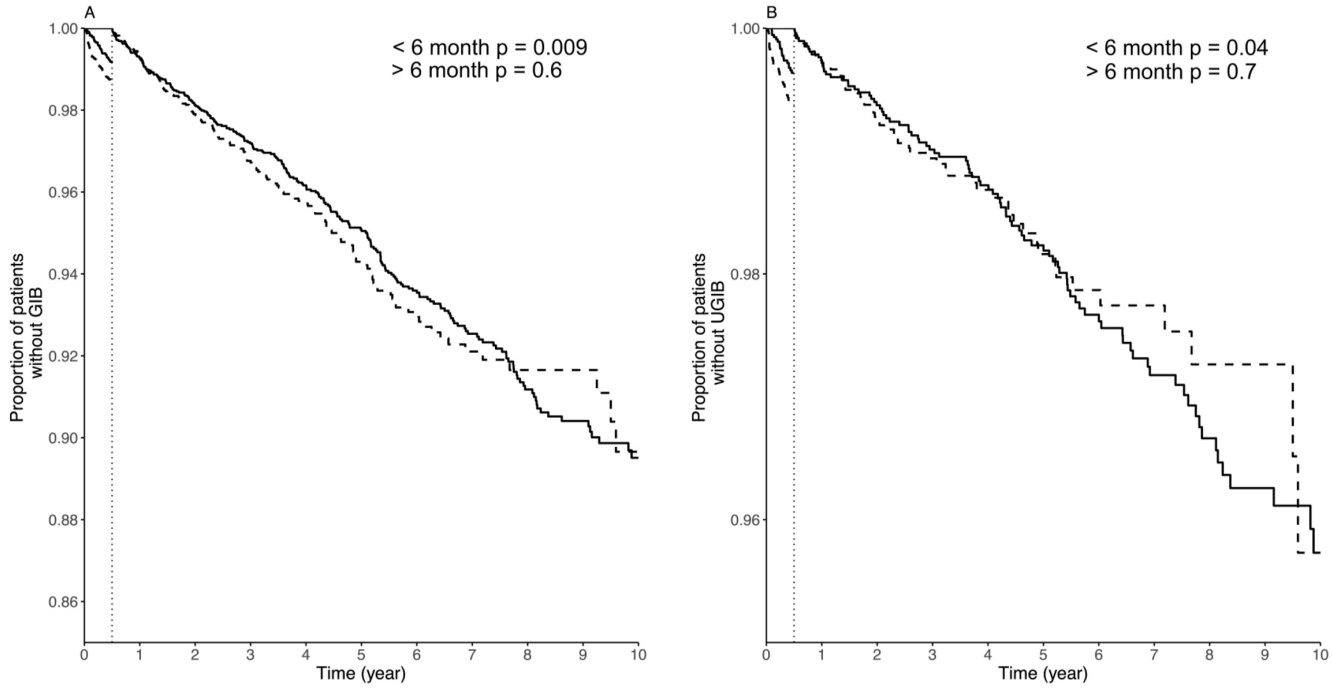

Figure 3 Kaplan-Meier curves of GI bleeding (GIB) (A) and upper GI bleeding (UGIB) (B) in the landmark analysis with the splitting time of 6 months (— chronic aspirin users; --- new aspirin users).

trends and risk factors of hospitalisation for all GIB, including both UGIB and LGIB, in a large cohort of *H. pylori*-infected patients who had received eradication therapy and were then newly started on aspirin or continued to use aspirin. We found that the incidences of GIB, including UGIB and LGIB, in both new and chronic aspirin users were significantly higher than non-users. More importantly, we showed that new aspirin users had a 1.9-fold (PS-matched analysis) higher risk of GIB when compared with chronic users. The risk of GIB, particularly UGIB, was significantly increased in new aspirin users during the initial 6 months of aspirin therapy in landmark analyses.

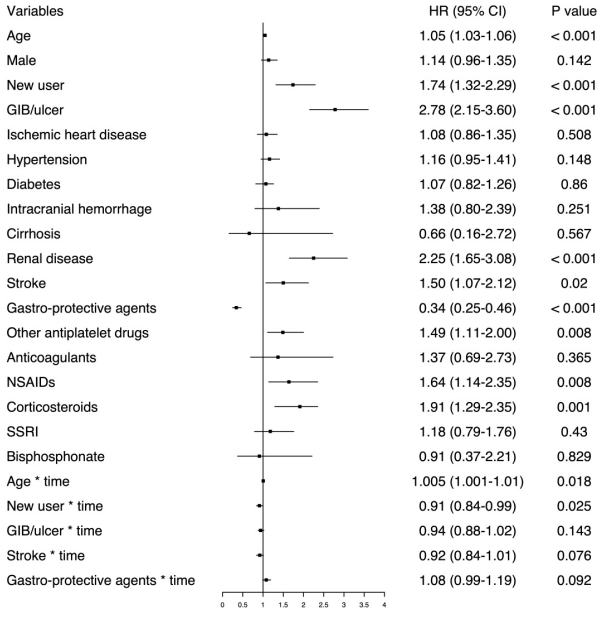

Figure 4 Risk factors of hospitalisation for GI bleeding (GIB) among aspirin users. NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

The risk of GIB and UGIB in new aspirin users, when compared with chronic users, decreased with time in most models, suggesting that the bleeding risk in aspirin users is time-dependent. Slattery *et al* showed that UGIB were three times more likely to occur in the initial 152 days of aspirin treatment.[14] Apart from aspirin, current literature also suggests that GIB are more likely to occur in the early course of treatment with NSAIDs, antiplatelet drugs or dual antiplatelet therapy.[14 28–30] Although previous studies have demonstrated the potential gastric adaptation to aspirin,[6 31 32] these studies failed to address the issue of concurrent *H. pylori* infection, which is an important confounding factor for UGIB. Our findings further showed that the gastric adaptive effects may not be related to *H. pylori* and remain even after eradication therapy. Arguably, the observed difference between new and chronic users could be accounted by the depletion of susceptible patients in chronic users who would have developed bleeding and then stopped aspirin treatment. In addition, the increase in early bleeding risk of new users could be explained by the effect of aspirin on pre-existing gastric pathology, which may lead to early bleeding.

In this study, we showed that new users had a higher in-hospital mortality of GIB than non-users, but there was no difference in mortality between chronic and new users or between chronic users and non-users. Thus far, data on aspirin and GIB mortality remains conflicting. Studies have shown that aspirin use was associated with a reduction in the risk of adverse outcomes in patients with UGIB.[33 34] On the other hand, there were reports of no increase in mortality of aspirin-related GIB.[35 36] These discrepancies may be related to the difference in patient characteristics including *H. pylori* infection, timings of aspirin use

(before or after GIB) and comorbidities (particularly underlying ischaemic diseases).

It is important to note that after treatment for *H. pylori*, LGIB accounted for about 45.3% of all GIB, which was even higher than UGIB. This may be a consequence of both *H. pylori* eradication and use of gastroprotective agents. In this study, >74% of patients were taking gastroprotective agents. LGIB was also significantly more frequent in both new and chronic aspirin users when compared with non-users. However, similar decline in the risk of LGIB with time between new and chronic aspirin users was not observed. Hence, similar adaptation of the small or large intestinal mucosa to aspirin may not exist. Aspirin users are therefore still at continuing risk of LGIB even years after aspirin therapy.

History of GIB or peptic ulcer are generally considered to be a risk factor for GIB. In this study, risk factors analysis also showed that history of GIB or peptic ulcer is an important risk factor of GIB in patients who used aspirin after *H. pylori* eradication, irrespective of whether they are new or chronic aspirin users. There was a 2.8-fold increase in GIB risk among those with history of peptic ulcer or GIB, which was consistent with previous studies.[37 38] Our study also found that, among patients without history of GIB or peptic ulcer, new aspirin users still have a higher risk of GIB than chronic users. According to current recommendations, long-term gastroprotective agent is recommended to high-risk patients including older age, previous GIB, peptic ulcer or ulcer complications, concomitant use of NSAIDs, anticoagulants, other antiplatelet drugs or other drugs increasing GIB risk.[10 39] Our subgroup analyses also confirmed that gastroprotective agents reduced the risk of aspirin-related GIB among elderly (≥60 years) and those with concurrent use of NSAIDs or other antiplatelet therapies. To our knowledge, there is no recommendation that specifically emphasised the higher risk of bleeding during the early course of aspirin treatment in patients after treatment for *H. pylori*. Hence, prophylactic gastroprotective agents are particularly warranted during this initial period of aspirin treatment. As yet, gastroprotective agents could not reduce the risk of LGIB which may account for the non-declining risk of LGIB with time.

The strengths of this study are the inclusion of a large cohort of *H. pylori* subjects who had received eradication therapy based on the comprehensive healthcare database in Hong Kong, which captures all bleeding episodes, concurrent medical illnesses and medications. In addition to UGIB, we have also demonstrated the high incidences of LGIB in aspirin users who had received treatment for *H. pylori*. To adjust for potential differences in the baseline characteristics between new and chronic aspirin users in this study, we had used multiple models including PS matching and weighting (IPTW and MW) to adjust for various potential biases. Time-dependent Cox regression model were also used to evaluate the time-dependent effect of aspirin, and other covariates in multivariable model on GIB.

Immortal time bias is an important methodological consideration which was common in observational studies.[40 41] However, when comparing new and chronic aspirin users, there should be minimal immortal time bias as both new and chronic users have same start point as the date of first aspirin prescription after *H. pylori* eradication. To further minimise immortal bias, we have also adopted time-dependent regression models in which all medications were treated as time-varying covariates.

Our study has limitations. First, post-treatment *H. pylori* statuses were not available in the electronic database and the success of treatment was only inferred by the needs of retreatment. Some patients who failed *H. pylori* eradication might not receive further therapy due to various reasons. Nonetheless, the overall retreatment rate of this study (11%) was comparable to the failure rate of clarithromycin-based triple therapy in a prospective study conducted in Hong Kong during the same period.[42] To verify the success of *H. pylori* eradication, we had performed a validation study of 51 bleeding patients from our centre who had been retested for *H. pylori*. Second, this study did not evaluate the independent effect of *H. pylori* on the risk of GIB or the interaction between *H. pylori* and aspirin, as only *H. pylori*-eradicated subjects were included. Ideally, this study should include a control group of *H. pylori*-infected patients with no prior treatment, but this may pose ethical issues not to treat infected subjects, particularly before starting aspirin therapy. The lack of a group of patients without *H. pylori* infection is another limitation of this study. However, it has been shown that the recurrent bleeding risk among low-dose aspirin users after *H. pylori* eradication did not differ from average risk individuals.[8] Third, the follow-up duration of the three groups were different due to higher censoring rate from bleeding and shorter duration of aspirin usage in new users. As yet, the bleeding rate was the lowest among non-users with the longest follow-up. Fourth, the electronic database could only determine the prescription and dispensation but not the actual compliance to aspirin. Lastly, although various models were used to adjust for potential bias including competing risk analysis and time-dependent regression, it is possible that some residual confounders may not be adequately adjusted. Despite these potential caveats, our findings support that *H. pylori* eradication is not risk proof in preventing subsequent GIB in aspirin users, particularly among new users and for the prevention of LGIB.

CONCLUSION

In this study involving a large cohort of patients who had received *H. pylori* eradication therapy, we showed that both new and chronic aspirin users continued to have a significantly higher risk of hospitalisations for GIB than non-users. The risk of GIB, UGIB in particular, was significantly higher for new aspirin users when compared with chronic aspirin users during the initial 6 months of aspirin treatment. LGIB became more frequent than UGIB among aspirin users who had received *H. pylori* treatment. Although treatment with gastroprotective agents appeared to reduce the risk of GIB after *H. pylori* treatment, the risks of LGIB between new and chronic aspirin users continued and showed no trend of decline.

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REFERENCES

1. Peery AF, Crockett SD, Barritt AS, *et al*. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. *Gastroenterology* 2015;149:1731–41.

2. Hunt RH, Bazzoli F. Review article: should NSAID/low-dose aspirin takers be tested routinely for H. pylori infection and treated if positive? Implications for primary risk of ulcer and ulcer relapse after initial healing. *Aliment Pharmacol Ther* 2004;19:9–16.
3. Laine L, Yang H, Chang SC, *et al*. Trends for incidence of hospitalization and death due to GI complications in the United States from 2001 to 2009. *Am J Gastroenterol* 2012;107:1190–5. quiz 1196.
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;91:37–41.
5. Guirguis-Blake JM, Evans CV, Senger CA, *et al*. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. preventive services task force. *Ann Intern Med* 2016;164:804–13.
6. Konturek JW, Dembinski A, Konturek SJ, *et al*. Infection of Helicobacter pylori in gastric adaptation to continued administration of aspirin in humans. *Gastroenterology* 1998;114:245–55.
7. Konturek JW, Fischer H, Konturek PC, *et al*. Heat shock protein 70 (HSP70) in gastric adaptation to aspirin in Helicobacter pylori infection. *J Physiol Pharmacol* 2001;52:153–64.
8. Chan FK, Ching JY, Suen BY, *et al*. Effects of Helicobacter pylori infection on long-term risk of peptic ulcer bleeding in low-dose aspirin users. *Gastroenterology* 2013;144:528–35.
9. Malfertheiner P, Megraud F, O'Morain CA, *et al*. Management of helicobacter pylori infection-the maastricht V/Florence consensus report. *Gut* 2017;66:6–30.
10. Leung Ki EL, Chan FK. Interaction of Helicobacter pylori infection and low-dose aspirin in the upper gastrointestinal tract: implications for clinical practice. *Best Pract Res Clin Gastroenterol* 2012;26:163–72.
11. Lanas Á, Carrera-Lasfuentes P, Arguedas Y, *et al*. Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants. *Clin Gastroenterol Hepatol* 2015;13:906–12.
12. Chen WC, Lin KH, Huang YT, *et al*. The risk of lower gastrointestinal bleeding in low-dose aspirin users. *Aliment Pharmacol Ther* 2017;45:1542–50.
13. Rothwell PM, Price JF, Fowkes FG, *et al*. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet* 2012;379:1602–12.
14. Slattery J, Warlow CP, Shorrock CJ, *et al*. Risks of gastrointestinal bleeding during secondary prevention of vascular events with aspirin--analysis of gastrointestinal bleeding during the UK-TIA trial. *Gut* 1995;37:509–11.
15. Leung WK, Wong IOL, Cheung KS, *et al*. Effects of helicobacter pylori treatment on incidence of gastric cancer in older individuals. *Gastroenterology* 2018;155:67–75.
16. Chan EW, Lau WC, Leung WK, *et al*. Prevention of dabigatran-related gastrointestinal bleeding with gastroprotective agents: a population-based study. *Gastroenterology* 2015;149:586–95.
17. Cheung KS, Chan EW, Wong AYS, *et al*. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for *Helicobacter pylori*: a population-based study. *Gut* 2018;67:28–35.
18. Cheung KS, Chan EW, Wong AYS, *et al*. Aspirin and risk of gastric cancer after helicobacter pylori eradication: a territory-wide study. *J Natl Cancer Inst* 2018;110:743–9.
19. Gisbert JP, Pajares JM. Systematic review and meta-analysis: is 1-week proton pump inhibitor-based triple therapy sufficient to heal peptic ulcer? *Aliment Pharmacol Ther* 2005;21:795–804.
20. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994;81:515–26.
21. Collett D. *Modelling survival data in medical research*. Boca Raton: CRC Press, Taylor & Francis Group, 2015.
22. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399–424.
23. Li L, Greene T. A weighting analogue to pair matching in propensity score analysis. *Int J Biostat* 2013;9:215–34.
24. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083–107.
25. Putter H, van Houwelingen HC. Understanding landmarking and its relation with time-dependent cox regression. *Stat Biosci* 2017;9:489–503.
26. De Bruyne B, Pijls NH, Kalesan B, *et al*. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367:991–1001.
27. Huang JQ, Sridhar S, Hunt RH. Role of Helicobacter pylori infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet* 2002;359:14–22.
28. Bonaca MP, Storey RF, Theroux P, *et al*. Efficacy and safety of ticagrelor over time in patients with prior MI in PEGASUS-TIMI 54. *J Am Coll Cardiol* 2017;70:1368–75.
29. Hilkens NA, Algra A, Kappelle LJ, *et al*. Early time course of major bleeding on antiplatelet therapy after TIA or ischemic stroke. *Neurology* 2018;90:e683–e689.
30. Langman MJ, Weil J, Wainwright P, *et al*. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994;343:1075–8.
31. Konturek JW, Dembinski A, Stoll R, *et al*. Mucosal adaptation to aspirin induced gastric damage in humans. Studies on blood flow, gastric mucosal growth, and neutrophil activation. *Gut* 1994;35:1197–204.
32. Pajdo R, Brzozowski T, Konturek PC, *et al*. W1725 Importance of Epi-Lipoxin A4 and Nitric Oxide (NO) in the Mechanism of Adaptation of Gastric Mucosa to Continuous Aspirin Administration. *Gastroenterology* 2008;134:A-703–0.
33. Wehbeh A, Tamim HM, Abu Daya H, *et al*. Aspirin has a protective effect against adverse outcomes in patients with nonvariceal upper gastrointestinal bleeding. *Dig Dis Sci* 2015;60:2077–87.
34. Lanas A, Aabakken L, Fonseca J, *et al*. Clinical predictors of poor outcomes among patients with nonvariceal upper gastrointestinal bleeding in Europe. *Aliment Pharmacol Ther* 2011;33:1225–33.
35. Elwood PC, Morgan G, Galante J, *et al*. Systematic review and meta-analysis of randomised trials to ascertain fatal gastrointestinal bleeding events attributable to preventive low-dose aspirin: no evidence of increased risk. *PLoS One* 2016;11:e0166166.
36. Mose H, Larsen M, Riis A, *et al*. Thirty-day mortality after peptic ulcer bleeding in hospitalized patients receiving low-dose aspirin at time of admission. *Am J Geriatr Pharmacother* 2006;4:244–50.
37. Valkhoff VE, Sturkenboom MC, Kuipers EJ. Risk factors for gastrointestinal bleeding associated with low-dose aspirin. *Best Pract Res Clin Gastroenterol* 2012;26:125–40.
38. Lanas A, Bajador E, Serrano P, *et al*. Nitrovasodilators, low-dose aspirin, other nonsteroidal antiinflammatory drugs, and the risk of upper gastrointestinal bleeding. *N Engl J Med* 2000;343:834–9.
39. Bhatt DL, Scheiman J, Abraham NS, *et al*. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. *Am J Gastroenterol* 2008;103:2890–907.
40. van Walraven C, Davis D, Forster AJ, *et al*. Time-dependent bias was common in survival analyses published in leading clinical journals. *J Clin Epidemiol* 2004;57:672–82.
41. Targownik LE, Suissa S. Understanding and avoiding immortal-time bias in gastrointestinal observational research. *Am J Gastroenterol* 2015;110:1647–50.
42. Gu Q, Xia HH, Wang JD, *et al*. Update on clarithromycin resistance in Helicobacter pylori in Hong Kong and its effect on clarithromycin-based triple therapy. *Digestion* 2006;73:101–6.