

GASTROENTEROLOGY

Risk of peptic ulcer bleeding associated with *Helicobacter pylori* infection, nonsteroidal anti-inflammatory drugs, low-dose aspirin, and antihypertensive drugs:**A case-control study**

Naoyoshi Nagata,* Ryota Niikura,* Katsunori Sekine,* Toshiyuki Sakurai,* Takuro Shimbo,[†] Yoshihiro Kishida,* Shohei Tanaka,* Tomonori Aoki,* Hidetaka Okubo,* Kazuhiro Watanabe,* Chizu Yokoi,* Junichi Akiyama,* Mikio Yanase,* Masashi Mizokami[‡] and Naomi Uemura[§]

Departments of *Gastroenterology and Hepatology and [†]Clinical Research and Informatics, International Clinical Research Center, Research Institute, National Center for Global Health and Medicine, Tokyo, [‡]Research Center for Hepatitis and Immunology, and [§]Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, Kohnodai Hospital, Chiba, Japan

Key words

acetylsalicylic acid, bleeding ulcer, *helicobacter pylori*, interaction, non-variceal upper gastrointestinal bleeding.

Accepted for publication 26 September 2014.

Correspondence

Dr Naoyoshi Nagata, Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine (NCGM) 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan. Email: nnagata_ncgm@yahoo.co.jp

Conflicts of Interest and Source of

Funding: The authors declare no conflicts of interest. This study was supported in part by a grant from the National Center for Global Health and Medicine (26A-201). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Background and Aim: The associations between antithrombotic or antihypertensive drugs and peptic ulcer bleeding (PUB) remain unknown, particularly in Asia, where *Helicobacter pylori* infection is prevalent. This study aims to evaluate the risks of PUB from antithrombotic drugs, angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, α -blockers, and β -blockers.

Methods: This prospective hospital-based case-control study included 230 patients with endoscopically verified PUB and 920 age and sex-matched controls (1:4) without bleeding on screening endoscopy. Adjusted odds ratios (AOR) for the risk of PUB were determined by conditional logistic regression analysis.

Results: In multivariate analysis, alcohol consumption (AOR, 2.2; $P < 0.001$), history of peptic ulcer (AOR, 4.8; $P < 0.001$), *H. pylori* infection (AOR, 2.1; $P < 0.001$), comorbidity index (AOR, 1.1; $P = 0.089$), nonsteroidal anti-inflammatory drugs (NSAIDs) (AOR, 2.0; $P = 0.025$), and low-dose aspirin (AOR, 2.8; $P = 0.003$) increased the risk of PUB, whereas *H. pylori* eradication (AOR, 0.03; $P < 0.001$), proton pump inhibitors (PPIs) (AOR, 0.1; $P < 0.001$), and histamine 2-receptor antagonists (H2RA) (AOR, 0.1; $P < 0.001$) reduced it. No significant interactions were observed between *H. pylori* infection and NSAIDs use for PUB ($P = 0.913$). ARBs ($P = 0.564$), ACE inhibitors ($P = 0.213$), calcium channel blockers ($P = 0.215$), α -blockers ($P = 0.810$), and β -blockers ($P = 0.864$) were not associated with PUB.

Conclusion: We found that alcohol consumption, history of peptic ulcer, *H. pylori* infection, NSAIDs use, and low-dose aspirin use were independent risk factors for PUB, whereas *H. pylori*-eradication, PPIs use, and H2RA use reduced its risk. Interactions between *H. pylori* and NSAIDs use in PUB were not observed. No antihypertensive drug was associated with PUB.

Introduction

Besides antithrombotic drugs, antihypertensive drugs are commonly used to prevent cerebro-cardiovascular disease,¹ and the risk of these drugs for upper gastrointestinal bleeding (UGIB) has been documented.^{2–4} Previous studies have shown that the use of calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors increases the risk of UGIB,^{2–5} while the use of angiotensin II receptor blockers (ARBs) decreases the risk of

UGIB and peptic ulcer.^{6,7} However, the association between antihypertensive drugs and peptic ulcer bleeding (PUB) remains controversial.^{8,9} Moreover, the interaction between antihypertensive drugs and antithrombotic drugs in PUB is unknown.

To date, many studies have evaluated the associations between antithrombotic drugs and PUB in Western countries,^{10–14} but few case-control studies have evaluated these associations in Asia,^{15–17} particularly in Vietnam, Bangladesh, India, Thailand, Korea, and Japan, where *Helicobacter pylori* infection is prevalent.¹⁸ In Japan,

which additionally has a high incidence of gastric cancer,¹⁸ elective endoscopy is frequently performed for gastric cancer screening,¹⁹ even as part of routine examinations for patients without symptoms of the disease. In addition, urgent endoscopy is common for cases of acute UGIB.

In this prospective case-control study (endoscopically verified ulcer bleeding vs no bleeding on screening endoscopy) with a large number of subjects, we assessed the associations between various drugs and PUB on the day of endoscopy. This study aimed to ascertain the risk of *H. pylori* infection and the use of antithrombotic drugs on PUB in Japan, and to evaluate the roles of various antihypertensive drugs on the risk of PUB.

Methods

Study design, setting, and participants. In this prospective case-control study (1:4 case-control ratio), case subjects were consecutive patients who presented with signs of acute, continuous, or frequent overt UGIB and fulfilled the following criteria: (i) ≥ 20 years old; (ii) Japanese nationality; (iii) outpatient onset of UGIB and emergently hospitalized at the National Center for Global Health and Medicine (NCGM) between October 2009 and June 2012; and (iv) endoscopically verified PUB.

Eligible controls were Japanese adults recruited from the Department of Gastroenterology and Hepatology, NCGM, who attended gastric cancer screening and had no apparent signs of gastrointestinal bleeding based on endoscopy, clinical, and laboratory findings on the day of endoscopy. Exclusion criteria were: (i) unknown use of medications; (ii) those who were not independent in activities of daily living; (iii) those who were not able to understand written documents; (iv) uncomplicated or iatrogenic (endoscopic submucosal dissection/mucosal resection) peptic ulcers; and (v) those who were unable to undergo serological testing. All inclusion and exclusion criteria were met before the patients were enrolled.

Because the risk of PUB depends on age and sex, controls were frequency-matched by age in 10-year bands and by sex to increase the precision and power of the case-control study.²⁰ This study was conducted at the NCGM, which has 900 beds and is the largest emergency hospital in metropolitan Tokyo, Japan. The institutional review board of the NCGM approved this study.

Data sources and assessment. A detailed questionnaire was completed by medical staff during a face-to-face interview with each patient at the endoscopy unit on the same day prior to colonoscopy.^{21,22} Medical research staff blinded to both the bleeding outcomes and endoscopic results cross-checked patient medical records for unanswered questionnaire items to avoid omissions. A structured interview covered the following potential risk factors: alcohol consumption, smoking, history of peptic ulcer, comorbidities, and medication use. A history of peptic ulcer was defined as a positive answer on the questionnaire or the presence of an ulcer scar on endoscopy. Comorbid conditions were calculated according to the Charlson comorbidity index,²³ which has been validated for UGIB risk.²⁴ For medications, patients were asked to indicate which drugs, if any, they had used by identifying drug pictures on the questionnaire, as previously reported.²² Use of a drug was defined as intermittent or regular oral administration in

the one month before the interview. Patients were asked about their use of eight kinds of NSAIDs (loxoprofen, diclofenac, naproxen, etodolac, zaltoprofen, meloxicam, lornoxicam, and celecoxib), two kinds of acetylsalicylic acid (ASA; enteric-coated aspirin and buffered aspirin), nine kinds of nonaspirin antiplatelets (ticlopidine, clopidogrel, cilostazol, dipyridamole, sarpogrelate hydrochloride, ethylcosapentate, dilazephydrochloride, limaprostalfadex, and beraprost), warfarin, acetaminophen, five kinds of ARB, five kinds of ACE inhibitors, 13 kinds of calcium channel blockers, two kinds of α -blockers, four kinds of β -blockers, four kinds of proton pump inhibitors (PPIs) (omeprazole, rabeprazole, lansoprazole, and esomeprazole), and six kinds of histamine 2-receptor antagonists (H2RA) (nizatidine, roxatidine acetate hydrochloride, famotidine, ranitidine hydrochloride, lafutidine, and cimetidine). We did not divide antithrombotic drugs into single and combined-use categories. Patients taking ASA, nonaspirin antiplatelets, warfarin, and antihypertensive drugs were all regular users (> 1 month).

***H. pylori* infection.** For the diagnosis of *H. pylori* infection, serological testing was used because histology, the rapid urease test, and culture have shown significantly higher false-negative rates than serological tests in patients with PUB.^{25,26} Blood samples were taken from subjects on admission to the hospital or at the time of endoscopy. *H. pylori* antibody in the samples was measured using the anti-*H. pylori* IgG assay kit (Eiken Chemical, Tokyo, Japan). Results above a cut-off level of 10 U/mL were considered positive. Information on the history of *H. pylori* eradication was collected from the patient medical records or endoscopic database.

Statistical analysis. Previous case-control studies have reported a rate of NSAIDs exposure in controls of approximately 10%,^{10,12,13,27} assuming an odds ratio for detection of 2.0. To calculate the differences in a case-control study with a 1:4 case-control ratio and an α value of 5% at a power of 80%, the expected number of subjects was 209 cases and 836 controls. However, the numbers were likely insufficient, or different sample sizes were needed depending on the kind of medications used because of different bleeding risks. Thus, we conducted the study over two years to exceed the expected sample size.

Patient characteristics were compared between cases and controls using Pearson's chi-squared test or the Mann-Whitney *U*-test as appropriate. We used conditional logistic regression analysis to compute the odds ratio (OR) as an estimate of PUB events associated with risk factors. The significance of each risk factor was examined by univariate and multivariate analysis. To determine the risk factors of PUB, a multivariate model was adjusted for alcohol consumption, smoking, history of gastric resection, history of peptic ulcer, *H. pylori* infection, history of *H. pylori* eradication, Charlson comorbidity index, NSAIDs, ASA, PPIs, and H2RA that had *P* values < 0.2 on univariate analysis in baseline characteristics, and which are well-known risk factors for PUB.^{14,24} In the logistic model, we also investigated whether an interaction between *H. pylori* infection and NSAIDs use in PUB occurred. To evaluate the associations between antihypertensive drugs use and PUB, a multivariate model was adjusted for alcohol consumption, smoking, history of peptic ulcer, *H. pylori* infection, history of

H. pylori eradication, NSAIDs, ASA, PPIs, and H2RA that had *P* values < 0.05 on multivariate analysis for risk factors. The OR and 95% confidence interval (CI) were estimated for each factor, and *P* < 0.05 was considered significant. All statistical analysis was performed using Stata version 10 software (StataCorp, College Station, TX).

Results

During the study period, 1050 patients with 230 bleeding ulcers and 920 non-bleeding controls met the study criteria (Fig. 1). Patient characteristics are shown in Table 1 and Table S1. The factors associated with PUB were alcohol consumption, smoking, history of peptic ulcer, *H. pylori* antibody positivity, high Charlson comorbidity index score, and the use of NSAIDs, enteric-coated aspirin, and buffered aspirin. Patients with *H. pylori* eradication, calcium channel blockers, and antacids had a significantly lower rate of PUB than those without.

Crude and adjusted ORs for PUB are shown in Table 2. Alcohol consumption, history of peptic ulcer, *H. pylori* infection, Charlson comorbidity index, NSAIDs use, ASA use significantly increased the risk of PUB. In contrast, *H. pylori* eradication, PPIs, and H2RA significantly reduced the risk of PUB. In the interaction model, no significant interactions were observed between *H. pylori* infection and NSAID use for PUB (*P* = 0.913). The associations between antihypertensive drug use and PUB are shown in Table 3. Multivariate analysis revealed that ARBs, ACE inhibitors, calcium channel blockers, α -blockers, and β -blockers were not associated with ulcer bleeding.

Discussion

In Japan, an *H. pylori* infection-endemic country, we confirmed that alcohol consumption, history of peptic ulcer, *H. pylori* infection, comorbidities, NSAIDs, and ASA use independently increased the risk of ulcer bleeding, whereas *H. pylori* eradication and the use of PPIs and H2RA decreased the risk. These findings are agreement with several studies from Western countries.^{10–14} We also observed that there was no significant interaction between *H. pylori* infection and NSAID use in PUB. Finally, none of the antihypertensive drugs including ARBs, ACE inhibitors, calcium channel blockers, α -blockers, and β -blockers were found to be associated with ulcer bleeding.

In this study, *H. pylori*-positive patients had approximately a twofold higher PUB risk than *H. pylori*-negative patients. Moreover, eradicated patients had approximately 33-fold lower PUB risk than non-eradicated patients. Papatheodoridis *et al.*²⁸ conducted a systematic review of nine studies and reported an OR of 2.56 for PUB in *H. pylori*-positive patients (76%, 798/1055) compared with control subjects (56%, 587/1043), which are consistent with our results. Chan *et al.*²⁹ conducted a long-term cohort study and showed that re-bleeding with ASA use was low after *H. pylori* infection was eradicated. In addition, ASA users without current or past *H. pylori* infections have an eightfold increase in the incidence rate of re-bleeding compared with the average-risk cohort. Gisbert *et al.*³⁰ evaluated the effect of *H. pylori* eradication on PUB recurrence in a cohort study that included 1000 patients with 41% being previous NSAIDs users, and showed that the incidence rate of re-bleeding was extremely low at 0.15% per patient-year of

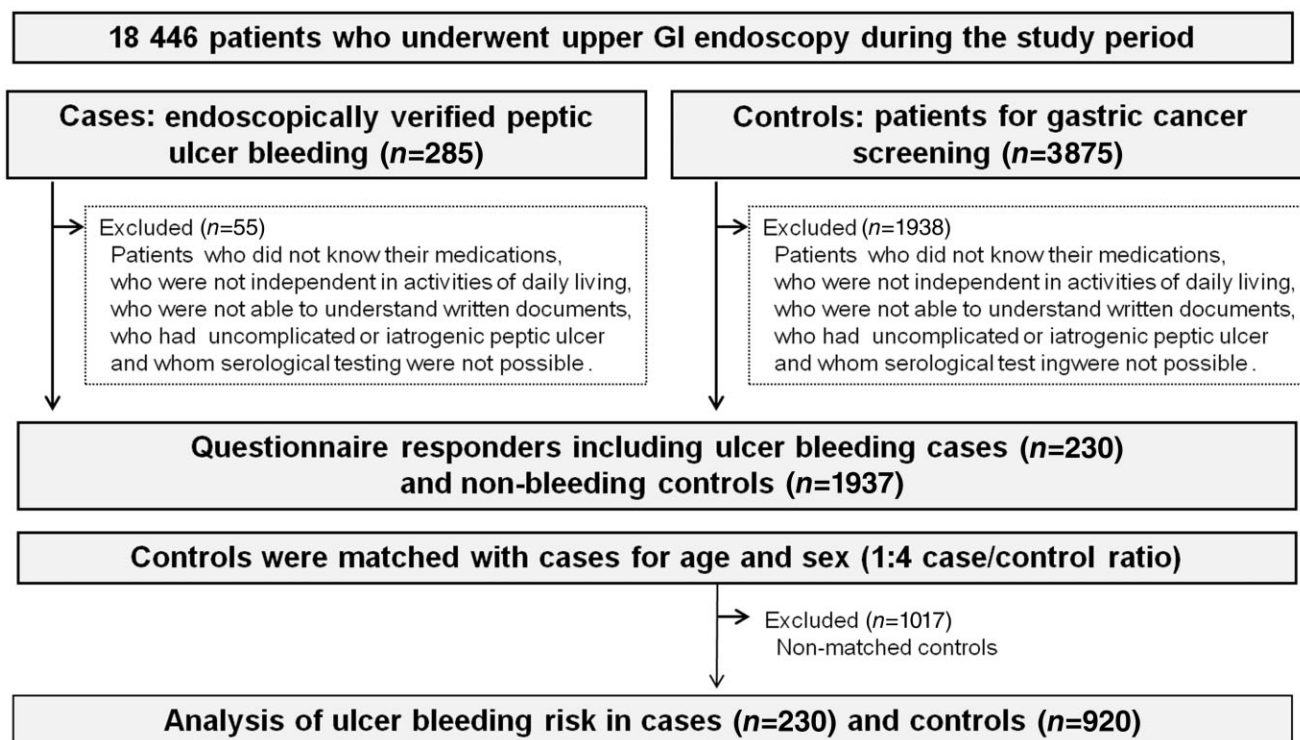


Figure 1 Study flowchart.

Table 1 Patient characteristics (*n* = 1050)

	Ulcer bleeding (<i>n</i> = 230)	Controls (<i>n</i> = 920)	<i>P</i>
Age group (years)			
20–29	6 (2.6)	24 (2.6)	
30–39	18 (7.8)	72 (7.8)	
40–49	25 (10.9)	100 (10.9)	
50–59	45 (20.0)	180 (20.0)	
60–69	58 (25.2)	232 (25.2)	
70–79	53 (23.0)	212 (23.0)	
80–89	25 (10.9)	100 (10.9)	1.00
Sex, male	164 (71.3)	656 (71.3)	1.00
Alcohol consumption	165 (71.7)	496 (53.9)	< 0.001
Smoking	71 (30.9)	231 (25.1)	0.076
History of gastric resection	2 (0.9)	21 (2.3)	0.171
History of peptic ulcer	56 (24.4)	85 (9.2)	< 0.001
<i>H. pylori</i> antibody positivity	123 (53.5)	386 (42.0)	0.002
History of <i>H. pylori</i> eradication	2 (0.9)	135 (14.7)	< 0.001
Charlson comorbidity index [†]	1.23 ± 1.97	0.98 ± 1.53	0.044
NSAIDs	34 (14.8)	77 (8.4)	0.003
Acetaminophen	7 (3.0)	20 (2.2)	0.436
ASA	26 (11.3)	70 (7.6)	0.070
	Ulcer bleeding (<i>n</i> = 230)	Controls (<i>n</i> = 920)	<i>P</i>
Enteric-coated aspirin (100 mg)	22 (26.8)	65 (7.1)	< 0.001
Buffered aspirin (81 mg)	4 (5.9)	5 (0.6)	< 0.001
Nonaspirin antiplatelets	8 (3.5)	54 (5.9)	0.151
Anticoagulants (warfarin)	4 (1.7)	25 (2.7)	0.397
Antihypertensive drugs	53 (23.0)	260 (28.3)	0.112
ARBs	38 (16.5)	139 (15.1)	0.595
ACE inhibitors	2 (0.9)	11 (1.2)	0.676
Calcium channel blockers	29 (12.6)	171 (18.6)	0.032
α-blockers	1 (0.4)	9 (1.0)	0.427
β-blockers	4 (1.7)	19 (2.1)	0.752
Antacids			
PPIs	12 (5.2)	264 (28.7)	< 0.001
H2RAs	4 (1.7)	77 (8.4)	< 0.001

[†]Mean ± SD. Numbers in parentheses show percentages.

ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; ASA, acetylsalicylic acid; *H. pylori*, *Helicobacter pylori*; H2RA, histamine 2-receptor antagonists; NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PPIs, proton pump inhibitors.

follow up. These and our findings suggest that assessment of *H. pylori* infection status (positive, negative, and eradicated) is useful for risk stratification of bleeding or re-bleeding ulcer, particularly for ASA or NSAIDs users.

Here, we found no interactions between *H. pylori* infection and NSAIDs with regard to ulcer bleeding (*P* = 0.913). Previous findings on the synergistic or additive effect of NSAID use and *H. pylori* infection in PUB have been conflicting,^{16,17,28} probably due to variations in study design, definition of ulcer bleeding, and different rates of *H. pylori* infection between countries.²⁸ Sakamoto *et al.*¹⁶ reported an adjusted OR of 4.9 for ulcer bleeding with *H. pylori* infection and 6.1 for ulcer bleeding in NSAIDs users, but the interaction OR was not significant (1.2; 95% CI, −5.8–8.1). The similar study design and prevalence of *H. pylori* infection in their study support our results.

In PUB, risk factors other than NSAIDs or ASA use and *H. pylori* infection were considered. We found an OR for ulcer bleeding of 4.8 for history of peptic ulcer, 0.1 for PPIs or H2RA

use. In the guideline for prevention of NSAID-related ulcer complication,¹⁴ patients with history of peptic ulcer had the highest risk of bleeding. Lanas *et al.*¹¹ reported a relative risk (RR) for ulcer bleeding of 0.33 for PPIs use and 0.65 for H2RA use. Recently, de Groot NL *et al.*³¹ conducted cohort study of 784 263 NSAIDs users and 235 531 ASA users and showed that history of peptic ulcer disease was a risk factor for primary non-variceal UGIB in both groups, and PPI use was protective in the ASA group. These findings support our results. Several studies have shown that antihypertensive drugs increase the risk of UGIB. Pahor *et al.*² reported a RR for gastrointestinal bleeding of 1.23 for ACE inhibitor use and 1.86 for calcium channel blocker use compared with β-blockers. On the contrary, Smalley *et al.*² reported an RR of 1.1 (95% CI, 0.7–1.7) for PUB in hospitalized patients using calcium channel blockers compared with nonusers. Kelly *et al.*⁴ reported an RR of 1.2 (95% CI, 0.9–1.6) for major UGIB in calcium channel blocker users compared with nonusers. In a large cohort of antihypertensive drug users, Kaplan *et al.* showed that calcium

Table 2 Risk factors for peptic ulcer bleeding ($n = 1050$)

	Crude OR	<i>P</i>	Adjusted OR [†] (without interaction)	<i>P</i>	Adjusted OR [†] (interaction term)	<i>P</i>
Alcohol consumption	2.4 (1.7–3.3)	< 0.001	2.2 (1.4–3.5)	< 0.001	2.2 (1.4–3.5)	< 0.001
Smoking	1.4 (1.0–1.9)	0.062	1.1 (0.7–1.7)	0.588	1.1 (0.7–1.7)	0.587
History of gastric resection	0.4 (0.09–1.6)	0.188	0.3 (0.06–1.9)	0.216	0.4 (0.06–1.7)	0.222
History of peptic ulcer	3.1 (2.2–4.6)	< 0.001	4.8 (2.8–8.2)	< 0.001	4.8 (2.8–8.2)	< 0.001
<i>H. pylori</i> antibody positivity	1.6 (1.2–2.2)	0.001	2.1 (1.4–3.1)	< 0.001	2.1 (1.4–3.2)	< 0.001
History of <i>H. pylori</i> eradication	0.06 (0.01–0.2)	< 0.001	0.03 (0.01–0.1)	< 0.001	0.03 (0.01–0.1)	< 0.001
Charlson comorbidity index [†]	1.1 (1.0–1.2)	0.032	1.1 (1.0–1.2)	0.089	1.1 (1.0–1.2)	0.093
NSAIDs	1.9 (1.2–2.8)	0.004	2.0 (1.1–3.5)	0.025	2.0 (1.0–4.1)	0.061
ASA (< 100 mg)	1.5 (1.0–2.5)	0.074	2.8 (1.4–5.7)	0.003	2.8 (1.4–5.6)	0.003
Non-ASA antiplatelets	0.6 (0.3–1.2)	0.152	0.4 (0.2–1.3)	0.144	0.4 (0.2–1.3)	0.142
Antihypertensive drugs	0.7 (0.5–1.1)	0.103	0.8 (0.5–1.3)	0.419	0.8 (0.5–1.3)	0.427
PPIs	0.1 (0.07–0.2)	< 0.001	0.1 (0.06–0.2)	< 0.001	0.1 (0.06–0.2)	< 0.001
H2RAs	0.2 (0.07–0.5)	0.002	0.1 (0.03–0.5)	0.006	0.1 (0.02–0.5)	< 0.001
<i>H. pylori</i> and NSAIDs [‡]	NA	NA	NA	NA	0.9 (0.3–3.4)	0.913

[†]OR were adjusted for all factors in univariate analysis (crude model).

[‡]Indicates testing of the interaction between *H. pylori* and NSAIDs use.

Numbers in parentheses represent the 95% confidence interval.

ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; ASA, acetylsalicylic acid; CI, confidential interval; *H. pylori*, *Helicobacter pylori*; H2RA, histamine 2-receptor antagonists; NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PPIs, proton pump inhibitors.

Table 3 Association of antihypertensive drugs use with the risk of peptic ulcer bleeding ($n = 1050$)

Drug use	Crude OR	<i>P</i>	Adjusted OR [†]	<i>P</i>
ARBs	1.1 (0.7–1.7)	0.589	1.2 (0.7–2.1)	0.564
ACE inhibitors	0.7 (0.2–3.3)	0.673	2.9 (0.5–15.8)	0.213
Calcium channel blockers	0.6 (0.4–1.0)	0.030	0.7 (0.4–1.2)	0.215
α -blockers	0.4 (0.06–3.5)	0.442	1.3 (0.1–11.5)	0.810
β -blockers	0.8 (0.3–2.5)	0.755	0.9 (0.2–3.2)	0.864

[†]Adjusted for alcohol consumption, history of peptic ulcer.

Numbers in parentheses represent the 95% confidence interval. *H. pylori* antibody positivity, history of *H. pylori* eradication, nonsteroidal anti-inflammatory drugs, low-dose aspirin, proton pump inhibitors, and histamine 2-receptor antagonists.

ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; OR, odds ratio.

channel blockers and not ACE inhibitors had an RR of 2.60 for gastrointestinal bleeding compared with β -blockers, but were not a significant risk factor for PUB. A randomized trial showed that the six-year rate of gastrointestinal bleeding in hospitalized patients was 8.8%, 8.0%, and 9.0% in diuretic, calcium channel blocker, and ACE inhibitor treatment groups.⁸ Although no studies have evaluated the history of peptic ulcer and *H. pylori* infection in relation to PUB, these previous findings and our findings suggest only a weak association between calcium channel blockers or ACE inhibitors and PUB.

In this study, we found no associations between PUB and ARB use. Shiotani *et al.*^{6,7} proposed that the anti-inflammatory effects of ARBs prevent aspirin-induced ulcers by preserving gastric blood flow. In contrast, Uemura *et al.*³² showed no association between

ARB use and mucosal erosion ($P = 0.4390$) or ulcers ($P = 1.00$). Nadatani *et al.*³³ also reported that no significant differences ($P = 1.00$) in ARB use between ulcer bleeding and controls. These and our findings suggest that the evidence of association between ARB use and PUB is weak. The present study has several strengths. First, it is an age and sex-matched case-control study with a relatively large sample population, which enabled us to adjust for confounders. Second, the definition of ulcer bleeding was based on endoscopy findings. This is in contrast to previous observational studies that did not endoscopically evaluate bleeding outcomes associated with antihypertensive drug use.^{2–4,8} This study also has some limitations. First, we did not assess the use of spironolactone or selective serotonin reuptake inhibitors, which are possible risk factors for UGIB.^{34,35} Second, the multiple questionnaire items in the pre-endoscopy setting did not provide sufficient information on the duration of medication use (intermittent or regular), frequency, or details of the dose. Third, the controls underwent endoscopy for cancer screening, which may not have been indicated in healthy controls.

In conclusion, this study demonstrated that alcohol consumption, history of peptic ulcer, *H. pylori* infection, NSAIDs, and low-dose aspirin increased the risk of PUB, whereas *H. pylori* eradication, PPIs, H2RA reduced the risk. Interactions between *H. pylori* and NSAID use in PUB were not observed. No antihypertensive drugs were associated with PUB.

Authorship statement

Nagata N was the primary author of the manuscript and participated in study design. Shimbo T participated in study design and contributed to statistical analysis. Niikura R, Sakurai T, and Sekine K performed data acquisition and data interpretation. Aoki T,

Kishida Y, Tanaka S, Okubo H, Watanabe K, Sakurai T, Yokoi C, and Akiyama J performed endoscopy. Yanase M, Mizokami M, and Naomi U advised on study design and contributed to the writing of the manuscript. All authors read and approved the submitted version of the manuscript.

Acknowledgments

The authors thank the following clinical research coordinators for their help with the data collection: Hisae Kawashiro, Sawako Iijima, Yoko Tanigawa, Aiko Gotanda, and Yaeko Sawada.

References

- Rothwell PM, Algra A, Amarenco P. Medical treatment in acute and long-term secondary prevention after transient ischaemic attack and ischaemic stroke. *Lancet* 2011; **377**: 1681–92.
- Pahor M, Guralnik JM, Furberg CD, Carbonin P, Havlik R. Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old. *Lancet* 1996; **347**: 1061–5.
- Smalley WE, Ray WA, Daugherty JR, Griffin MR. No association between calcium channel blocker use and confirmed bleeding peptic ulcer disease. *Am. J. Epidemiol.* 1998; **148**: 350–4.
- Kelly JP, Laszlo A, Kaufman DW, Sundstrom A, Shapiro S. Major upper gastrointestinal bleeding and the use of calcium channel blockers. *Lancet* 1999; **353**: 559.
- Lanas A, Fuentes J, Benito R, Serrano P, Bajador E, Sainz R. *Helicobacter pylori* increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. *Aliment. Pharmacol. Ther.* 2002; **16**: 779–86.
- Shiotani A, Nishi R, Yamanaka Y *et al.* Renin-angiotensin system associated with risk of upper GI mucosal injury induced by low dose aspirin: renin angiotensin system genes' polymorphism. *Dig. Dis. Sci.* 2011; **56**: 465–71.
- Shiotani A, Sakakibara T, Yamanaka Y *et al.* Upper gastrointestinal ulcer in Japanese patients taking low-dose aspirin. *J. Gastroenterol.* 2009; **44**: 126–31.
- Kaplan RC, Heckbert SR, Koepsell TD, Rosendaal FR, Psaty BM. Use of calcium channel blockers and risk of hospitalized gastrointestinal tract bleeding. *Arch. Intern. Med.* 2000; **160**: 1849–55.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA* 2002; **288**: 2981–97.
- Lanas A, Garcia-Rodriguez LA, Arroyo MT *et al.* Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. *Gut* 2006; **55**: 1731–8.
- Lanas A, Garcia-Rodriguez LA, Arroyo MT *et al.* Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. *Am. J. Gastroenterol.* 2007; **102**: 507–15.
- Delaney JA, Opatrný L, Brophy JM, Suissa S. Drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. *CMAJ* 2007; **177**: 347–51.
- Hallas J, Dall M, Andries A *et al.* Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. *BMJ* 2006; **333**: 726.
- Lanza FL, Chan FK, Quigley EM. Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. *Am. J. Gastroenterol.* 2009; **104**: 728–38.
- Wu CY, Poon SK, Chen GH, Chang CS, Yeh HZ. Interaction between *Helicobacter pylori* and non-steroidal anti-inflammatory drugs in peptic ulcer bleeding. *Scand. J. Gastroenterol.* 1999; **34**: 234–7.
- Sakamoto C, Sugano K, Ota S *et al.* Case-control study on the association of upper gastrointestinal bleeding and nonsteroidal anti-inflammatory drugs in Japan. *Eur. J. Clin. Pharmacol.* 2006; **62**: 765–72.
- Kang JM, Kim N, Lee BH *et al.* Risk factors for peptic ulcer bleeding in terms of *Helicobacter pylori*, NSAIDs, and antiplatelet agents. *Scand. J. Gastroenterol.* 2011; **46**: 1295–301.
- Fock KM, Ang TL. Epidemiology of *Helicobacter pylori* infection and gastric cancer in Asia. *J. Gastroenterol. Hepatol.* 2010; **25**: 479–86.
- Uemura N, Okamoto S, Yamamoto S *et al.* *Helicobacter pylori* infection and the development of gastric cancer. *N. Engl. J. Med.* 2001; **345**: 784–9.
- Sturmer T, Brenner H. Potential gain in precision and power by matching on strong risk factors in case-control studies: the example of laryngeal cancer. *J. Epidemiol. Biostat.* 2000; **5**: 125–31.
- Nagata N, Niikura R, Aoki T *et al.* Lower GI bleeding risk of nonsteroidal anti-inflammatory drugs and antiplatelet drug use alone and the effect of combined therapy. *Gastrointest. Endosc.* 2014; pii: S0016-5107(14)01930-0. doi: 10.1016/j.gie.2014.06.039. [Epub ahead of print].
- Nagata N, Niikura R, Aoki T *et al.* Colonic diverticular hemorrhage associated with the use of NSAIDs, low-dose aspirin, antiplatelet drugs, and dual therapy. *J. Gastroenterol. Hepatol.* 2014; **29**: 1786–93.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* 1987; **40**: 373–83.
- Crooks CJ, West J, Card TR. Comorbidities affect risk of nonvariceal upper gastrointestinal bleeding. *Gastroenterology* 2013; **144**: 1384–93. 1393.e1–2; quiz e18–9.
- Tu TC, Lee CL, Wu CH *et al.* Comparison of invasive and noninvasive tests for detecting *Helicobacter pylori* infection in bleeding peptic ulcers. *Gastrointest. Endosc.* 1999; **49**: 302–6.
- Colin R, Czernichow P, Baty V *et al.* Low sensitivity of invasive tests for the detection of *Helicobacter pylori* infection in patients with bleeding ulcer. *Gastroenterol. Clin. Biol.* 2000; **24**: 31–5.
- 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.
- Papatheodoridis GV, Sougioultzis S, Archimandritis AJ. Effects of *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs on peptic ulcer disease: a systematic review. *Clin. Gastroenterol. Hepatol.* 2006; **4**: 130–42.
- Chan FK, Ching JY, Suen BY, Tse YK, Wu JC, Sung JJ. Effects of *Helicobacter pylori* infection on long-term risk of peptic ulcer bleeding in low-dose aspirin users. *Gastroenterology* 2013; **144**: 528–35.
- Gisbert JP, Calvet X, Cosme A *et al.* Long-term follow-up of 1000 patients cured of *Helicobacter pylori* infection following an episode of peptic ulcer bleeding. *Am. J. Gastroenterol.* 2012; **107**: 1197–204.
- de Groot NL, Hagens MP, Smeets HM, Steyerberg EW, Siersema PD, van Oijen MG. Primary non-variceal upper gastrointestinal bleeding in NSAID and low-dose aspirin users: development and validation of risk scores for either medication in two large dutch cohorts. *J. Gastroenterol.* 2014; **49**: 245–53.

- 32 Uemura N, Sugano K, Hiraishi H *et al.* Risk factor profiles, drug usage, and prevalence of aspirin-associated gastroduodenal injuries among high-risk cardiovascular Japanese patients: the results from the MAGIC study. *J. Gastroenterol.* 2014; **49**: 814–24.
- 33 Nadatani Y, Watanabe T, Tanigawa T *et al.* Incidence and risk factors of gastrointestinal bleeding in patients on low-dose aspirin therapy after percutaneous coronary intervention in Japan. *Scand. J. Gastroenterol.* 2013; **48**: 320–5.
- 34 Anglin R, Yuan Y, Moayyedi P, Tse F, Armstrong D, Leontiadis GI. Risk of upper gastrointestinal bleeding with selective serotonin reuptake inhibitors with or without concurrent nonsteroidal anti-inflammatory use: a systematic review and meta-analysis. *Am. J. Gastroenterol.* 2014; **109**: 811–19.
- 35 Verhamme K, Mosis G, Dieleman J, Stricker B, Sturkenboom M. Spironolactone and risk of upper gastrointestinal events: population based case-control study. *BMJ* 2006; **333**: 330.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Detailed drugs exposure in case and control ($n = 1050$).