ORIGINAL RESEARCH

Prevention of recurrent idiopathic gastroduodenal ulcer bleeding: a double-blind, randomised trial

Grace L H Wong ,[1] Louis H S Lau,[1] Jessica Y L Ching,[1] Yee-Kit Tse,[2] Rachel H Y Ling,[1] Vincent W S Wong ,[1] Philip W Y Chiu ,[3] James Y W Lau,[3] Francis K L Chan [1]

[1]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China
[2]Institute of Digestive Diseases, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China
[3]Department of Surgery, The Chinese University of Hong Kong, Hong Kong, China

Correspondence to
Professor Francis K L Chan, Medicine and Therapeutics, Chinese University of Hong Kong, Hong Kong, China; fklchan@cuhk.edu.hk

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ABSTRACT

Objective Patients with a history of *Helicobacter pylori*-negative idiopathic bleeding ulcers have a considerable risk of recurrent ulcer complications. We hypothesised that a proton pump inhibitor (lansoprazole) is superior to a histamine 2 receptor antagonist (famotidine) for the prevention of recurrent ulcer bleeding in such patients.

Design In this industry-independent, double-blind, randomised trial, we recruited patients with a history of idiopathic bleeding ulcers. After ulcer healing, we randomly assigned (1:1) patients to receive oral lansoprazole 30 mg or famotidine 40 mg daily for 24 months. The primary endpoint was recurrent upper GI bleeding within 24 months, analysed in the intention-to-treat population as determined by an independent adjudication committee.

Results Between 2010 and 2018, we enrolled 228 patients (114 patients in each study group). Recurrent upper GI bleeding occurred in one patient receiving lansoprazole (duodenal ulcer) and three receiving famotidine (two gastric ulcers and one duodenal ulcer). The cumulative incidence of recurrent upper GI bleeding in 24 months was 0.88% (95% CI 0.08% to 4.37%) in the lansoprazole arm and 2.63% (95% CI 0.71% to 6.91%) in the famotidine arm (p=0.313; crude HR 0.33, 95% CI 0.03 to 3.16, p=0.336). None of the patients who rebled used aspirin, non-steroidal anti-inflammatory drugs or other antithrombotic drugs.

Conclusion This 2-year, double-blind randomised trial showed that among patients with a history of *H. pylori*-negative idiopathic ulcer bleeding, recurrent bleeding rates were comparable between users of lansoprazole and famotidine, although a small difference in efficacy cannot be excluded.

Trial registration number NCT01180179; Results.

Significance of this study

What is already known on this subject?

- Peptic ulcers not related to *Helicobacter pylori* infection or use of non-steroidal anti-inflammatory drugs, including low-dose aspirin, are increasingly recognised.
- *H. pylori*-negative idiopathic gastroduodenal ulcer bleeding has a high relapse rate (about 6.0%–13.4% per year).
- The efficacy of acid suppressive prophylaxis for prevention of *H. pylori*-negative idiopathic bleeding ulcers is unknown.

What are the new findings?

- In this 24-month, double-blind randomised trial, the cumulative incidence of recurrent bleeding was 0.88% with lansoprazole and 2.63% with famotidine.

How might it impact on clinical practice in the foreseeable future?

- The incidence of recurrent *H. pylori*-negative idiopathic ulcer bleeding is low with lansoprazole and famotidine.
- A small difference in efficacy between lansoprazole and famotidine cannot be excluded.

INTRODUCTION

Peptic ulcers not related to *Helicobacter pylori* infection or use of non-steroidal anti-inflammatory drugs (NSAIDs), including low-dose aspirin, have been established to be a distinct disease entity.[1] A significant proportion (ranging from 11% to 44%) of peptic ulcers were found to be idiopathic in North America.[2–4] On the other hand, up to 20% of patients with *H. pylori*-associated ulcers developed recurrent ulcers within 6 months after successful *H. pylori* eradication in the absence of NSAID use.[5] Furthermore, more than a quarter of 2900 duodenal ulcers were not related to NSAID use or *H. pylori* infection in a grouped analysis of six large clinical trials.[6] This kind of idiopathic ulcer is also an emerging problem in Asia. At the end of the last century, idiopathic peptic ulcers accounted for less than 5% of peptic ulcers in Asia.[7] After approximately a decade, idiopathic peptic ulcers accounted for more than 20% of the peptic ulcers in a Korean study.[8] We previously reported that the absolute incidence of idiopathic gastroduodenal ulcer bleeding has increased fourfold in the past decade.[9 10] Currently, this distinct group of peptic ulcers has contributed to about 10%–15% of patients with bleeding ulcers.[11 12]

Patients with idiopathic gastroduodenal ulcer bleeding have a poor prognosis because of the high relapse rate.[13] Idiopathic ulcer bleeding has now been established as a major risk factor of recurrent ulcer bleeding and even death.[11 12] We first demonstrated a high rate of recurrent bleeding, 13.4% in 1 year, in the absence of acid suppression.[10]

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This finding is consistent with our subsequent study that in the annual incidence of recurrent bleeding is high (6.0% per year) without regular acid suppressive therapy.[12] In this prospective, long-term cohort study with a median follow-up of 7 years, we demonstrated a 10-fold increased risk of recurrent ulcer bleeding in patients with a history of idiopathic ulcer bleeding compared with patients with a history of *H. pylori* ulcer bleeding even after adjusting for old age and comorbidity.[12] Accordingly, current treatment guidelines recommend prescribing long-term proton pump inhibitor (PPI) to patients with a history of *H. pylori*-negative idiopathic ulcer bleeding.[14] However, whether PPI is superior to a histamine H2 receptor antagonist (H2RA) for prevention of recurrent idiopathic ulcer bleeding is unknown. This is a clinically relevant question since our previous study showed that many patients with *H. pylori*-negative idiopathic ulcer bleeding had histological features of achlorhydria.

We aimed to test the hypothesis that a PPI lansoprazole is superior to an H2RA famotidine for the prevention of recurrent upper GI bleeding in patients with a history of *H. pylori*-negative idiopathic gastroduodenal ulcer bleeding.

METHODS

Study design and population

This industry-independent, double-blind, double-dummy, randomised trial was done at Prince of Wales Hospital of The Chinese University of Hong Kong between 24 June 2010 and 15 August 2018. This study was registered at ClinicalTrials.gov.

We screened patients presenting with upper GI bleeding who had *H. pylori*-negative idiopathic peptic ulcers, defined as patients who had no exposure to aspirin, NSAIDs or drugs of unknown nature including traditional Chinese medicine within the 4 weeks before hospitalisation. The patients underwent endoscopy to identify the site of bleeding, and gastric biopsies taken during endoscopy must be negative for both the urease test and histology for *H. pylori* in the absence of acid suppressive therapy, and patients should have no other causes of ulceration identified.[10 12] Follow-up endoscopy was done to confirm ulcer healing and to repeat urease test and histology for *H. pylori* in the absence of acid suppressive therapy for all patients.

Patients were eligible if they had endoscopically confirmed ulcer healing and negative results for *H. pylori*; who would not require low-dose aspirin for cardiothrombotic diseases; and neither did have chronic arthritis pain nor anticipate to require regular use of NSAIDs for the duration of the trial. The exclusion criteria were concomitant use of NSAIDs, aspirin, cyclo-oxygenase type 2 inhibitors, steroid or anticoagulants; previous gastric surgery; who would need maintenance PPI (eg, reflux oesophagitis); who had advanced comorbidity (defined as American Society of Anesthesiologists physical status classification 4 or above) or active malignancy; who were pregnant or lactating, or is intending to become pregnant before, during or within 1 month after participating in this study; who had known hypersensitivity or allergies to any component of lansoprazole; or who had current or historical evidence of Zollinger-Ellison syndrome or other hypersecretory condition.

Randomisation and masking

Eligible patients were randomly assigned (1:1) with a computer-generated list of random numbers to one of the two treatment groups: lansoprazole or famotidine. An independent staff member assigned the treatments according to consecutive numbers that were kept in sealed opaque envelopes.

Both patients and investigators were masked to their treatments. Treatment allocation was masked by repackaging and encapsulation of lansoprazole and famotidine as lookalike green capsules by the School of Pharmacy at The Chinese University of Hong Kong according to the International Good Manufacturing Practice Guidelines for Pharmaceuticals. Consecutively numbered, sealed bottles of the study drugs are dispensed by a research nurse.

Procedures

Before enrolment, all patients had a physical examination, laboratory testing and an assessment of upper GI symptoms. Enrolled patients received oral administrations of either lansoprazole 30 mg once per day or famotidine 40 mg once per day for 24 months. All patients were advised to avoid prohibited drugs, namely anticoagulant agents, NSAIDs, cyclo-oxygenase-2 inhibitors, over-the-counter analgesics (including herbal products), corticosteroids, misoprostol and H2RAs other than the study drugs, sucralfate, antiplatelet drugs, bisphosphonates and PPIs.

Patients were followed up 2 months after randomisation, and then subsequently returned to the study centre every 4 months until month 22, and finally received end-of-study endoscopy at month 24. At each visit, haemoglobin concentrations, serum biochemical values, drug compliance, efficacy and safety were assessed. Drug compliance was assessed by pill counts. Assessment of safety was based on the physical examination, laboratory tests, and observed or reported adverse events. A direct telephone line was provided so that the patients could report any adverse events between the scheduled visits. Unscheduled visits were arranged when patients recognised haematemesis, melaena, anaemia and so on that associated with bleeding even if such symptoms happened between scheduled visits. This unscheduled visit enabled to protect patient safety associated with bleeding ulcer and also may enable to increase frequency of idiopathic bleeding ulcer. Patients were permitted to take antacids to relieve dyspepsia and simple analgesics (paracetamol or tramadol) for any pain if needed. We followed up patients who withdrew early until the end of the study.

Outcomes

The primary endpoint was a safety endpoint of recurrent upper GI bleeding within 24 months according to prespecified criteria—namely, haematemesis or melaena documented by the admitting physician, with ulcers or bleeding erosions confirmed by endoscopy, or a decrease in haemoglobin > 20 g/L in the presence of endoscopically proven ulcers or bleeding erosions. An ulcer was defined as a circumscribed mucosal break at least 0.5 cm in diameter and with a perceptible depth. Bleeding erosions were defined as flat mucosal breaks of any size in the presence of blood in the stomach. Members of an independent, masked adjudication committee determined whether recurrent upper GI bleeding had occurred according to the prespecified criteria. Only events that were confirmed by the adjudication committee and that occurred during treatment were regarded as endpoint reached.

The secondary endpoint was lower GI bleeding, which was defined as overt bleeding (melaena or haematochezia without an upper GI source) or a drop in haemoglobin >2 g/dL, without an upper GI source or other non-GI causes of anaemia. We excluded haemorrhoidal bleeding and colorectal cancer as lower GI outcomes.[15]

Statistical analysis

We determined the size of the sample on the assumptions that about 12% of patients with *H. pylori*-negative idiopathic ulcer

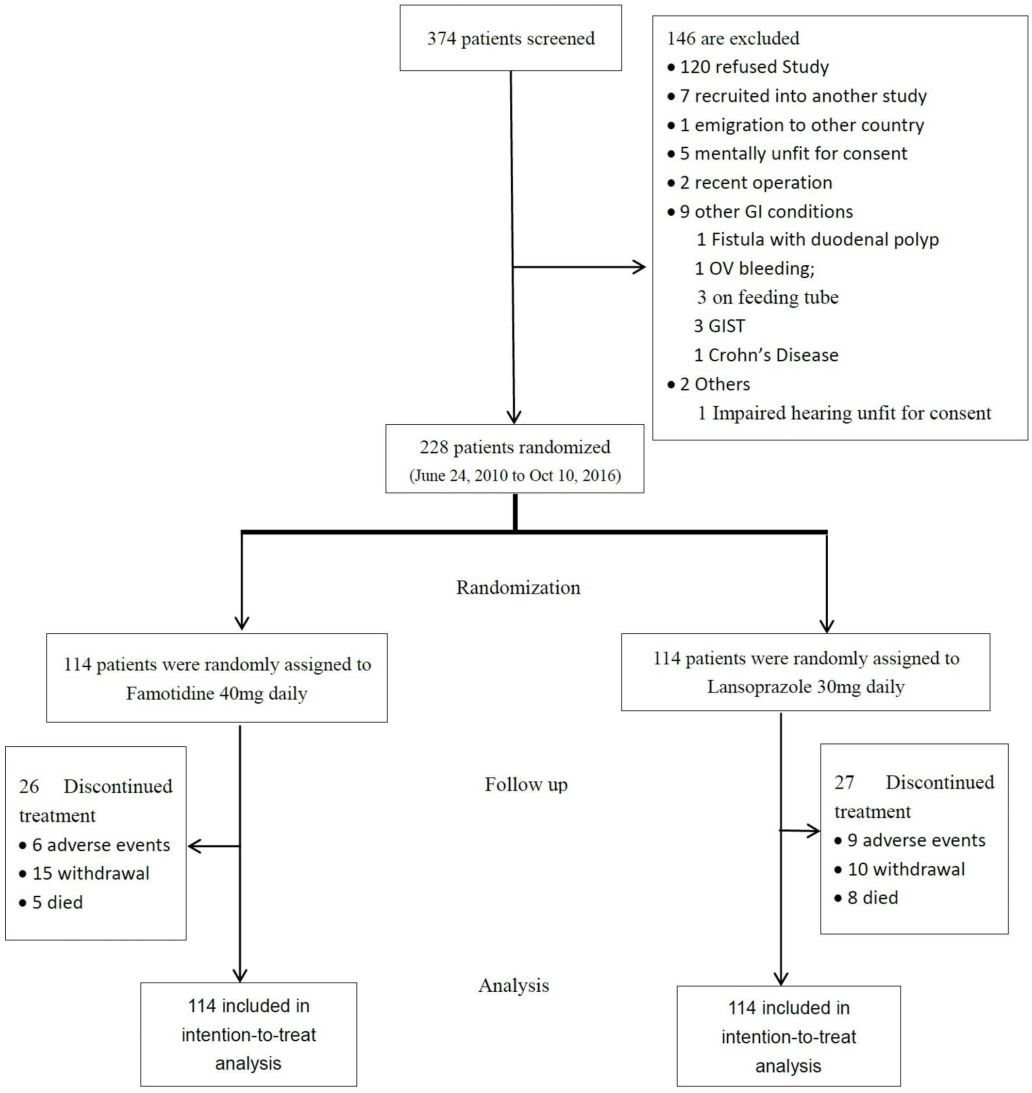

Figure 1 Trial profile. GIST, gastrointestinal stromal tumour; OV, oesophageal varices.

receiving famotidine would have recurrent ulcer bleeding within 24 months[10 11] and that patients with *H. pylori*-negative idiopathic ulcer receiving lansoprazole would have 3% (ie, 9% reduction) of recurrent ulcer bleeding. Accordingly, 103 patients per arm (total of 206 patients) were needed for 80% power and 5% level of significance with the use of a two-sided superiority test for a group-sequential log-rank test.[16] Assuming that 10% of patients would not complete follow-up, a total sample of 228 patients were required and enrolled. The intention-to-treat population consisted of all randomised subjects who had attended the randomisation visit. The intention-to-treat population was used for the endpoint analysis. We followed up patients who withdrew early until the end of the study if they agreed, while patients who were lost to follow-up or died were censored at the last clinic visit.

Continuous variables were expressed as mean (SD) or median (IQR) where appropriate. Categorical variables were presented as n (%). Primary and secondary outcomes were analysed in both the intention-to-treat and modified intention-to-treat populations (the latter was defined as all patients who had received at least one dose of the study drugs). We used the Kaplan-Meier method to estimate the likelihood of reaching the endpoint of recurrent upper GI bleeding, recurrent lower GI bleeding and death within 24. We compared time-to-event curves between the two groups with the log-rank test. We estimated HRs and 95% CIs for recurrent upper GI bleeding using Cox proportional hazards regression. For secondary categorical variable (recurrent ulcer detected by endoscopy at 24 months), the effect between the two groups was analysed using χ^2 test. Death was considered to be a competing risk when it occurred prior to recurrent upper GI bleeding. In post-hoc analyses, we calculated the cumulative incidence of recurrent upper GI bleeding in the presence of competing risk events. Gray's test was used to compare cumulative incidence between the two groups. Competing risks regression based on the method described by Fine and Gray[17] and considering death as a competing risk was also performed. Statistical tests were done using IBM SPSS Statistics V.25 and SAS V.9.4 for competing risk analysis. All statistical tests were two-sided. Statistical significance was taken as $p<0.05$. A data and safety monitoring committee (DSMC), consisting of two physicians and one biostatistician who were not involved in this study, monitored the progress of the trial and the safety and welfare of participants.

A prespecified interim analysis was performed on the primary endpoint when all patients had been randomised and had completed the 12-month follow-up to ascertain safety.[18] The

Table 1 Baseline clinical characteristics of patients at time of randomisation

	Lansoprazole arm n=114	Famotidine arm n=114
Male gender, n (%)	78 (68.4)	63 (55.3)
Age (years)	67.6 (16.3)	69.6 (15.8)
Haemoglobin (g/L)	107 (2.8)	91 (2.4)
Haematocrit (L/L)	0.361 (0.077)	0.346 (0.078)
White cell count (×10^9/L)	9.3 (4.8)	9.5 (5.1)
Platelet (×10^9/L)	219.6 (78.2)	220.0 (80.0)
Prothrombin time (s)	11.41 (1.16)	11.43 (1.17)
International normalised ratio	1.06 (0.11)	1.07 (0.11)
Urea (mmol/L)	8.18 (5.56)	8.71 (5.83)
Creatinine (µmol/L)	113 (109)	117 (90)
Index ulcer location (%)		
Gastric ulcer	36.0	37.7
Duodenal ulcer	50.0	50.0
Gastroduodenal ulcer	14.0	12.3

All data, unless stated otherwise, represent mean values (SD).

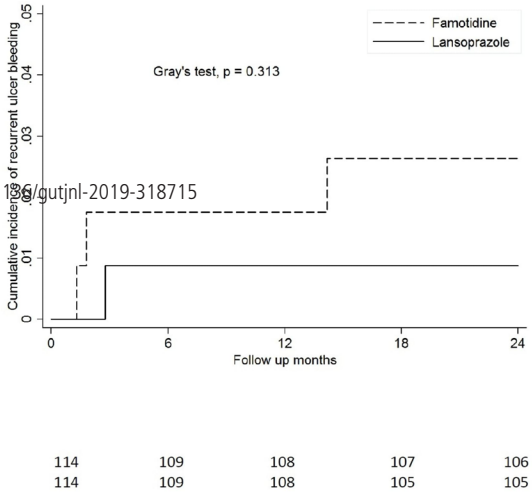

Figure 2 Time-to-outcome analysis of recurrent upper GI bleeding (adjustment for death as competing risk).

interim analysis was performed by an independent statistician in November 2017, blinded for the treatment allocation. The statistician reported the results to the independent DSMC. The DSMC had blinded access to all data and discussed the results of the interim analysis with the steering committee in a joint meeting. The steering committee decided to continue the trial after the interim analysis and reported the decision to the ethics committee. The Peto approach was used: the trial would be ended using symmetric stopping boundaries at $p<0.001$.[19] The trial would not be stopped in case of futility, unless the DSMC during the course of safety monitoring advised otherwise. In this case, the DSMC would discuss potential stopping for futility with the trial steering committee.[20] A blinded interim analysis of findings without revealing the allocation of study arms at 12 months was performed in November 2017 to ascertain safety.[18]

RESULTS

Between 24 June 2010 and 10 October 2016, we screened 374 consecutive patients who were diagnosed to have upper GI bleeding who underwent endoscopy within 24 hours of onset of bleeding and did not receive aspirin or NSAIDs and were negative for *H. pylori*.[11] We enrolled 228 of these patients for a study period of 24 months (114 were randomly assigned to receive lansoprazole and 114 to receive famotidine; figure 1). Baseline characteristics were similar between groups (table 1). The median follow-up was 24.0 months in both groups (range 0.3–24; IQR 24.0–24.0). Of the patients 105 (92.1%) in the lansoprazole arm and 96 (84.2%) in the famotidine arm took at least 70% of the assigned study drugs. The proportion of patients who discontinued treatment, excluding patients who reached the study endpoints, was similar in the two groups: 27 (23.7%) in the lansoprazole arm (9 (7.9%) because of adverse event, 10 (8.8%) withdrew consent and 8 (7.0%) died) and 26 (22.8%) in the famotidine arm (6 (5.3%) because of adverse event, 15 (13.2%) withdrew consent and 5 (4.4%) died). The adverse events leading to discontinuation of treatment in the lansoprazole arm and in the famotidine arm are listed in table 2. No patient who discontinued medication early had recurrent upper GI bleeding within the study period. Three patients in the lansoprazole arm took aspirin, while two patients in the famotidine arm took aspirin and warfarin, respectively.

Primary endpoint

Twenty cases with suspected GI bleeding were assessed by the adjudication committee. The committee identified four cases

Table 2 Adverse events leading to discontinuation of treatment

	Lansoprazole arm n=114	Famotidine arm n=114
Ischaemic heart disease warrants aspirin	2	1
Transient ischaemic attack warrants aspirin	1	0
Small vessel disease of the brain warrants aspirin	1	0
Calcified heart valve warrants warfarin	0	1
Atrial fibrillation warrants warfarin	1	0
Severe epigastric pain	0	1
Stomach cancer	0	1
Diverticulum bleeding	0	1
Rectosigmoid cancer	1	0
Chronic kidney disease	1	0
Clostridium difficile infection	1	0
Allergic reaction with facial oedema	0	1
Pregnancy	1	0

Table 3 Primary and secondary endpoints and other clinical events at 24 months

	Lansoprazole arm n=114	Famotidine arm n=114	P value*
Suspected GI bleeding	10 (8.8)	10 (8.8)	1.000
Primary endpoint			
Recurrent upper GI bleeding	1 (0.9)	3 (2.6)	0.313
Secondary endpoints			
Recurrent ulcer at end-of-study endoscopy	5 (4.4)	9 (7.9)	0.270
Other clinical events			
Recurrent lower GI bleeding	2 (1.7)	1 (0.9)	0.989
Death	8 (7.0)	5 (4.4)	0.392

*Survival analysis.
Data are numbers (percentage).

of recurrent upper GI bleeding: one in the lansoprazole arm (duodenal ulcer) and three in the famotidine arm (one gastric ulcer and two duodenal ulcers). All patients with recurrent upper GI bleeding presented with recurrent melaena, coffee-ground vomiting or a haemoglobin drop of more than 2 g/dL requiring hospital treatment. One of these patients, who was randomised to the famotidine arm, required endoscopic control of active bleeding and three needed blood transfusions. The median diameter of recurrent ulcers ranged from 0.5 cm to 1 cm. None of the patients with recurrent upper GI bleeding had *H. pylori* infection or used aspirin or NSAIDs.

The cumulative incidence of recurrent upper GI bleeding during the 24-month study in the intention-to-treat population was 0.88% (95% CI 0.08% to 4.37%) in the lansoprazole arm and 2.63% (95% CI 0.71% to 6.91%) in the famotidine arm (p=0.313; crude HR 0.33, 95% CI 0.03 to 3.16, p=0.336; figure 2 and table 3). In the modified intention-to-treat population (after excluding one patient randomised to the famotidine arm who did not receive any study drug), the cumulative incidence of recurrent upper GI bleeding was 0.88% (95% CI 0.08% to 4.37%) in the lansoprazole arm and 2.65% (95% CI 0.71% to 6.97%) in the famotidine arm (p=0.309; crude HR 0.33, 95% CI 0.03 to 3.13, p=0.333).

Secondary endpoint

Fourteen patients had recurrent ulcers detected by endoscopy at the end-of-study visit at 24 months; five were in the lansoprazole arm (two gastric ulcers, two duodenal ulcers, one coexisting gastric and duodenal ulcers) and nine were in the famotidine arm (six gastric ulcers and three duodenal ulcers, in which one patient with duodenal ulcers had positive rapid urease test for *H. pylori*). All these patients reported dyspepsia or epigastric pain during the study periods, yet none of these 14 patients reported symptoms of overt GI bleeding.

Sixteen patients fulfilled the criteria for GI bleeding but had negative findings on upper GI endoscopy: nine were in the lansoprazole arm (two had lower GI bleeding and seven had anaemia or suspected tarry stool not due to GI blood loss) and seven were in the famotidine arm (one had lower GI bleeding and six had anaemia or suspected not due to GI blood loss). The causes of lower GI bleeding in the lansoprazole arm were confirmed in two patients with colonoscopy: colonic diverticula (n=1) and cancer of the colon (n=1). The cause of lower GI bleeding in the famotidine arm was confirmed in only one patient with colonoscopy: colonic polyp and internal haemorrhoids (n=1). The causes of anaemia not due to GI blood loss in the lansoprazole arm were bone fracture (n=2), acute or chronic renal failure (n=2), menorrhagia (n=1) and unknown (n=2), and in the famotidine arm were haemoptysis (n=2), vitamin B_{12} deficiency (n=1), chronic renal failure (n=1) and unknown (n=2). The cumulative incidence of lower GI bleeding after 24 months was 1.75% in the lansoprazole arm and 0.88% in the famotidine arm.

Death

A total of thirteen patients died during the study period: eight were in the lansoprazole arm (two patients died from cardiac arrest with no cause identified, one from pneumonia, one from renal failure, one from sepsis, one from multiorgan failure, one from myocardial infarction and one from rectosigmoid cancer with liver metastasis) and five were in the famotidine arm (two patients died from pneumonia, one from renal failure, one from multiorgan failure and one from cardiac arrest with no cause identified). No GI bleeding-related deaths occurred.

DISCUSSION

We set out to test the hypothesis that PPI (lansoprazole) is superior to H2RA (famotidine) for the prevention of recurrent upper GI bleeding in patients with a history of *H. pylori*-negative idiopathic ulcer bleeding. Our results showed that there was no significant difference in recurrent upper GI bleeding between the two treatment arms (lansoprazole arm, 0.88%; famotidine arm, 2.63%; p=0.313). Therefore, our findings indicate that both treatments are comparable in preventing recurrent upper GI bleeding in these high-risk patients, although a small difference in efficacy cannot be excluded. These patients are at high risk of recurrent ulcer bleeding since a substantial proportion of patients had recurrent ulcer at end-of-study endoscopy despite receiving prophylactic acid suppressive therapy (4.4% in the lansoprazole arm; 7.9% in the famotidine arm). The rates of recurrent ulcer bleeding in the two treatment arms were 4.6–30 times lower than our previous reports on patients with a history of *H. pylori*-negative idiopathic ulcer bleeding who received none or irregular acid suppressive therapy.[10 12] Our findings address the major unmet need in the present guidelines[21 22] on the management of patients with a history of idiopathic ulcer bleeding. These patients have been largely neglected because none of the published studies sought to identify treatments to reduce the risk of life-threatening complications in these patients.

Our findings are supported by a recent systematic review with meta-analysis and trial sequential analysis involving 42 trials randomising 6899 patients admitted to intensive care unit. PPIs and/or H2RAs reduce the occurrence of any GI bleeding as compared with placebo/no prophylaxis (0.60, 95% CI 0.47 to 0.77).[23] On the other hand, there have been observations that such acid suppressive therapy might not reduce the risk of recurrent bleeding or mortality in patients with *H pylori*-negative idiopathic bleeding ulcers in real-world settings.[11] Such contradictory evidence may be partly explained by the inconsistent usage of acid suppressive therapy in real-world settings, compared with clinical trial setting. Potent acid suppression with PPI is recommended for patients who are at high risk for ulcer-related bleeding from NSAIDs.[14] Yet gastric atrophy and hypochlorhydria, instead of acid hypersecretion, are often observed in patients with *H pylori*-negative idiopathic ulcers.[12] This observation suggests acid suppressive therapy is useful, although incomplete protection, such that additional gastroprotective agents may have an extra benefit in preventing recurrent idiopathic ulcer bleeding.

The strengths of our study include the randomised, double-blind design that minimises bias in treatment assignment, selection bias and confounding, such that level I evidence is generated. The stringent definition of primary and secondary endpoints reinforces the robustness of our findings. From this RCT we found that acid suppression alone by either PPI or H2RA is not sufficient to completely abolish the risk of recurrent ulcer or GI bleeding. Additional mucoprotective agent would be warranted. One well-known mucoprotective agent is misoprostol, which is a synthetic prostaglandin E1, which prevents NSAID-induced peptic ulcers by inhibiting the secretion of gastric acid by G-protein coupled receptor-mediated inhibition of adenylate cyclase, which leads to decreased intracellular cyclic AMP levels and decreased proton pump activity at the apical surface of the gastric parietal cell.[24] There is an ongoing RCT now testing the hypothesis that a combination therapy of misoprostol and lansoprazole is superior to lansoprazole alone for the prevention of recurrent ulcer bleeding in patients with a history of idiopathic ulcer bleeding (ClinicalTrials.gov trial registration number NCT03675672).

Our study had limitations. First, the risk reduction achieved by PPI or H2RA could not be determined because we did not include a placebo group. It would be unethical to withhold a gastroprotective agent knowing that recurrent *H. pylori*-negative idiopathic ulcer bleeding may occur in up to 13.4% of patients per annum.[10] Second, we did observe a numerically higher incidence rate of primary endpoint in the famotidine arm compared with the lansoprazole arm (2.63% vs 0.88%); a multicentre study of a much larger sample size will be required to determine if there is a meaningful difference in therapeutic efficacy. Third, we acknowledge the limitations of our single-centre study design, although we found no evidence of ethnic or geographical variations in the risk of recurrent GI bleeding. Fourth, our study had a long recruitment period and possible confounders might have arisen during this time. Our randomised study design would have reduced the bias arisen from such confounders.

In conclusion, this 2-year, double-blind randomised trial showed that among patients with a history of *H. pylori*-negative idiopathic ulcer bleeding, recurrent bleeding rates were comparable between users of lansoprazole and famotidine, although a small difference in efficacy cannot be excluded. Our findings provide novel data towards future practice guidelines in the management of patients with a history of *H. pylori*-negative idiopathic bleeding ulcers.

Contributors GL-HL-HW, JYLC and FKLC were responsible for the conception, design of the study and the development of methodology. GL-HL-HW, LHSL, JYLC, RHYL, VW-SW, PWYC, JL and FKLC were responsible for patient care, data collection and analysis. GL-HL-HW, LHSL, JYLC, YKT and RHYL were responsible for data analysis. All authors were responsible for the interpretation of data, writing, review and final approval of the manuscript. All authors had access to the study data.

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Competing interests GL-HL-HW has served as a speaker for Abbott, AbbVie, Bristol-Myers Squibb, Echosens, Gilead and Janssen, and an advisory committee member for Gilead and Janssen. VW-SW has served as a speaker for AbbVie, Bristol-Myers Squibb, Roche, Novartis, Abbott Diagnostics and Echosens, and an advisory committee member for AbbVie, Roche, Novartis, Gilead and Otsuka. PWYC has served as a speaker for Olympus and an advisory committee member for EndoMASTER and Aptorum. JL has served as a speaker for Boston Scientific. FKLC has served as a consultant to Eisai, Pfizer, Takeda and Otsuka, and has been paid lecture fees by Eisai, Pfizer, AstraZeneca and Takeda.

Patient consent for publication Obtained.

Ethics approval The study was done in compliance with the principles of Good Clinical Practice and the Declaration of Helsinki. The local ethics committee approved the study protocol. All patients gave written informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Grace L H Wong http://orcid.org/0000-0002-2863-9389
Vincent W S Wong http://orcid.org/0000-0003-2215-9410
Philip W Y Chiu http://orcid.org/0000-0001-9292-112X
Francis K L Chan http://orcid.org/0000-0001-7388-2436

REFERENCES

1 McColl KE. Helicobacter pylori-negative nonsteroidal anti-inflammatory drug-negative ulcer. *Gastroenterol Clin North Am* 2009;38:353–61.
2 Jyotheeswaran S, Shah AN, Jin HO, *et al*. Prevalence of Helicobacter pylori in peptic ulcer patients in greater Rochester, NY: is empirical triple therapy justified? *Am J Gastroenterol* 1998;93:574–8.
3 Kurata JH, Nogawa AN. Meta-analysis of risk factors for peptic ulcer. Nonsteroidal antiinflammatory drugs, Helicobacter pylori, and smoking. *J Clin Gastroenterol* 1997;24:2–17.
4 Sprung DJ, Apter MN. What is the role of Helicobacter pylori in peptic ulcer and gastric cancer outside the big cities? *J Clin Gastroenterol* 1998;26:60–3.
5 Laine L, Hopkins RJ, Girardi LS. Has the impact of Helicobacter pylori therapy on ulcer recurrence in the United States been overstated? A meta-analysis of rigorously designed trials. *Am J Gastroenterol* 1998;93:1409–15.
6 Ciociola AA, McSorley DJ, Turner K, *et al*. Helicobacter pylori infection rates in duodenal ulcer patients in the United States may be lower than previously estimated. *Am J Gastroenterol* 1999;94:1834–40.
7 Nishikawa K, Sugiyama T, Kato M, *et al*. Non-Helicobacter pylori and non-NSAID peptic ulcer disease in the Japanese population. *Eur J Gastroenterol Hepatol* 2000;12:635–40.
8 Jang HJ, Choi MH, Shin WG, *et al*. Has peptic ulcer disease changed during the past ten years in Korea? A prospective multi-center study. *Dig Dis Sci* 2008;53:1527–31.
9 Chan HL, Wu JC, Chan FK, *et al*. Is non-Helicobacter pylori, non-NSAID peptic ulcer a common cause of upper GI bleeding? A prospective study of 977 patients. *Gastrointest Endosc* 2001;53:438–42.
10 Hung LC, Ching JY, Sung JJ, *et al*. Long-term outcome of Helicobacter pylori-negative idiopathic bleeding ulcers: a prospective cohort study. *Gastroenterology* 2005;128:1845–50.
11 Wong GL, Au KW, Lo AO, *et al*. Gastroprotective therapy does not improve outcomes of patients with Helicobacter pylori-negative idiopathic bleeding ulcers. *Clin Gastroenterol Hepatol* 2012;10:1124–9.
12 Wong GL, Wong VW, Chan Y, *et al*. High incidence of mortality and recurrent bleeding in patients with Helicobacter pylori-negative idiopathic bleeding ulcers. *Gastroenterology* 2009;137:525–31.
13 Bytzer P, Teglbjaerg PS. Danish Ulcer Study Group. Helicobacter pylori-negative duodenal ulcers: prevalence, clinical characteristics, and prognosis--results from a randomized trial with 2-year follow-up. *Am J Gastroenterol* 2001;96:1409–16.
14 Freedberg DE, Kim LS, Yang YX. The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association. *Gastroenterology* 2017;152:706–15.
15 Chan FK, Leung Ki EL, Wong GL, *et al*. Risks of Bleeding Recurrence and Cardiovascular Events With Continued Aspirin Use After Lower Gastrointestinal Hemorrhage. *Gastroenterology* 2016;151:271–7.
16 Julious SA, Owen RJ. Sample size calculations for clinical studies allowing for uncertainty about the variance. *Pharm Stat* 2006;5:29–37.
17 Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc* 1999;94:496–509.
18 Lau LH, Chan FK, Ching JY, *et al*. Mo1179 - Prevention of Recurrent Idiopathic Gastroduodenal Ulcer Bleeding: Year 1 Interim Analysis of a Double-Blind Randomized Trial (NRT Study). *Gastroenterology* 2018;154:S-697.
19 Peto R, Pike MC, Armitage P, *et al*. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 1976;34:585–612.
20 Bakker OJ, van Santvoort HC, van Brunschot S, *et al*. Pancreatitis, very early compared with normal start of enteral feeding (PYTHON trial): design and rationale of a randomised controlled multicenter trial. *Trials* 2011;12:73.
21 Chan FK, Abraham NS, Scheiman JM, *et al*. Management of patients on nonsteroidal anti-inflammatory drugs: a clinical practice recommendation from the First International Working Party on Gastrointestinal and Cardiovascular Effects of Nonsteroidal Anti-inflammatory Drugs and Anti-platelet Agents. *Am J Gastroenterol* 2008;103:2908–18.
22 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.
23 Barbateskovic M, Marker S, Granholm A, *et al*. Stress ulcer prophylaxis with proton pump inhibitors or histamin-2 receptor antagonists in adult intensive care patients: a systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med* 2019;45:143–58.
24 Medlock S, Eslami S, Askari M, *et al*. Co-prescription of gastroprotective agents and their efficacy in elderly patients taking nonsteroidal anti-inflammatory drugs: a systematic review of observational studies. *Clin Gastroenterol Hepatol* 2013;11:1259–69.