



Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a phase III, randomised, double-blind, placebo-controlled trial

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Summary

Background There are few therapeutic options for the prevention of gastrointestinal mucosal damage caused by low-dose aspirin. We therefore investigated the efficacy of famotidine, a well-tolerated histamine H₂-receptor antagonist, in the prevention of peptic ulcers and erosive oesophagitis in patients receiving low-dose aspirin for vascular protection.

Methods Adult patients (aged ≥18 years) from the cardiovascular, cerebrovascular, and diabetes clinics at Crosshouse Hospital, Kilmarnock, UK, were eligible for enrolment in this phase III, randomised, double-blind, placebo-controlled trial if they were taking aspirin 75–325 mg per day with or without other cardioprotective drugs. Patients without ulcers or erosive oesophagitis on endoscopy at baseline were randomly assigned by computer-generated randomisation sequence to receive famotidine 20 mg twice daily (n=204) or placebo twice daily (n=200). Patients had a final endoscopic examination at 12 weeks. The primary endpoint was the development of new ulcers in the stomach or duodenum or erosive oesophagitis at 12 weeks after randomisation. Analysis was by intention to treat, including all randomised patients who received at least one dose of study drug (famotidine or placebo). This trial is registered as an International Standard Randomised Clinical Trial, number ISRCTN96975557.

Findings All randomised patients received at least one dose and were included in the ITT population. 82 patients (famotidine, n=33; placebo, n=49) did not have the final endoscopic examination and were assumed to have had normal findings; the main reason for participant withdrawal was refusal to continue. At 12 weeks, comparing patients assigned to famotidine with patients assigned to placebo, gastric ulcers had developed in seven (3·4%) of 204 patients compared with 30 (15·0%) of 200 patients (odds ratio [OR] 0·20, 95% CI 0·09–0·47; p=0·0002); duodenal ulcers had developed in one (0·5%) patient compared with 17 (8·5%; OR 0·05, 0·01–0·40; p=0·0045); and erosive oesophagitis in nine (4·4%) compared with 38 (19·0%; OR 0·20, 0·09–0·42; p<0·0001), respectively. There were fewer adverse events in the famotidine group than in the placebo group (nine vs 15); four patients in the placebo group were admitted to hospital with upper gastrointestinal haemorrhage. The other most common adverse event was angina (famotidine, n=2; placebo, n=4).

Interpretation Famotidine is effective in the prevention of gastric and duodenal ulcers, and erosive oesophagitis in patients taking low-dose aspirin. These findings widen the therapeutic options for the prevention of gastrointestinal damage in patients needing vascular protection.

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Introduction

Low-dose aspirin (ie, 75–325 mg), is one of the most widely used drugs in the world. Increasingly, it is being bought over-the-counter or prescribed for its anti-thrombotic activity in cardiovascular and cerebrovascular diseases, and in diabetes mellitus.^{1–3} Despite the benefits of antithrombotic strategies, there has been a rise in the incidence of major upper gastrointestinal complications in patients taking aspirin, such as peptic ulcer bleeding, perforation, and sometimes death.^{4–6} The prevention of these side-effects has been hindered by two main factors: the scarcity of studies on gastrointestinal mucosal damage in patients with vascular disorders who require low-dose aspirin, and the few therapeutic options that are currently available. Proton-pump inhibitors are known to be effective in the treatment and prevention of ulcers

related to aspirin or non-steroidal anti-inflammatory drugs (NSAIDs),^{7,8} but there have been concerns about their costs,⁹ safety,^{10–12} and risk of interaction with clopidogrel, which is frequently prescribed concurrently with aspirin.^{13,14} Also, although studies have focused on peptic ulcers caused by NSAIDs,¹⁵ recent evidence suggests that erosive oesophagitis is frequently seen in patients taking low-dose aspirin for vascular protection.^{7,16}

Famotidine is a histamine H₂-receptor antagonist that has proved to be well tolerated and able to prevent and heal peptic ulcers in patients receiving conventional NSAIDs.^{17–19} The FAMOUS trial (Famotidine for the Prevention of Peptic Ulcers in Users of Low-dose Aspirin) was designed to assess the efficacy of this drug, at a standard dose of 20 mg twice daily, in the prevention of

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See [Comment](#) page 93

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gastric and duodenal ulcers, and erosive oesophagitis in patients receiving low-dose aspirin for vascular protection.

Methods

Participants

This phase III, randomised, double-blind, parallel-group, placebo-controlled trial recruited patients from the cardiovascular, cerebrovascular, and diabetes clinics at Crosshouse Hospital, Kilmarnock, UK (affiliated to the University of Glasgow, UK), who were receiving anti-thrombotic low-dose aspirin (75–325 mg daily).

Adult patients, aged 18 years or over, were eligible for enrolment if they had an indication for the antithrombotic effect of aspirin that was stable at the time of randomisation, such as angina, previous myocardial infarction (12 weeks or more before recruitment), cerebrovascular disease, diabetes, or peripheral vascular disease. Also, the use of aspirin had to be likely to continue for 12 weeks or longer, in the presence or absence of mild to moderate dyspeptic or reflux symptoms, or gastric or duodenal scars or erosions on endoscopy at baseline. Enrolled patients were allowed to continue to take other antiplatelet agents, such as clopidogrel and dipyridamole, and other treatments for their basic or coexisting medical conditions. Patients were excluded if they had current malignancy, or a history of oesophageal, gastric, or duodenal surgery, Zollinger-Ellison syndrome, or primary oesophageal motility disorder. Women of childbearing potential were required to maintain effective contraception—as judged by the investigator—during the study period, and excluded if they were pregnant or lactating. Patients were also excluded if they had contraindications to study drugs, if they used proton-pump inhibitors, H₂-receptor antagonists, or sucralfate within a week of the first endoscopy, or if they had ever been treated for *Helicobacter pylori*, since these treatments might interfere with the risk of ulcer development. The intake of the following agents also precluded patients from entering the trial: other investigational compounds, anticholinergic drugs, prostaglandin analogues, warfarin, high-dose steroids (more than 7.5 mg of prednisolone or its equivalent daily), cytotoxic drugs, NSAIDs, or bisphosphonates.

The recruitment was undertaken by a team of four researchers, who invited all eligible patients to consider participating in the trial. Patients who accepted the invitation had an endoscopic examination after a cooling-off period. The study protocol was approved by the local ethics committee, and written informed consent was obtained from all patients.

Endoscopic findings were recorded for the oesophagus, stomach, and duodenum. The definitions of ulcers, erosions, scars, Lanza scores, and oesophagitis,^{17–22} and method for *H pylori* detection are all detailed in webappendix p 1.

Patients were not randomised if they had any of the following endoscopic findings at baseline: malignancy,

erosive oesophagitis, oesophageal strictures, or gastric or duodenal ulcers.

To standardise the reporting criteria for the endoscopic findings, the two endoscopists (AST and CMcC) attended each other's endoscopic sessions before and regularly after the start of the trial.

The trial was managed by the National Health Service of Greater Glasgow and Clyde (UK) in line with the European Directive on Medical Research. The study was registered with the Medicines and Healthcare Products Regulatory Agency of the UK. The study and its data were controlled by an independent data and safety monitoring committee, who considered the safety aspects of the trial and decided on the interim analyses and their effect on the duration and future of the trial.

Randomisation and masking

Patients were randomly assigned by computer-generated randomisation sequence to receive one 20 mg tablet of famotidine (Pepcid, Merck, Hoddesdon, UK) twice daily or one placebo tablet twice daily. This sequence was generated by the Production Unit, Pharmacy Department, Western Infirmary, Glasgow, UK. The assignments of participants were concealed in sealed opaque envelopes and without knowledge of the next assignment in the sequence. The randomisation codes and numbers were kept at the Pharmacy Department, Western Infirmary, on behalf of the sponsors, and at the office of the Chief Pharmacist, Crosshouse Hospital, in case of emergencies related to the trial. The codes were broken by the independent data and safety monitoring committee at the time of statistical analyses without the involvement of the research team. The placebo tablets contained lactose and were identical in shape and taste to the famotidine tablets. Both the participants and those giving the interventions were masked to group assignment.

Procedures

Antacid tablets (magaldrate, alginate, and sodium bicarbonate mixture; Bisodol, Forest Laboratories, Bexley, Kent, UK) were provided for patients from both treatment groups for the relief of heartburn and dyspeptic symptoms. Endoscopic assessments were done at baseline and 12 weeks, and clinical assessments were done at baseline, 6 weeks, and 12 weeks after randomisation. The procedures for these assessments are detailed in webappendix pp 1–2.

Comorbid conditions were recorded by calculating the Charlson index (scale 1–6) for each patient.^{6,23} Three levels of comorbidity were defined according to this index: low (0 points), medium (1–2) and high (3 or more).

The primary endpoint was the development of new ulcers (size ≥ 3 mm) in the stomach or duodenum or erosive oesophagitis at 12 weeks after randomisation. The secondary endpoints included the Lanza scores for gastric and duodenal erosions, abdominal and vascular symptoms scores, overall treatment assessment, and

antacid consumption. Premature exit from the trial for any reason and adverse events were recorded as part of the safety analysis.

Statistical analysis

In a 12-week study on low-dose aspirin, Laine and colleagues²⁴ based their sample size calculations on the assumption of an aspirin-related peptic ulcer rate of 10%. They reported that in patients with osteoarthritis who were taking aspirin, 12-week ulcer rates were 7% in all aspirin users, 13% in those with baseline erosions, and 27% in those with previous history of ulcers or their complications.

We planned to study the rate of ulcer formation in patients taking low-dose aspirin for vascular protection in the presence or absence of dyspeptic symptoms, previous history of ulcers, *H pylori* infection, gastric scars or erosions, or duodenal scars or erosions. We assumed that mucosal scars represented an objective evidence of previous peptic ulcers. By contrast with the patients with osteoarthritis who were in fairly good health, erosive or ulcerative lesions were found in about 48% of patients taking low-dose aspirin for vascular protection.²⁵ We also previously found that erosive oesophagitis was present in 27% of patients taking low-dose aspirin and presenting with upper gastrointestinal bleeding.¹⁶ Yeomans and colleagues⁷ reported that oesophagitis developed in 18% of non-bleeding patients on low-dose aspirin. In the current study, and taking these previously reported ulcer rates and hypotheses into account, we assumed that peptic ulcers or oesophagitis, or both, would develop in 13% of patients in our trial. To show a halving of this rate to 6.5% in the active group compared with placebo, with 80% power and at a 5% significance level, we calculated that a sample size of 700 patients would be needed (350 in each group).

Three interim analyses were planned, with the first scheduled after the randomisation of the first 200 patients. However, we later decided to carry out an interim analysis after 100 patients had been recruited because of safety factors: comorbidity of volunteers, cardiac deaths, and admissions with severe chest pain were all higher than expected, and there was a higher overall ulcer rate than originally predicted.

The interim analyses included formal statistical comparisons between treatment groups for the outcome measures. Additional factors in relation to the review of safety data were also taken into account. For consideration of early termination of the trial because of overwhelming evidence of benefit with respect to the primary endpoint, we used the method of Lan and DeMets²⁶ with the modified O'Brien and Fleming²⁷ alpha spending function. After approximately 300 patients had been recruited, a nominal value of $p < 0.00107$ was needed before early termination would be considered. On the basis of the third analysis, the independent data and safety monitoring committee recommended that no further patients should be recruited and that the study should be stopped once

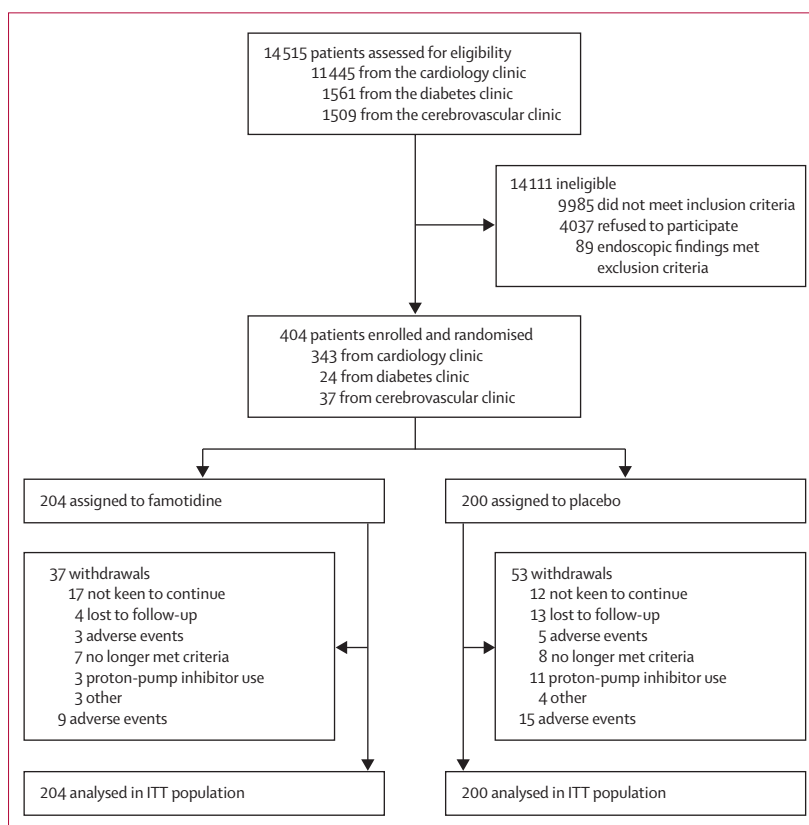


Figure 1: Trial profile

ITT=intention-to-treat.

the remaining and already randomised patients had completed follow-up.

Data were summarised as categorical (the numbers and proportions of patients in each category), and continuous variables (mean, median, SD, minimum, and maximum values). For the analysis of the primary outcome, frequencies, proportions, and totals are presented. The odds ratios (ORs) and 95% CIs for famotidine versus placebo were calculated by logistic regression without adjustment for other covariates. The proportional odds model and 95% CIs were used to compare the grades of oesophagitis in the famotidine and placebo groups at the completion of the trial. *p* values for the primary analysis were calculated by use of logistic regression and the Wald test. For the analysis of secondary outcomes, categorical variables and the percentage of patients were compared between treatment groups by use of logistic regression. For rank variables (Lanza scores, cardiovascular and gastrointestinal symptoms), the effect of famotidine was estimated by use of the non-parametric Wilcoxon's rank sum test. Analysis was by intention to treat (ITT) and per protocol (PP). The intention-to-treat population included all randomised patients who received at least one dose of study drug (famotidine or placebo). Patients who did not have the final endoscopic examination were assumed to have had

	Famotidine (n=204)	Placebo (n=200)
Age (years)	63 (36–86)	63 (37–86)
Male sex	138 (67.6%)	139 (69.5%)
Duration of aspirin use (years)	3 (0–24)	3 (0–33)
Aspirin dose		
75 mg per day	198 (97.1%)	184 (92.0%)
150 mg per day	4 (2.0%)	14 (7.0%)
300 mg per day	2 (1.0%)	2 (1.0%)
Current smoker	42 (20.6%)	51 (25.5%)
Alcohol consumption	143 (70.1%)	137 (68.5%)
Cardiovascular conditions		
Angina	71 (34.8%)	62 (31.0%)
Hypertension	64 (31.4%)	36 (18.0%)
Myocardial infarction	39 (19.1%)	32 (16.0%)
Atrial fibrillation	15 (7.4%)	12 (6.0%)
Heart failure	11 (5.4%)	11 (5.5%)
Valve disease	4 (2.0%)	7 (3.5%)
Diabetes mellitus	38 (18.6%)	46 (23.0%)
Cerebrovascular disease	33 (16.2%)	34 (17.0%)
Comorbidity score*		
Low (0)	83 (40.7%)	73 (36.5%)
Medium (1–2)	100 (49.0%)	101 (50.5%)
High (3 or more)	21 (10.3%)	26 (13.0%)
Concurrently prescribed drugs		
Clopidogrel	38 (18.6%)	32 (16.0%)
Dipyridamole	12 (5.9%)	11 (5.5%)
Clopidogrel plus dipyridamole	2 (1.0%)	1 (0.5%)
β blockers	126 (61.8%)	100 (50.0%)
ACE inhibitors	110 (53.9%)	99 (49.5%)
Nitrates	85 (41.7%)	77 (38.5%)
Diuretics	68 (33.3%)	55 (27.5%)
Other drugs	194 (95.1%)	190 (95.0%)
Heartburn	65 (31.9%)	56 (28.0%)
Epigastric pain	41 (20.1%)	32 (16.0%)
Mucosal scarring		
Gastric	40 (19.6%)	36 (18.0%)
Duodenal	50 (24.5%)	36 (18.0%)
Both	18 (8.8%)	22 (11.0%)
Mucosal erosions		
Gastric	60 (29.4%)	57 (28.5%)
Duodenal	28 (13.7%)	14 (7.0%)
Both	30 (14.7%)	26 (13.0%)
<i>Helicobacter pylori</i> infection	58 (28.4%)	71 (35.5%)

Data are n (%) or median (range). ACE=angiotensin-converting enzyme.
*Recorded by use of the Charlson index (scale 1–6).^{6,23}

Table 1: Baseline characteristics of study participants

normal findings. The PP population included all those in the ITT population who took more than 80% of the study drugs, did not take NSAIDs or other anti-ulcer drugs (with the exception of antacids), and who underwent the final endoscopic examination. Statistical analyses were done with SAS version 9.1 and carried out and validated, independent of the investigators, at the Robertson Centre

for Biostatistics, University of Glasgow. This trial is registered as an International Standard Randomised Clinical Trial, number ISRCTN96975557.

Role of the funding source

This was an investigator-initiated trial. Neither Merck Laboratories nor Astellas Pharma had any input or influence on the study design, data collection, data analysis, data interpretation, or writing of the report, or the decision to submit the article for publication. The sponsors' support was totally unrestricted. However, copies of the protocol and the manuscript were forwarded to them for their records. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. All 404 randomised patients received at least one dose and were included in the ITT population. 82 patients (famotidine, n=33; placebo, n=49) did not have the final endoscopic examination and were assumed to have had normal findings. Table 1 shows the baseline characteristics of all study participants. 277 (68.6%) patients were men, and the median age was 63 years. Although only a few patients had gastrointestinal symptoms at baseline (famotidine, n=100; placebo, n=83), a substantial proportion had scars (famotidine, n=108 [52.9%]; placebo, n=94 [47.0%]) or erosions (famotidine, n=118 [57.8%]; placebo, n=97 [48.5%]) in the gastroduodenal mucosa. Also, most patients (famotidine, n=121 [59.3%]; placebo, n=127 [63.5%]) had other medical conditions, reflected by their medium and high comorbidity scores.

Table 2 and figure 2 show the number of patients with gastric and duodenal ulcers, and erosive oesophagitis at 12 weeks. All but one duodenal ulcer in the famotidine group and two gastric ulcers in the placebo group were 5 mm or more. The proportion of patients who developed peptic ulcers of any size or erosive oesophagitis, or both, was lower in the famotidine group than in the placebo group (5.4% vs 32.5%; OR 0.12, 95% CI 0.06–0.23; p<0.0001; table 2).

A subgroup analysis in patients who developed peptic ulcers showed that *H pylori* infection was present in 16 (42.1%) of 38 patients in the placebo group and in none of eight in the famotidine group.

The grades of erosive oesophagitis are shown in figure 2. The famotidine group had more patients with grade 0, or normal oesophagus (OR 0.20, 0.09–0.42; p<0.0001), and fewer patients with other grades of oesophagitis than did the placebo group.

Multiple lesions (combinations of erosive oesophagitis, gastric ulcers, or duodenal ulcers) were present in five (2.5%) patients assigned to famotidine and in 17 (8.5%) patients assigned to placebo (webappendix p 2). The distribution of the primary endoscopic endpoints by age-group is shown in webappendix p 3.

322 patients underwent the final endoscopic assessment at 12 weeks. At this assessment, the famotidine group had more patients with a Lanza score of 0 (ie, no erosions or ulcers) in the stomach (110 [64.3%] of 171 vs 40 [26.5%] of 151; $p < 0.0001$) and in the duodenum (155 [90.6%] of 171 vs 93 [62.0%] of 150; $p < 0.0001$) than did the control group. 165 (95.9%) of 172 patients assigned to famotidine did not have dysphagia compared with 131 (89.1%) of 147 assigned to placebo ($p = 0.019$). At 12 weeks, patients were invited to provide their overall treatment assessment of the trial, graded as better, the same, or worse than their assessment at baseline. A better assessment was reported by 40 (23.5%) of 170 patients in the famotidine group compared with 21 (14.6%) of 144 in the placebo group ($p = 0.012$).

We investigated the effects of several factors on the risk of development of new ulcers in the stomach or duodenum or of erosive oesophagitis. Patients taking β blockers had a higher risk of these lesions: they were found in 54 (23.9%) of 226 patients taking β blockers compared with 24 (13.5%) of 178 patients not taking these agents (OR 2.57, 1.43–4.62; $p = 0.0017$ [multivariate analysis after adjustment for treatment with famotidine]). The presence of all other concurrently prescribed drugs did not affect risk of lesion development. Baseline endoscopic abnormalities in the stomach or duodenum (ie, scars or erosions), were also associated with a higher risk of development of ulcers or erosive oesophagitis. These lesions developed in 70 (20.6%) of 339 patients who had scars or erosions at baseline compared with eight (12.3%) of 65 who did not (OR 12.27, 1.63–92.63; $p = 0.0015$ [multivariate analysis, after adjustment for treatment with famotidine]).

More details of the secondary analyses are shown in webappendix p 3. The results of the PP analysis for the primary endpoint were consistent with those of the ITT analysis (webappendix p 4).

The reasons for withdrawal are shown in figure 1 and the details of adverse events are shown in table 3. Although there were no significant differences between the two groups, patients assigned to placebo were more likely to dropout (placebo $n = 25$ vs famotidine $n = 21$) and to have used proton-pump inhibitors ($n = 11$ vs $n = 3$) than were patients assigned to famotidine. Fewer adverse events were reported in the famotidine group ($n = 9$) than in controls ($n = 15$). All adverse events were judged not related to study drug. Four patients from the placebo group developed upper gastrointestinal haemorrhage and were admitted to hospital. Two of these patients needed blood transfusion, three were on β blockers, and one was on clopidogrel in addition to aspirin. More details on these four patients are provided in webappendix p 4.

We tested for an interaction between famotidine and clopidogrel. We found that adverse events were not increased by taking the two agents together compared with taking only one (ie, famotidine alone or placebo plus clopidogrel). Five (55.6%) of the nine patients with

	Famotidine (n=204)	Placebo (n=200)	Odds ratio (95% CI)	p value
Gastric ulcer*	7 (3.4%)	30 (15.0%)	0.20 (0.09–0.47)	0.0002
Duodenal ulcer*	1 (0.5%)	17 (8.5%)	0.05 (0.01–0.40)	0.0045
Erosive oesophagitis†	9 (4.4%)	38 (19.0%)	0.20 (0.09–0.42)	<0.0001
Erosive oesophagitis and/or ulcer	12 (5.9%)	66 (33.0%)	0.13 (0.07–0.24)	<0.0001
Gastric ulcer >5 mm	7 (3.4%)	28 (14.0%)	0.22 (0.09–0.51)	0.0005
Duodenal ulcer >5 mm	0	17 (8.5%)	n/a	n/a
Erosive oesophagitis and/or ulcer >5 mm	11 (5.4%)	65 (32.5%)	0.12 (0.06–0.23)	<0.0001

Data are n (%). n/a=not applicable. *An ulcer was defined as an excavated and deep mucosal lesion measuring 3 mm or more in diameter. †Grades of erosive oesophagitis are shown in figure 2 and defined in webappendix p 1.

Table 2: Patients with endoscopic lesions at 12 weeks

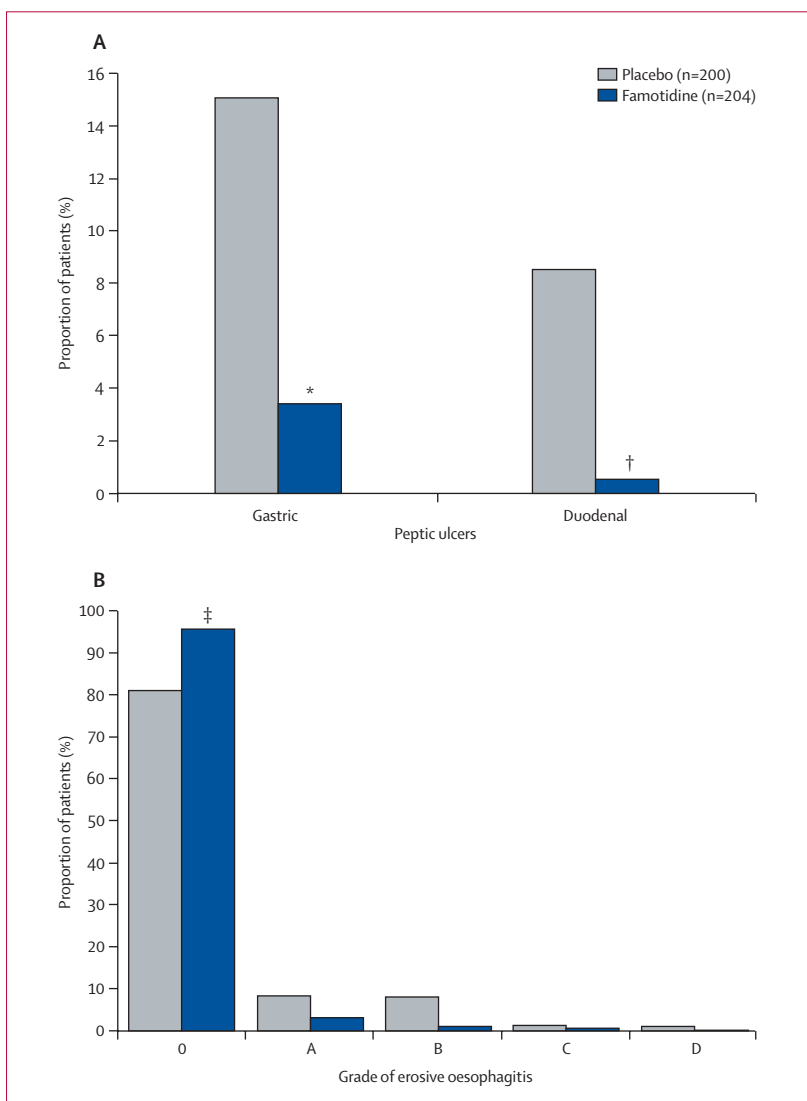


Figure 2: Primary endoscopic endpoints at 12 weeks

(A) Peptic ulcers. Compared with placebo, patients taking famotidine had significantly fewer cases of gastric (* $p = 0.0002$), or duodenal ulcers († $p = 0.0045$) measuring 3 mm or more in diameter. (B) Grades of erosive oesophagitis. There were fewer cases of erosive oesophagitis and more patients with grade 0 or normal oesophagitis (‡ $p < 0.0001$) in the famotidine group than in the placebo group. For definition of grades see webappendix p 1.

	Famotidine (n=204)	Placebo (n=200)
Angina pectoris	2 (1.0%)	4 (2.0%)
Atrial fibrillation	1 (0.5%)	0
Cardiac failure*	0	1 (0.5%)
Myocardial infarction*	1 (0.5%)	1 (0.5%)
Upper gastrointestinal haemorrhage	0	4 (2.0%)
Fallopian tube abscess	0	1 (0.5%)
Injury (fall)	1 (0.5%)	0
Colonic polyp	1 (0.5%)	0
Metastases to lung	0	1 (0.5%)
Cerebrovascular accident	1 (0.5%)	0
Depression	0	1 (0.5%)
Emphysematous bulla	0	1 (0.5%)
Atrial septal defect repair	1 (0.5%)	1 (0.5%)
Coronary angioplasty	1 (0.5%)	0
Total	9 (4.4%)	15 (7.5%)

Data are n (%). No patient had more than one event. *The patient with cardiac failure and the two patients with myocardial infarction died.

Table 3: Adverse events

adverse events in the famotidine group were on clopidogrel, compared with six (40.0%) of 15 in the placebo group (OR 0.90, 0.58–1.40; $p=0.6412$). Also, no increase in cardiac events was reported in patients assigned to famotidine (table 3).

Discussion

This study shows that famotidine is effective for the prevention of peptic ulcers and erosive oesophagitis in patients taking low-dose aspirin. The risk of developing these lesions is increased in patients treated concurrently with β blockers and in those with gastrointestinal mucosal scarring or erosions at baseline.

Although our main aim was to investigate the effects of famotidine on the development of peptic ulcers and erosive oesophagitis, it is still important to compare the ulcer rates found in this study with those of previous studies, while being aware that such rates will vary according to the characteristics of the populations studied. The rate of ulcers in our study population (11.4%) is higher than the rates in some recently reported trials (5.4%⁷ and 7.0%²⁴), but a clearer view emerges when the individual study populations are considered.

Since most of the patients in our trial had erosions or scars at baseline, our findings can be compared with ulcer rates reported by Laine and colleagues²⁴ in patients with osteoarthritis (ie, 13% in those with baseline erosions, and 27% in those with previous history of ulcers or their complications).²⁴ When the clinical indication for the use of aspirin is considered, erosive or ulcerative lesions were found in about 48% of patients taking low-dose aspirin for vascular protection.²⁵ The important effect of study population on ulcer rates in users of low-dose aspirin has

been highlighted in a recent multicentre trial by Yeomans and co-workers:⁷ such rates ranged from 0% to 15% among the participating centres, probably reflecting the doses of aspirin used, presence or absence of *H pylori*, and inter-observer variation in reporting the endoscopic findings.⁷ In our trial, we deemed the presence of scars as indicative of healed or previous history of ulcers. In addition to enrolling patients with scars and erosions, which are known to increase the risk of ulcers,^{15,24} we also took into account the possible affect of drugs concurrently prescribed with aspirin. In particular, we found that β blockers act as an independent factor in increasing the risk of erosive or ulcerative lesions in patients on aspirin, which might suggest a role for mucosal ischaemia in patients taking aspirin with already compromised circulation. However, our analysis of concurrently prescribed drugs was exploratory in nature and might represent a chance finding.

Our work differs from other similar studies because it was a single-centre trial, which kept inter-observer variation to a minimum. One cannot exclude the possibility that compliance with aspirin intake improved in the study population because of the emphasis by the research team and the study literature on the importance of taking study drugs as well as other concurrently prescribed agents (including aspirin). Such an improvement might have contributed to more ulcer formation related to aspirin. It is also possible that patients who were at a greater risk of ulceration were more likely to participate in the study. However, these factors do not affect our main findings or conclusions with respect to the efficacy of famotidine.

We have shown that famotidine is capable of preventing oesophagitis in patients taking low-dose aspirin. We previously identified the disorder in 27% of patients taking aspirin who presented with upper gastrointestinal bleeding.¹⁶ The frequency of oesophagitis in the placebo group in this study (19%) is similar to that described by Yeomans and colleagues⁷ in non-bleeding patients taking aspirin (ie, 18%).⁷ Not unlike peptic ulcers, oesophagitis could be related to interference with mucosal prostaglandins by aspirin, or greater vulnerability to acid, hence the beneficial effect of famotidine.^{16,28}

Gastrointestinal mucosal damage related to low-dose aspirin (similarly to damage associated with NSAIDs) is frequently asymptomatic.^{7,16} Only a small proportion of patients had upper abdominal complaints at enrolment, which reflects their random inclusion. The individual symptoms scores did not change by the end of the study. However, patients assigned to famotidine were less likely to complain of dysphagia and their overall treatment assessment was better than those assigned to placebo. Also, more patients in the placebo group dropped out because of the use of proton-pump inhibitors than did patients assigned to famotidine.

Although this trial was not powered to study serious ulcer complications, it is noteworthy that all patients

presenting with upper gastrointestinal bleeding were in the placebo group. Ulcer complications, such as bleeding, generally depend on the size and depth of mucosal damage. Besides its ulcerogenic effect, aspirin brings the added risk of its antiplatelet activity, which might aggravate the bleeding potential of gastrointestinal mucosal damage. We found no evidence of an interaction between famotidine and clopidogrel. This could be because of the fairly small size of our trial, or the fact that the metabolism of famotidine plus clopidogrel differs from that of proton-pump inhibitors plus clopidogrel.^{13,14}

Despite their proven efficacy against NSAID-related and aspirin-related ulcers,^{7,8} concerns continue to be expressed about the overprescribing⁹ and long-term use of proton-pump inhibitors,¹⁰⁻¹⁴ and alternative management strategies have been proposed, including the use of H₂-receptor antagonists.²⁹ Thus, famotidine might be a useful alternative for proton-pump inhibitors in patients taking low-dose aspirin.

Contributors

AST wrote the protocol and the draft manuscript. AST and CMcC undertook the endoscopic assessments. RP helped with the clinical assessments. VB helped with the interpretation of the statistical results. All authors have seen and approved the final version of the report.

Conflicts of interest

AST previously received research grants and travel expenses from Astellas, AstraZeneca, Merck Laboratories, and Yamanouchi. AST also sat on advisory panels for Ferring and Shire Pharmaceutical. All other authors declare that they have no conflicts of interest.

Acknowledgments

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