Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial

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Summary

Background **Guidelines on pain management recommend that patients at risk of ulcers receive either a cyclo-oxygenase (COX 2) inhibitor or a non-steroidal anti-inflammatory drug (NSAID) with a proton-pump inhibitor (PPI). These two treatments have similar effectiveness, but they are insufficient for protection of patients at very high risk for ulcer bleeding. We aimed to test the hypothesis that in patients with previous ulcer bleeding induced by non-selective NSAIDs, combined treatment with the COX 2 inhibitor celecoxib and the PPI esomeprazole would be better than celecoxib alone for prevention of recurrent ulcer bleeding.**

Methods **441 consecutively presenting patients who were taking non-selective NSAIDs for arthritis were recruited to our single-centre, prospective, randomised, double-blind trial after admission to hospital with upper-gastrointestinal bleeding. Patients were enrolled after their ulcers had healed and a histological test for *Helicobacter pylori* was negative. All patients were given 200 mg celecoxib twice daily. 137 patients were randomly assigned to receive 20 mg esomeprazole twice daily (combined-treatment group), and 136 to receive a placebo (control group) for 12 months. The primary endpoint was recurrent ulcer bleeding during treatment or within 1 month of the end of treatment. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00365313.**

Findings **Combination treatment was more effective than celecoxib alone for prevention of ulcer bleeding in patients at high risk. The 13-month cumulative incidence of the primary endpoint was 0% in the combined-treatment group and 12 (8·9%) in the controls (95% CI difference, 4·1 to 13·7; p=0·0004). The median follow-up was 13 months (range 0·4–13·0). Discontinuation of treatment and the incidence of adverse events were similar in the two treatment groups.**

Interpretation **Patients at very high risk for recurrent ulcer bleeding who need anti-inflammatory analgesics should receive combination treatment with a COX 2 inhibitor and a PPI. Our findings should encourage guideline committees to review their recommendations for patients at very high risk of recurrent ulcer bleeding.**

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) can induce ulcer complications such as bleeding and perforation that remain an important cause of hospital admissions and death worldwide. NSAIDs are thought to cause at least 7000 deaths every year in the USA[1] and 1000 deaths every year in the UK in those aged 60 years or older.[2] Patients with a history of ulcer bleeding are at the highest risk of NSAID-induced ulcer complications.[3] We previously reported that about 19% of patients with a history of ulcer bleeding who took the NSAID naproxen developed recurrent bleeding within 6 months.[4] Prophylaxis with a proton-pump inhibitor (PPI)[4–6] or substitution of NSAIDs with a selective inhibitor of cyclo-oxygenase-2 (COX 2)[7–9] reduces the risk of ulcer complications. The American College of Rheumatology guidelines for the management of osteoarthritis and an international working group on pain management recommend use of COX 2 inhibitors or the combination of NSAIDs and a PPI in patients at risk of ulcers whose symptoms cannot be relieved by simple analgesics.[10,11]

However, emerging data suggest that these recommendations do not adequately protect patients at very high risk of gastrointestinal problems. In a randomised trial of patients who had had previous NSAID-induced ulcer bleeding, the COX 2 inhibitor celecoxib was shown to be as effective as a combination of the NSAID diclofenac and the PPI omeprazole for prevention of recurrent ulcer bleeding.[12] However, about 5% of patients in either treatment group still had recurrent bleeding within 6 months.[12] The rate of recurrent endoscopic or complicated ulcers was unacceptably high with either treatment in patients with previous ulcer bleeding; one study reported that the 6-month incidence of recurrent endoscopic ulcers was 18·7% with a COX 2 inhibitor and 25·6% with NSAIDs and a PPI.[13] In another study, the 6-month incidence of recurrent complicated ulcers was 3·7% with celecoxib and 6·3% with NSAIDs and a PPI.[14] Thus, neither a COX 2

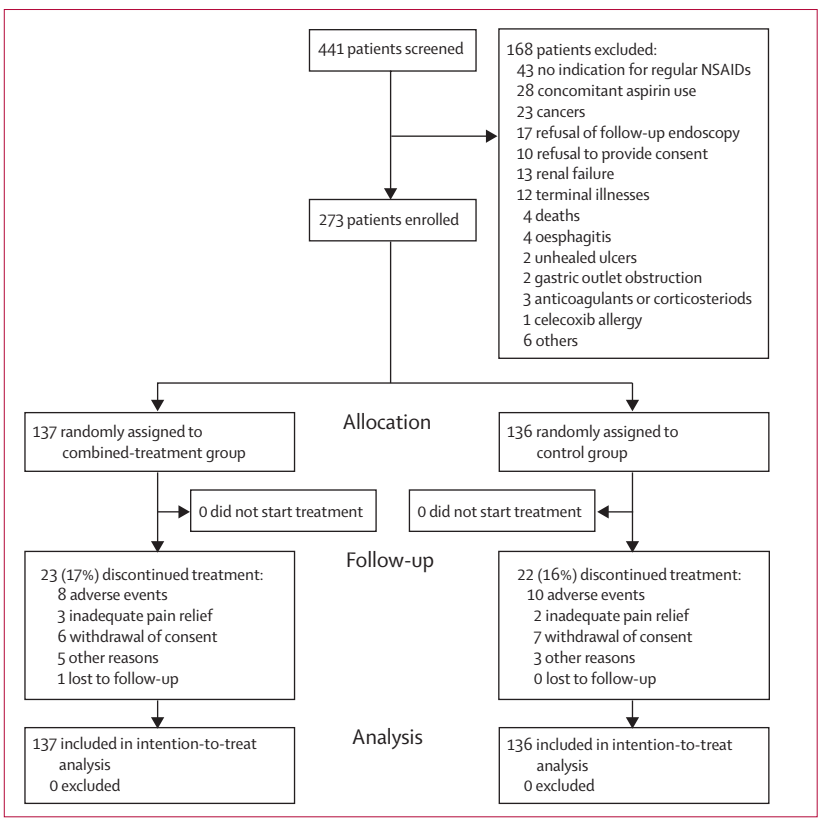

Figure 1: **Trial profile**

inhibitor nor non-selective NSAIDs plus a PPI seem to be effective when used as a stand-alone strategy in patients at very high gastrointestinal risk.[15,16]

Might a COX 2 inhibitor combined with a PPI provide the best protection in patients at very high gastrointestinal risk?[17,18] A 6-month endoscopic study showed that PPIs reduced the rate of ulcers in long-term users of NSAIDs, including a subgroup of patients given COX 2 inhibitors.[19] However, that study was not randomised and was not powered to assess whether a COX 2 inhibitor with a PPI provided greater gastrointestinal protection than a non-selective NSAID with a PPI. No randomised gastrointestinal outcome trials have yet been designed to assess the benefit of combined treatment with a COX 2 inhibitor and a PPI. We aimed to test the hypothesis that combined treatment with celecoxib and esomeprazole would be better than celecoxib alone for prevention of recurrent ulcer bleeding in patients with previous NSAID-induced ulcer bleeding who continued to need anti-inflammatory analgesics.

Methods

Patients

Our single-centre, prospective, randomised, double-blind trial was based at the Prince of Wales Hospital in Hong Kong. The hospital's ethics committee approved the protocol. All patients gave written informed consent. We screened 441 patients who presented consecutively to the hospital with upper-gastrointestinal bleeding and were taking non-selective NSAIDs for arthritis. Endoscopy was used to confirm ulcer bleeding. Patients with *Helicobacter pylori* infection were given 1 week of a PPI-based triple treatment. All patients discontinued NSAIDs and received an 8-week course of PPI to promote ulcer healing. Patients were eligible for inclusion if their ulcers were shown to be healed by follow-up endoscopy after the course of PPIs, if they had a negative histological test for *H pylori*, and if regular use of NSAIDs was indicated for the duration of the trial. Those who had persistent ulcers received another 8-week course of PPI, after which they were eligible if endoscopy confirmed that their ulcers were healed. Exclusion criteria were unhealed ulcers, concomitant use of low-dose aspirin, anticoagulants, or corticosteroids before the index bleeding; previous gastric or duodenal surgery other than a patch repair; allergy to celecoxib; or erosive oesophagitis, gastric outlet obstruction, terminal illness, cancer, or renal failure (defined as serum creatinine of more than 200 µmol/L).

Procedures

All eligible patients received 200 mg celecoxib (Pfizer, New York) twice daily. They were randomly assigned to receive either 20 mg esomeprazole (AstraZeneca, Mölndal) twice daily (combined-treatment group) or a placebo twice daily (control group) for 12 months. A computer-generated randomisation schedule, with permuted blocks of ten, was used to assign patients to the treatment sequences. Randomisation was stratified for gastric and non-gastric ulcers. Treatment allocation was masked by repackaging of esomeprazole and its dummy as green capsules with identical appearance, according to international good manufacturing practice guidelines for pharmaceuticals. To ensure concealment of allocation, an independent team member dispensed consecutively numbered, identically designed treatment packs that contained sealed bottles of the study drugs.

Patients were contacted by telephone after 1 month, and returned to the hospital after 2, 4, 6, 8, 10, 12, and 13 months. At each visit, we assessed haemoglobin concentrations, biochemical values, compliance with drug regimens, and the efficacy and safety of the treatment. Drug compliance was assessed by pill counts. Patients were permitted to take antacids, paracetamol, non-NSAID analgesics, and disease-modifying anti-rheumatic drugs. Assessment of treatment efficacy included the patients' global assessments of disease activity and arthritis pain, as previously described.[5] Assessment of safety was based on physical examination, laboratory tests, and observation or reports of adverse events. A direct telephone line was provided so that patients could report any serious adverse events between scheduled visits. Patients who discontinued the study drugs before the study ended were followed up until month 13, to establish the occurrence of any gastrointestinal events.

The primary endpoint was recurrent ulcer bleeding, defined as haematemesis or melaena with ulcers or bleeding erosions confirmed by endoscopy, or a decrease in haemoglobin of at least 20 g/L in the presence of endoscopically proven ulcers or erosions. An ulcer was defined as a circumscribed mucosal break that was at least 0·5 cm in diameter and had a perceptible depth, and a bleeding erosion was defined as a flat mucosal break of any size in the presence of blood in the stomach. We did endoscopy if haematemesis or melaena was confirmed by the admitting medical officer, or if there was a prespecified decrease in haemoglobin without other explanations for the anaemia. Lower-gastrointestinal bleeding was defined by either melaena or rectal bleeding causing hospital admission or transfusion, with negative results on upper endoscopy, or by a decrease in haemoglobin of at least 20 g/L in association with a positive test for faecal occult blood and negative results on upper endoscopy. Only events that were verified by an independent, masked adjudication committee, and that happened during treatment or within 1 month after the discontinuation of treatment, were included in the analysis. The secondary endpoint was the efficacy of treatments for arthritis.

Statistical analysis

We assumed that 10% of high-risk patients given celecoxib would develop recurrent ulcer bleeding in 13 months.[5] We specified that combined treatment with celecoxib and esomeprazole would be regarded as effective if it could reduce the risk of ulcer bleeding to average (between 1% and 2% per year[20]). To achieve a relative-risk reduction of 85%, with 80% power at 5% significance, by a two-sided log-rank test, we calculated we would need a sample size of 244 (122 patients in each group). However, on the assumption that we would be able to assess only 90% of patients, we planned to recruit 270 patients.

We used the Kaplan-Meier method to estimate the likelihood of the primary endpoint within 13 months in the intention-to-treat population (defined as all patients who had taken at least one dose of study medication). We used the log-rank test to compare time-to-event curves in the two groups. Failure to take at least 70% of the study drugs or use of prohibited drugs was regarded as non-compliance with the protocol. All p values and 95% CIs were two-sided. The per-protocol analysis included all patients who had taken at least 70% of the study drugs and who had not used low-dose aspirin, NSAIDs, another PPI, misoprostol, histamine-receptor antagonists, or sucralfate during the trial period. We did not incorporate the effects of permuted blocks in data analysis, since the estimated intrablock correlation coefficient was –0·065.[21]

We analysed prespecified secondary efficacy variables by repeated-measures ANOVA, with time as the within-participant factor, and treatment as the between-participant factor, to test for any difference in time or group. The term for the interaction between group and time was also inspected to assess whether changes over time were the same in the two treatment groups. We analysed data with SPSS software (version 10·0). We averaged efficacy endpoints across visits, and imputed missing results with a last-observation-carried-forward approach.[12] The analysis was repeated, with missing values removed from the dataset. We used Mauchly's test to verify the assumption of sphericity, and the Huynh-Feldt test to measure the change in patients' global assessment of disease activity score and arthritis pain if the assumption of sphericity was violated. This trial is registered with ClinicalTrials.gov, number NCT00365313.

Role of the funding source

The funding organisation had no role in study design, execution, data analysis, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Between August, 2002, and August, 2004, we screened 441 patients who had ulcer bleeding while taking non-selective NSAIDs. 273 patients were eligible for the intention-to-treat analysis: 137 were randomly assigned to a combined-treatment group, and 136 to a control group

	Combined-treatment group (n=137)	Control group (n=136)
Sex		
Male	65 (47%)	67 (49%)
Female	72 (53%)	69 (51%)
Mean age in years (SD)	70 (12)	72 (11)
Tobacco smokers*	14 (10%)	14 (10%)
Alcohol drinkers*	13 (10%)	12 (9%)
Location of bleeding ulcers		
Gastric	79 (58%)	78 (57%)
Duodenal	47 (34%)	49 (36%)
Gastric and duodenal	11 (8%)	9 (7%)
More than one episode of ulcer bleeding	25 (18%)	26 (19%)
Diameter of ulcer in cm (SD)	1·0 (0·5)	1·2 (0·8)
Ulcers with active bleeding or visible vessels	32 (23%)	36 (27%)
Transfusion needed	54 (39%)	60 (44%)
Types of arthritis		
Osteoarthritis	114 (83%)	122 (90%)
Rheumatoid arthritis	4 (3%)	2 (2%)
Others	19 (14%)	12 (9%)
Coexisting medical conditions†	47 (34%)	47 (35%)
More than one coexisting medical condition†	39 (29%)	33 (24%)
Serum creatinine >100 µmol/L	44 (32%)	48 (35%)
Previous *H pylori* infection	60 (44%)	69 (51%)

Data are number (%) unless otherwise specified. *Smokers were defined as those who smoked daily (irrespective of quantity); drinkers as those who consumed more than one standard drink per day. †Medical conditions included compensated heart failure, chronic obstructive airway disease, cirrhosis, renal diseases, and diabetes mellitus.

Table 1: **Baseline characteristics**

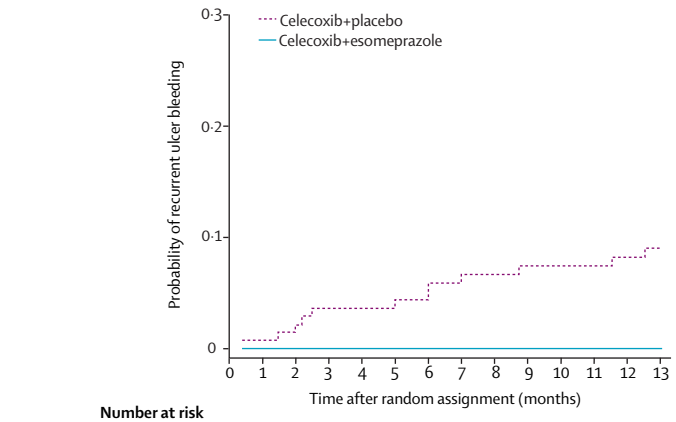

Figure 2: **Cumulative probability of the primary endpoint in the two treatment groups**

(figure 1). Table 1 shows demographic variables at baseline for the two groups. The median follow-up time was 13 months in both groups (range 0·4–13·0). Similar numbers in the combined-treatment group (129, 94%) and the control group (126, 93%) complied with the treatment regimen. Four patients in each group used other antisecretory drugs. Five patients in the combined-treatment group and six controls used similar quantities of antacids. Seven patients used other NSAIDs because of inadequate pain relief (two in the combined-treatment group and five controls). The rate of discontinuation was higher in controls than in the combined-treatment group, mainly because of serious gastrointestinal events. If patients who had events such as upper gastrointestinal bleeding were excluded, rates of discontinuation were similar in the two groups (figure 1). No patient who discontinued medications early had recurrent ulcer bleeding or anaemia within the study period.

In response to the withdrawal of the COX 2 inhibitor rofecoxib in late 2004, the ethics committee reviewed the protocol and approved the continuation of the study. We had excluded patients who required aspirin for cardiovascular prophylaxis because aspirin is known to negate the gastric sparing effect of COX 2 inhibitors. However, concerns about the cardiovascular safety of COX 2 inhibitors led 22 patients (16%) in the combined-treatment group and 21 controls (15%) to begin concomitant low-dose aspirin (80 mg daily) for primary prevention during follow-up.

	Probability of recurrent bleeding		p*
	Combined-treatment group	Control group	
All patients	0% (0 to 0)	8·9 (4·1 to 13·7)	0·0004
Patients who did not take concomitant aspirin	0% (0 to 0)	7·1 (2·4 to 11·8)	0·004
Patients who took concomitant aspirin	0% (0 to 0)	19·0 (2·2 to 35·8)	0·03
Per-protocol analysis	0% (0 to 0)	6·0 (1·4 to 10·6)	0·01

Data are percentage (95% CI). *Calculated with the log-rank test. We used the Kaplan-Meier method because the probability of recurrent ulcer bleeding depended on the duration of treatment, which was assumed to be stable with time.

Table 2: **Kaplan-Meier estimates of the likelihood of recurrent ulcer bleeding at 13 months**

	Disease-activity score*		Pain scale†	
	Combined treatment	Controls	Combined treatment	Controls
Baseline	3·2 (0·7)	3·1 (0·8)	63·9 (18·9)	60·3 (18·9)
At month 12	2·4 (0·8)	2·4 (0·7)	46·6 (19·0)	43·3 (17·7)

Data are mean (SD). *Patients' global assessments of disease activity were scored on a scale from 1 (no limitation of normal activities) to 5 (inability to carry out all normal activities). †Patients' assessments of arthritis pain were marked on a visual analogue scale from 0 mm (no pain) to 100 mm (severe pain). The assumption of sphericity was violated (p<0·0001).

Table 3: **Efficacy of combined treatment versus celecoxib alone for arthritis**

21 suspected serious gastrointestinal events were assessed by the adjudication committee. Of these, the committee identified 12 cases of recurrent ulcer bleeding (seven gastric ulcers and five duodenal ulcers); all were in the group given celecoxib alone. Two of the patients with recurrent ulcers had relapses of *H pylori* infection. All the patients with recurrent ulcer bleeding had been admitted to hospital with melaena, haematemesis, or both. Nine of these patients had a decrease in haemoglobin of at least 20 g/L. Four patients needed endoscopic treatment for active bleeding and eight needed transfusions (median 2 units, range 1–3). Ten of the bleeding ulcers (83%) recurred at their previous locations. The median diameter of the recurrent ulcers was 1·0 cm (range 0·5–3·0).

Figure 2 and table 2 show that the cumulative incidence of recurrent ulcer bleeding during the 13-month study in the intention-to-treat population was 0% in patients who were assigned the combined treatment and 8·9% in patients who were assigned celecoxib alone. The difference between groups in the rate of recurrent ulcer bleeding remained significant in both the intention-to-treat and per-protocol analyses, and irrespective of concomitant use of aspirin (table 2).

Of nine patients who were found on adjudication not to have recurrent ulcer bleeding, six met the prespecified criteria for lower-gastrointestinal bleeding and three had anaemia that was not due to gastrointestinal blood loss. Of six patents with lower-gastrointestinal bleeding, four had been assigned combined treatment and two celecoxib alone. The cumulative incidence of lower-gastrointestinal bleeding was 3·0% (95% CI 0·1–5·8) in the combined-treatment group and 1·6% (95% CI –0·6 to 3·7) in the control group (p=0·46).

Table 3 shows significant improvement in patients' global assessment of disease activity (p<0·0001) and arthritis pain (p<0·0001) in both groups. The change of disease activity score (p=0·85) or arthritis pain (p=0·74) did not differ between groups over time. The proportion of missing efficacy data in the two groups was similar: 10·4% in the combined-treatment group and 13·7% of

	Combined treatment	Celecoxib alone	p
Severe adverse events*			
Upper-gastrointestinal bleeding	0	12	0·0004
Lower-gastrointestinal bleeding	4	2	0·46
Non-gastrointestinal causes of anaemia	1	2	0·62
Renal failure†	4	4	1·00
Unstable angina	1	0	1·00
Stroke	0	2	0·25
Heart failure	1	1	1·00
Peripheral vascular disease	0	1	0·50
Others‡	7	7	0·72
Death§	1	2	0·62
Other important adverse events			
Hypertension¶	25	28	0·63
Dyspepsia	7	13	0·16
Peripheral oedema	5	10	0·18
Skin allergy	1	1	1·00

Data are number of participants. *A serious adverse event was defined as an untoward medical occurrence that was life-threatening, led to admission to hospital or extended stay in hospital, or led to persistent disability or death. †Renal failure was defined as a progressive rise in creatinine concentration to above 200 µmol/L. ‡Other serious adverse events included six patients with pneumonia, and one each with chronic obstructive airways disease, hypoglycaemia, hypocalcaemia, hyponatraemia, vertigo, head injury, knee arthritis, and carcinoma of the larynx. These events were regarded as unrelated to study drugs. §One patient in the combined-treatment group died of pneumonia; one control died of head injury and another of cor pulmonale. ¶Hypertension was defined as new-onset hypertension or worsening of pre-existing hypertension that required treatment.

Table 4: **Incidence of severe and important adverse events**

controls. Results of the two efficacy variables remained consistent when analysis was repeated with missing values removed from the dataset (not shown). The incidence of adverse events was similar in the two treatment groups (table 4). One patient in the combined-treatment group died of pneumonia; in the control group one died of head injury and one of cor pulmonale.

Discussion

All patients enrolled in this study had a recent history of ulcer bleeding. Most also had additional risk factors such as old age and comorbid illnesses. None of these patients at very high risk for ulcer bleeding, who were assigned celecoxib plus esomeprazole had recurrent ulcer bleeding for 13 months, compared with 12 (8·9%) of patients given celecoxib alone. Our finding suggests that combination of a COX 2 inhibitor and a PPI is effective for prevention of recurrent ulcer bleeding in patients with high risk.

The optimum doses of COX 2 inhibitors and PPIs deserve further consideration. We chose a dose of celecoxib that was regularly used in real-world practice before the cardiovascular hazard of COX 2 inhibitors became apparent.[22,23] Physicians are now advised to prescribe the lowest effective dose of COX 2 inhibitors, in view of their potential cardiovascular hazards. However, because low-dose celecoxib has not been shown to have a lower risk of gastroduodenal damage than high-dose celecoxib,[24] PPI prophylaxis is still recommended in patients at risk for ulcer bleeding even if they are receiving low-dose celecoxib. The optimum dose of PPIs for prevention of NSAID-induced ulcer complications also remains undefined. An endoscopic study suggested that 40 mg esomeprazole once daily was not better than 20 mg esomeprazole once daily for prevention of NSAID-associated ulcers.[19] We chose a twice-daily dose of esomeprazole because this regimen is proven to control acid better than a once-daily dose.[25,26]

The long-term rates of ulcer complications with COX 2 inhibitors in patients with high risk of ulcer bleeding have not been comprehensively investigated. We previously showed in a 6-month randomised trial that 4·9% of patients with a history of ulcer bleeding who were assigned celecoxib had recurrent ulcer bleeding.[12] In our 13-month study, the rate of recurrent bleeding with celecoxib was 8·9%. Other evidence shows that COX 2 inhibitors are not equivalent to placebo in terms of gastroduodenal damage even in patients with average ulcer-bleeding risk.[27] These findings suggest that the incidence of ulcer bleeding with COX 2 inhibitors increases with the duration of treatment. Prophylaxis with a PPI therefore is indicated in patients receiving long-term treatment with COX 2 inhibitors and who are at high ulcer-bleeding risk.

Our study has limitations. First, we did not compare the combination of a COX 2 inhibitor and a PPI with a non-selective NSAID and a PPI. In a study of patients who were taking either a PPI or its placebo along with their non-selective NSAIDs or COX 2 inhibitors, subgroup analysis showed that combined treatment with a COX 2 inhibitor and a PPI was no more effective than a non-selective NSAID plus a PPI for prevention of endoscopic ulcers.[19] However, that study was not designed to assess the gastroprotective efficacy of a PPI plus a COX 2 inhibitor in high-risk patients: patients were not randomly assigned to treatment groups and most patients did not have previous ulcer complications.[19] Previously, we showed that for patients with a history of NSAID-induced ulcer bleeding, celecoxib was equivalent to diclofenac plus omeprazole for prevention of recurrent ulcer bleeding.[12] Neither treatment, however, was sufficient to eliminate the risk of recurrent bleeding.[13] Thus, a non-selective NSAID plus a PPI would be unlikely to be comparable to a COX 2 inhibitor plus a PPI for very high risk patients, although this remains to be shown by randomised outcome trials.

Second, our study was not designed to assess the best possible management of patients with high cardiovascular risk, and we did not study patients with a history of cardiovascular disease before enrolment. Although many patients started low-dose aspirin for primary

prevention during the study period, concomitant aspirin has not yet been shown to abrogate the cardiovascular hazard of COX 2 inhibitors such as celecoxib.[28,29]

Contributors

FKLC, VWSW, and JJYS designed the study. VWYL prepared the study medications. LCTH, AJH, LHL, GLHW, DKLC, and VKSL recruited patients. An independent, blinded committee, of WKL, KFT, PWYC, YTL, JYWL, and EKWN, adjudicated potential events. An independent data review committee, of JCYW and HLYC, and BYS, analysed the data. JYLC was responsible for the accuracy of the data. FKLC prepared the manuscript, and all authors read, revised, and approved the final version.

Conflict of interest statement

This study was not sponsored by pharmaceutical companies. FKLC has received an independent research grant and a consulting fee from Pfizer and lecture fees from TAP Pharmaceuticals. JCYW has received grant support from the US National Institute of Health. WKL has received research grants from the Research Grant Council of Hong Kong and the Health and Welfare Bureau of the Hong Kong SAR Government. JYWL has received a consulting fee and been paid lecture fees by AstraZeneca. HLYC has received a consulting fee from Schering-Plough and Novartis. JJYS has received consulting fees from the National Health Research Institutes of Taipei, the Hong Kong Police Force, Lippincott Williams & Wilkins, and the Hong Kong College of Physicians, and has also been paid lecture fees by AstraZeneca Hong Kong Limited, GSK Pharmaceuticals International, and the American Society for Gastrointestinal Endoscopy.

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