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Prevention of Ulcers by Esomeprazole in At-Risk Patients Using Non-Selective NSAIDs and COX-2 Inhibitors

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OBJECTIVES: Proton pump inhibitors reduce ulcer recurrence in non-steroidal anti-inflammatory drug (NSAID) users, but their impact in at-risk ulcer-free patients using the current spectrum of prescribed agents has not been clearly defined. We assessed esomeprazole for ulcer prevention in at-risk patients (≥60 yr and/or ulcer history) taking NSAIDs, including COX-2 inhibitors. Such studies are particularly relevant, given that concerns regarding adverse cardiovascular outcomes among COX-2 inhibitor users may prompt re-evaluation of their use.

METHODS: We conducted two similar double-blind, placebo-controlled, randomized, multicenter studies; VENUS (United States) and PLUTO (multinational). A total of 844 and 585 patients requiring daily NSAIDs, including COX-2 inhibitors were randomized to receive esomeprazole (20 or 40 mg) or placebo, daily for 6 months.

RESULTS: In the VENUS study, the life table estimated proportion of patients who developed ulcers over 6 months (primary variable, intent-to-treat population) was 20.4% on placebo, 5.3% on esomeprazole 20 mg ($p < 0.001$), and 4.7% on esomeprazole 40 mg ($p < 0.0001$). In the PLUTO study, the values were 12.3% on placebo, 5.2% with esomeprazole 20 mg ($p = 0.018$), and 4.4% with esomeprazole 40 mg ($p = 0.007$). Significant reductions were observed for users of both non-selective NSAIDs and COX-2 inhibitors. Pooled ulcer rates for patients using COX-2 inhibitors (n = 400) were 16.5% on placebo, 0.9% on esomeprazole 20 mg ($p < 0.001$) and 4.1% on esomeprazole 40 mg ($p = 0.002$). Esomeprazole was well tolerated and associated with better symptom control than placebo.

CONCLUSIONS: For at-risk patients, esomeprazole was effective in preventing ulcers in long-term users of NSAIDs, including COX-2 inhibitors.

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most widely prescribed treatments worldwide (1). However, NSAIDs are well recognized as causing gastric ulcers (GU) and duodenal ulcers (DU). In addition, NSAIDs are associated with a high rate of upper gastrointestinal (GI) symptoms (2, 3), which are sufficient to cause discontinuation in 5–15% of patients (4).

NSAIDs inhibit cyclo-oxygenase (COX) enzymes to reduce prostaglandin synthesis, which derives principally from COX-2 in inflamed joints and from COX-1 in the normal gastric mucosa (5). Drugs that selectively inhibit COX-2 should therefore relieve joint pain and inflammation with less GI toxicity than non-selective NSAIDs. While there is evidence that COX-2 inhibitors may reduce ulcers and their complications, these effects are not completely eliminated and the residual event rate is high in at-risk patients (6, 7).

An alternative approach to ulcer prevention and upper GI symptom management in NSAID users is to suppress the production of gastric acid, which is critical in ulcer pathogenesis. Therefore, a rationale exists for combining NSAID treatment with acid suppression therapy. Proton pump inhibitors (PPIs) have been shown to provide a greater level of acid suppression than histamine (H2)-receptor antagonists (8), and have been shown to prevent ulcers associated with NSAID use (9).

PPI co-therapy may be particularly suitable as an alternative or adjunct to COX-2 inhibitors in at-risk patients because they affect both NSAID specific and drug-unrelated risks of ulcer development (7). To evaluate the role of PPI co-therapy in two 6-month studies, we studied the effect of esomeprazole treatment in patients at risk of developing ulcers who were chronically using non-selective NSAIDs or COX-2 inhibitors. The primary outcome measure was the effect of esomeprazole (20 and 40 mg/daily) in preventing GU and DU in patients at risk of ulcer development. Secondary outcome measures included the effect of esomeprazole treatment on NSAID-associated upper GI symptoms and the safety and tolerability of esomeprazole in these patients.

METHODS

Study Design and Patients

We performed two randomized, double-blind, placebo-controlled, parallel-group, multicenter studies using protocols that were similar, except for minor local variations. The Verification of Esomeprazole for NSAID Ulcers and Symptoms (VENUS, SH-NEN-0014) study was conducted in 110 centers in the United States between February 1, 2001 and March 5, 2003. A second multinational study, the Prevention of Latent Ulceration Treatment Options (PLUTO, SH-NEN-0013) was carried out at 56 centers in 11 countries; Argentina, Brazil, Bulgaria, China, Hungary, Mexico, Poland, Singapore, South Africa, Sweden, and the United States between March 23, 2001 and December 28, 2002. Both studies were carried out in accordance with the ethical principles of the Declaration of Helsinki. The final study protocols were approved by the relevant local independent ethics committee or institutional review board. Patients gave written informed consent before enrolment.

Patients had a chronic musculoskeletal condition (*e.g.*, osteoarthritis or rheumatoid arthritis) and were receiving treatment with non-selective NSAIDs or COX-2 inhibitors. Study entry requirements included being at risk of developing GU or DU as a result of older age ($\geq$60 yr), and/or a documented GU or DU in the 5 yr before study entry. NSAID therapy must have been stable during the 4 wks before baseline endoscopy and throughout the study. The patients had no ulcers detectable by endoscopy at baseline, were required to be free of *Helicobacter pylori* infection (assessed by urea breath test, serology, and biopsy), and had no evidence of GI bleeding or perforation within 6 months before study entry.

The exclusion criteria were: evidence of esophagitis, esophageal stricture or Barrett's esophagus, gastric outlet obstruction, previous upper GI surgery (except for simple ulcer closure), or significant disease affecting other bodily systems. For the 2 wks before baseline endoscopy, patients who needed concomitant corticosteroids, or had used a PPI, prostaglandin analogue, or a daily H2-receptor antagonist (< daily use was permitted during this period) were also ineligible for study entry.

Stratification and Randomization

At baseline in both studies, patients were stratified into those using non-selective NSAIDs or COX-2 inhibitors (mainly rofecoxib and celecoxib). Patients could receive concomitant treatment with aspirin for prophylaxis of cardiovascular diseases; the dosage had to remain stable throughout the study and could not exceed 325 mg/day. Regardless of the type of other NSAID that these patients on low dose aspirin were using, they were categorized as using non-selective NSAIDs.

In both studies, there were two randomization lists, one for each NSAID group. Patients were randomly assigned in a ratio of 1:1:1, to oral treatment with placebo, esomeprazole 20 mg or esomeprazole 40 mg daily, taken every morning before breakfast, for 6 months. The allocation schedule at each center consisted of blocks of 6 (blocks of 3 for the PLUTO study) created by computer software at AstraZeneca. All study medication was packaged and labeled identically to maintain blinding. Rescue medication of up to 6 antacid capsules daily (aluminum hydroxide 200 mg, magnesium hydroxide 200 mg) was permitted in both studies for upper GI symptom relief.

Assessments

Patients underwent upper endoscopy at baseline (randomization visit) and after 1, 3, and 6 months of treatment or at premature withdrawal. Patients who developed ulcers during the study were withdrawn. For the primary outcome measure, ulcers were defined as mucosal lesions with the following features:

1. a base—a circular or elliptical white or gray-white punched-out effect in the mucosa that could be smooth and regular;
2. a margin—discrete, sharply demarcated, regular, smooth, and usually raised in relation to the ulcer base; and
3. lack of an associated mass, lesion, or other features suggesting malignancy.

For the secondary outcome measure, the investigator asked the patient about NSAID-associated upper GI symptoms experienced during the 7 days before each visit. The primary NSAID-associated upper GI symptom of pain, discomfort or burning in the upper abdomen was assessed in the VENUS study only, while heartburn, acid regurgitation, upper abdominal bloating, nausea, and sleep disturbance (associated with pain, discomfort, or burning in the upper abdomen) were assessed as none, mild, moderate, or severe in both studies.

Physical examinations were done at baseline and at the final study visit. Blood pressure, pulse rate, and weight were

measured at each visit. Spontaneously-reported adverse events (AEs) and AEs that were reported in response to a standardized question about health problems that had occurred since the previous visit were recorded by the investigator and rated as mild, moderate, or severe. In addition, blood and urine samples for laboratory testing were taken at each visit.

Overall usage of study and rescue medication was assessed by counting the numbers of capsules returned. Information on compliance with NSAID medication was collected weekly (VENUS: interactive voice response system; PLUTO: diary card).

Statistical Analysis

Analyses were performed with the use of SAS software (version 8.0). The primary analysis and all secondary analyses were based on the intent-to-treat (ITT) population, which comprised all patients who had no baseline ulcer and took at least one dose of study medication. Unless stated, all data relate to the ITT population. Analogous per protocol (PP) analyses were also carried out. The safety population included all patients who had taken at least one dose of study medication and for whom any post-dose data were available. A significance level of 0.05 was used to determine differences between the treatment groups. All statistical tests performed were 2-tailed.

For each study and treatment group (placebo *vs* active treatment) an overall ulcer rate was estimated based on the expected proportion of COX-2 inhibitor and non-selective NSAID users in the study, respectively, combined with the estimated ulcer rate for each study treatment combined with each NSAID type: 5% for the esomeprazole groups and 14% for the placebo group in the VENUS study, 5% for the esomeprazole groups and 17% for the placebo group in the PLUTO study. These overall ulcer rates were used for the sample size calculation. The studies were not powered to document benefit in the COX-2 inhibitor and non-selective NSAID groups separately. However, the analysis for the total group was stratified based on NSAID type to avoid imbalance between the treatment groups.

The primary outcome measure was the estimated maintenance rate at month 6. This was defined as the proportion of patients without GU or DU through 6 months of treatment. The analysis was derived by a life-table estimate of the failure time, defined as the time from the start of treatment to ulcer occurrence. The Kaplan–Meier method was used to estimate time-to-event curves for each treatment. Life table estimates of the proportion of patients developing ulcers at 6 months for each study and the pooled study population were analyzed using a log-rank test stratified by baseline NSAID use. The observed proportions of patients developing ulcers at months 1, 3, and 6 were analyzed using a Cochran–Mantel-Haenszel (CMH) test stratified by baseline NSAID use and time.

The secondary outcome measure was the presence or absence of each investigator-assessed NSAID-associated upper GI symptom and was assessed using a CMH analysis of symptom resolution (defined as a rating of "none" for the past 7 days). Differences in antacid consumption between treatment groups were assessed *post hoc* using a *t*-test.

RESULTS

Baseline Characteristics

Figure 1 shows the flow of patients through the study. Most patients were women and the treatment groups were well balanced with regard to age, weight, and type of arthritis (Table 1). There were some differences between the two study populations; most notably, a lower proportion of patients in the VENUS study had a history of ulcer as their sole risk factor (approximately 10%) compared with patients in the PLUTO study (approximately 25%). Some patients, who were initially judged to be *H. pylori* negative, had evidence of infection when biopsies were tested. *H. pylori* infection was the main reason for exclusion from the PP populations, which numbered 691 and 434 in the VENUS and PLUTO studies, respectively.

Compliance with study treatment in the VENUS and PLUTO studies, respectively, was 93.6% and 96.2% for placebo, 93.6% and 96.9% for esomeprazole 20 mg, and 97.8% and 96.4% for esomeprazole 40 mg. The corresponding values for NSAID medication compliance was 93.6% and 84.9% for placebo, 94.0% and 93.8% for esomeprazole 20 mg, and 97.4% and 91.8% for esomeprazole 40 mg.

To determine if patients taking COX-2 inhibitors had more risk factors for ulcer development than non-selective NSAID users, we determined the proportion of patients with the two pre-defined risk factors in each placebo group. A similar proportion of patients taking COX-2 inhibitors (34.3%) and non-selective NSAIDs (33.1%) had a history of peptic ulcer ($p = 0.89$). Patients using selective COX-2 inhibitors were slightly, but significantly, older than those using non-selective NSAIDs (mean age: 66.6 yr [$\pm$8.7] *vs* 64.2 yr [$\pm$11.0], $p = 0.03$). Additionally, the proportion of patients taking low dose aspirin was 3% and 11.6% ($p = 0.006$), in COX-2 inhibitor users and non-selective NSAID users, respectively. Demographic and clinical characteristics of the patients according to the NSAID group are shown for the two studies in Table 2.

Ulcer Development

OVERALL DATA. Kaplan–Meier time-to-event curves for the cumulative proportion of patients developing ulcers in each study are shown in Figure 2. When data from each study were pooled, the life-table estimate of the cumulative proportion of patients developing GU and DU at 6 months was 17.0% (95% confidence interval [CI]: 13.2–20.8) with placebo, 5.2% (95% CI: 3.0–7.4) with esomeprazole 20 mg ($p < 0.001$ *vs* placebo) and 4.6% (95% CI: 2.6–6.6) with esomeprazole 40 mg ($p < 0.001$ *vs* placebo). Similar results were obtained in the PP population (placebo: 17.1% [95% CI: 13.0–21.2], esomeprazole 20 mg: 6.1% [3.5–8.7], esomeprazole 40 mg 3.9% [1.9–6.0]).

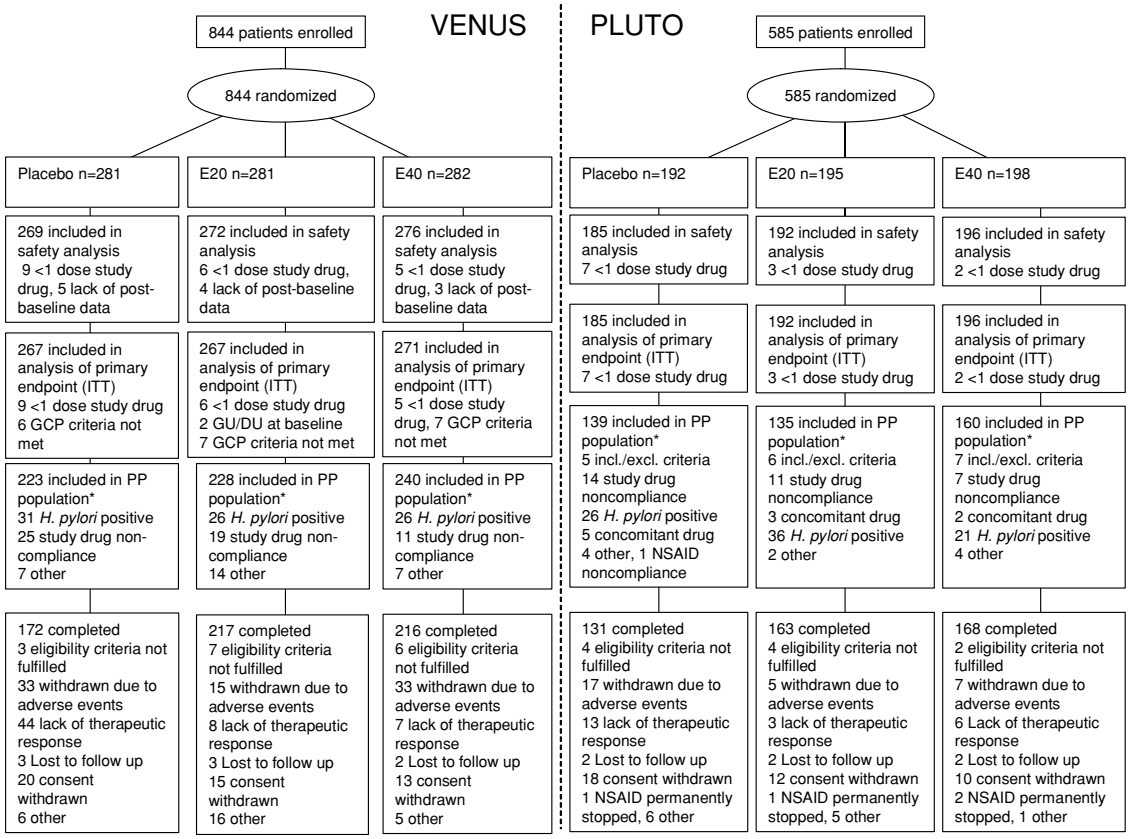

Figure 1. Diagram of patient flow. *A patient could be counted under more than one reason for exclusion from the PP population.

At 1, 3, and 6 months, the observed proportion of patients who developed ulcers with either dosage of esomeprazole was significantly lower than in the placebo group in both studies (Table 3). GUs were more prevalent than DUs in both studies (Table 4). There were too few ulcers that developed in the duodenum to independently analyze the effect of treatment in this location alone.

Among patients taking concomitant low-dose aspirin, the ulcer incidence at 6 months was similar to that of the whole population in all three treatment groups (placebo: 12.2%, esomeprazole 20 mg: 4.7%, esomeprazole 40 mg: 4.2%).

NON-SELECTIVE NSAIDS AND COX-2 INHIBITORS. . In the pooled analysis of individual NSAID types, significantly fewer patients on esomeprazole compared with placebo developed ulcers whether taking a non-selective NSAID or a COX-2 inhibitor. Among patients who received COX-2 inhibitors and placebo, 16.5% (95% CI: 9.7–23.4) of patients developed ulcers over 6 months compared with 0.9% (95% CI: 0–2.6) of patients who received esomeprazole 20 mg and 4.1% (95% CI: 0.6–7.6) who received esomeprazole 40 mg ($p < 0.001$, $p = 0.002$, *vs* placebo, respectively; Fig. 3A). For patients who received non-selective NSAIDs and placebo, 17.1% (95% CI: 12.6–21.6) developed ulcers compared with 6.8% (95% CI: 3.9–9.7) who received esomeprazole 20 mg ($p < 0.001$ *vs* placebo) and 4.8% (95% CI: 2.3–7.2, $p < 0.001$ *vs* placebo) who received esomeprazole 40 mg (Fig. 3A). As shown in Figure 3B and C, significant reductions in ulcer occurrence, were observed for COX-2 inhibitor users in each study. For the non-selective NSAID users, esomeprazole treatment significantly reduced ulcer occurrence in theVENUS study but not in the PLUTO study.

Symptom Assessment

Figure 4 shows the proportions of patients at month 1 free from investigator-assessed upper GI symptoms. In the VENUS study, a significantly lower proportion of esomeprazole recipients had pain, discomfort, or burning in the upper abdomen associated with chronic NSAID use than those receiving placebo ($p < 0.001$ *vs* placebo, for both esomeprazole 20 mg and 40 mg; Fig. 4). In both studies, the proportion of patients with heartburn, acid regurgitation, and sleep disturbance was significantly lower with esomeprazole than with placebo, although not all comparisons reached statistical significance for esomeprazole 40 mg.

At 6 months, the proportion of patients with heartburn and acid regurgitation in each study, and those with pain, discomfort, or burning in the upper abdomen in the VENUS study, were all significantly reduced with each dose of esomeprazole compared with placebo. Patients taking esomeprazole 20 and 40 mg used less antacid medication; 0.55 and 0.48 capsules per day *versus* 0.93 capsules on placebo in the VENUS study ($p < 0.0001$ *vs.* placebo for both esomeprazole doses), and 0.74 and 0.59 capsules *versus* 0.82 capsules in

Table 1. Baseline Characteristics

	VENUS Study			PLUTO Study		
	Placebo	Esomeprazole 20 mg	Esomeprazole 40 mg	Placebo	Esomeprazole 20 mg	Esomeprazole 40 mg
Number of patients	267	267	271	185	192	196
Sex [female (%)]	182 (68.2)	173 (64.8)	184 (67.9)	143 (77.3)	153 (79.7)	147 (75.0)
Age, years [mean (SD)]	65.6 (9.3)	66.0 (9.0)	66.0 (8.8)	64 (11.8)	63.9 (10.7)	63.6 (10.7)
Range	21–88	25–88	29–88	19–88	21–89	24–84
Weight, kg [mean (SD)]	84.8 (18.4)	84.7 (20.1)	83.4 (19.7)	71.7 (17.1)	72.1 (15.5)	72.6 (16.4)
Range	48–168	44–173	45–166	40–137	40–118	42–124
Type of chronic condition [n (%)]						
OA	182 (68.2)	193 (72.3)	197 (72.7)	111 (60)	102 (53.1)	108 (55.1)
RA	44 (16.5)	37 (13.9)	33 (12.2)	46 (24.9)	53 (27.6)	52 (26.5)
Other	41 (15.4)	37 (13.9)	41 (15.1)	28 (15.1)	37 (19.3)	36 (18.4)
H. pylori positive [n (%)]	28 (10.5)	20 (7.5)	23 (8.5)	25 (13.5)	35 (18.2)	22 (11.2)
Risk factor [n (%)]						
Age ≥60yr	203 (76.0)	209 (78.3)	204 (75.3)	114 (61.6)	128 (66.7)	123 (62.8)
Ulcer in past 5 yr	33 (12.4)	22 (8.2)	28 (10.3)	49 (26.5)	46 (24.0)	51 (26.0)
Both risk factors	24 (9.0)	27 (10.1)	30 (11.1)	21 (11.4)	16 (8.3)	21 (10.7)
Low dose ASA, [n (%)]	25 (9.4)	41 (15.4)	30 (11.1)	16 (8.6)	23 (12.0)	18 (9.2)
NSAID type, [n (%)]						
COX-2 inhibitor	99 (37.1)	101 (37.8)	112 (41.3)	35 (18.9)	24 (12.5)	29 (14.8)
Non-selective NSAID	168 (62.9)	166 (62.2)	159 (58.7)	150 (81.1)	168 (87.5)	167 (85.2)

OA = osteoarthritis, RA = rheumatoid arthritis, other = *e.g.*, chronic pain syndromes that require chronic NSAID treatment, COX-2 = cyclo-oxygenase, NSAID = non-steroidal anti-inflammatory drug, *H. pylori* = *Helicobacter pylori.*

the PLUTO study ($p = 0.01$ *vs* placebo for the esomeprazole 40 mg dose).

Tolerability and Safety

Both doses of esomeprazole were well tolerated in each study and the frequency of AEs in patients taking either dose of esomeprazole was similar to that for patients taking placebo. Withdrawals due to AEs were higher in the placebo group in both the VENUS and PLUTO studies (45 [16.7%] and 24 [13%], respectively) than in the esomeprazole 20 mg (22 [8.1%] and 11 [5.7%], respectively) and 40 mg group (35 [12.7%] and 11 [5.6%], respectively).

The number of patients who experienced a serious adverse event with placebo, esomeprazole 20 mg and 40 mg was 9, 11, and 18, respectively, in the VENUS study and 21, 16, and 15, respectively, in the PLUTO study. The type of SAEs that were reported were diverse, with no more than 2 patients experiencing any given SAE in each study. However, the most commonly reported SAEs in both studies (affecting 21 patients) were in the class GI Disorders. Of these 21 SAEs, 12 patients were in the placebo group).

Table 2. Baseline Demographic and Clinical Characteristics of Patients (Treatment Arms Pooled) According to Non-Selective NSAIDs or COX-2 Inhibitor Use in the Two Studies

	VENUS Study		PLUTO Study	
	Non-selective NSAID	COX-2 inhibitor	Non-selective NSAID	COX-2 inhibitor
Number of patients	493	312	485	88
Sex [female (%)]	311 (63.1)	228 (73.1)	375 (77.3)	68 (77.3)
Age [n (%)]				
<65 yr	209 (42.4)	127 (40.7)	221 (45.6)	46 (52.3)
65–74 yr	216 (43.8)	134 (42.9)	205 (42.3)	24 (27.3)
≥75 yr	68 (13.8)	51 (16.3)	59 (12.2)	18 (20.5)
Type of chronic condition [n (%)]				
OA	341 (69.2)	231 (74.0)	270 (55.7)	51 (58.0)
RA	61 (12.4)	53 (17.0)	136 (28.0)	15 (17.0)
Other	91 (18.5)	28 (9.0)	79 (16.3)	22 (25.0)
H. pylori positive [n (%)]	44 (8.9)	27 (8.7)	73 (15.1)	9 (10.2)
Risk factor [n (%)]				
Age ≥60 yr	374 (75.9)	242 (77.6)	314 (64.7)	51 (58.0)
Ulcer in past 5 yr	57 (11.6)	26 (8.3)	122 (25.2)	24 (27.3)
Both risk factors	49 (9.9)	32 (10.3)	46 (9.5)	12 (13.6)

OA = osteoarthritis, RA = rheumatoid arthritis, COX-2 = cyclo-oxygenase, NSAID = non-steroidal anti-inflammatory drug, *H. pylori* = *Helicobacter pylori.*

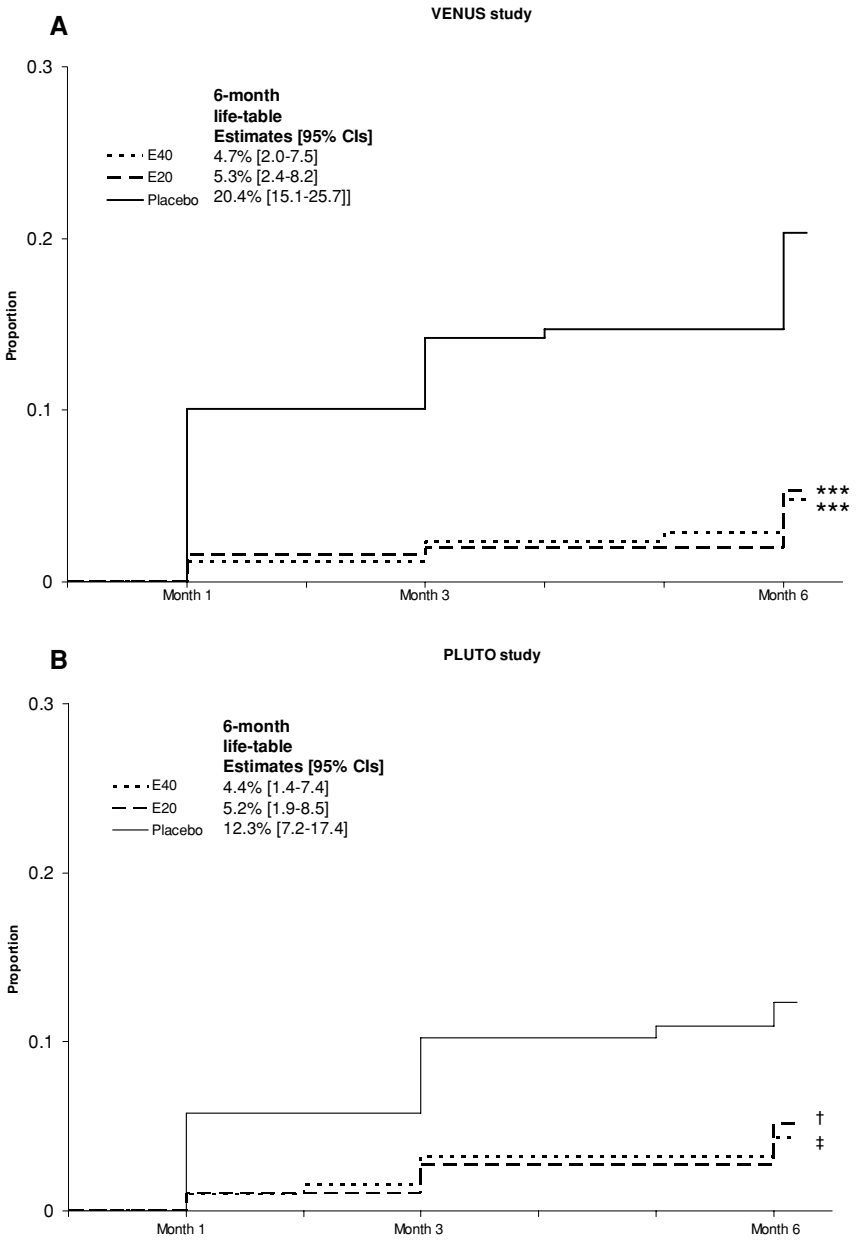

Figure 2. Kaplan–Meier time-to-event curves of the cumulative proportion of patients in the (A) VENUS study, and the (B) PLUTO study developing a gastric ulcer (GU) or duodenal ulcer (DU) through 6 months of treatment, intent-to-treat population (E20 = esomeprazole 20 mg, E40 = esomeprazole 40 mg). $^{***}p < 0.001$, $\ddagger p = 0.007$, $\dagger p = 0.018$ *versus* placebo.

All SAEs were considered to be unrelated to esomeprazole treatment. There was one death in the VENUS study (esomeprazole 40 mg group [+ naproxen]: non-small cell lung cancer) and two in the PLUTO study (placebo group [+ diclofenac]: myocardial infarction; esomeprazole 40 mg group [+ diclofenac]: sudden death), which were all considered by the investigator to be unrelated to the study drug. Four patients, all in the placebo group, were hospitalized with confirmed upper GI bleeding. Two of these patients were taking COX-2 inhibitors (1 of whom was also taking 325 mg/day of aspirin). All 4 patients had only one of the risk factors for ulcer development (≥60 yr or GU/DU history).

DISCUSSION

Previous studies have shown that PPIs can prevent the development or recurrence of endoscopically detected ulcers (10–12). However, current practice differs importantly from that which prevailed when these studies were done. Firstly, management guidelines have emerged that recommend the use of GI supportive therapy only in patients at risk of ulceration rather than in all NSAID users. Secondly, COX-2 inhibitor development has resulted in an alternative treatment strategy for patients at risk of ulcer development.

Table 3. Cumulative Observed Proportions of Patients Who Developed a Gastric Ulcer (GU) or Duodenal Ulcer (DU) by Months 1, 3, and 6 in Each Study (Intent-to-Treat Population)

	Proportion of Patients Developing Ulcers at Each Time Point				
	Placebo	Esomeprazole 20 mg	*p* Value *vs* placebo*	Esomeprazole 40 mg	*p* Value *vs* placebo*
VENUS study: N	267	267		271	
Month 1	9.4%	1.5%	$p < 0.001$	1.1%	$p < 0.001$
Month 3	12.7%	1.9%	$p < 0.001$	2.2%	$p < 0.001$
Month 6	17.2%	4.5%	$p < 0.001$	4.1%	$p < 0.001$
PLUTO study: N	185	192		196	
Month 1	5.4%	1.0%	$p = 0.02$	1.0%	$p = 0.02$
Month 3	9.2%	2.6%	$p = 0.007$	3.1%	$p = 0.01$
Month 6	10.8%	4.7%	$p = 0.007$	4.1%	$p = 0.01$

*Cochran–Mantel-Haenszel test.

We designed the studies reported here to reflect these current prescribing realities and therefore restricted enrolment to patients with the two most common risk factors identified as imposing the highest risk of developing an ulcer; older age (>60 yr) and/or past history of an ulcer. Only ulcer-free patients were enrolled into these studies, differing from previous studies in which patients with healed ulcers (after initial treatment) were included in the ulcer prevention phase of the trial (10, 11). Data from each study show that in chronic NSAID users at risk of developing ulcers, significantly more patients remained ulcer-free with esomeprazole 20 and 40 mg than with placebo. Differences from placebo were detectable from month 1 and maintained throughout the 6-month duration of both studies. In each study, both doses of esomeprazole were well tolerated and esomeprazole treatment was associated with a lower incidence of heartburn, acid regurgitation and sleep disturbance than placebo.

It is of some interest that in our studies the rate of ulcer development with both dosages of esomeprazole was lower than with placebo, in patients taking either COX-2 inhibitors or non-selective NSAIDs. Previous endoscopy and outcome studies have shown that COX-2 inhibitors reduce endoscopic ulcers and ulcer complications compared to non-selective NSAIDs, although it is not clear whether they are reduced to the level seen with placebo. Therefore, COX-2 inhibitors have been recommended for patients at risk of developing ulcers or their complications. However, it has been argued that such patients might be better managed with PPI co-therapy (7), particularly because higher residual event rates have been documented in patients taking COX-2 inhibitors (2, 6, 13, 14, 15). It is of note that the COX-2 inhibitor, rofecoxib, was withdrawn from the market in September 2004, due to an increased risk of cardiovascular events. This withdrawal will likely increase the number of patients taking a combination of a COX-2 inhibitor and low dose aspirin, as well as leading to an increased use of non-selective NSAIDs. Since the combination of low-dose aspirin with a COX-2 inhibitor leads to similar ulcer risk (16) as non-selective NSAIDs, the recognition that PPI co-therapy reduces risk irrespective of the NSAID chosen is clinically relevant.

It was interesting to note that there was a lack of an obvious dose response in the level of ulcer prevention with esomeprazole 20 mg and the 40 mg dose. Although this contrasts with the dose response that has been demonstrated previously in the treatment of erosive esophagitis and GERD symptoms (17), it is in agreement with the lack of dose response seen in previous studies examining omeprazole 20 and 40 mg for the treatment of ulcers (10, 11). These results suggest that, unless esomeprazole 40 mg is required for a separate condition (*e.g.*, GERD), esomeprazole 20 mg is an effective dose for ulcer prevention in long-term NSAID users.

The two studies reported here are consistent with earlier studies in showing the presence of ulcers in COX-2 inhibitor users who have ulcer risk factors (older age and/or ulcer history) (18). Our studies were not designed to investigate whether COX-2 inhibitors are associated with a lower ulcer risk than non-selective NSAIDs, but it is of interest that the proportion of patients developing ulcers was similar in each sub-group. Based on current guidelines (17, 19–21), this observation may in part reflect channeling of higher-risk patients to COX-2 inhibitor use. In our study, the mean age was higher in the COX-2 inhibitor group than in the non-selective

Table 4. Occurrence of Gastric and/or Duodenal Ulcer at Month 6 (Intent-to-Treat Populations)

Study	Ulcer Type	Placebo	Esomeprazole 20 mg	Esomeprazole 40 mg
VENUS	Gastric only	34/267 (12.7%)	12/267 (4.5%)	10/271 (3.7%)
	Duodenal only	10/267 (3.7%)	0/267 (0.0%)	0/271 (0.0%)
	Gastric & duodenal	2/267 (0.7%)	0/267 (0%)	1/271 (0.4%)
PLUTO	Gastric only	19/185 (10.3%)	7/192 (3.6%)	6/196 (3.1%)
	Duodenal only	1/185 (0.5%)	1/192 (0.5%)	2/196 (1.0%)
	Gastric & duodenal	0/185 (0%)	1/192 (0.5%)	0/196 (0%)

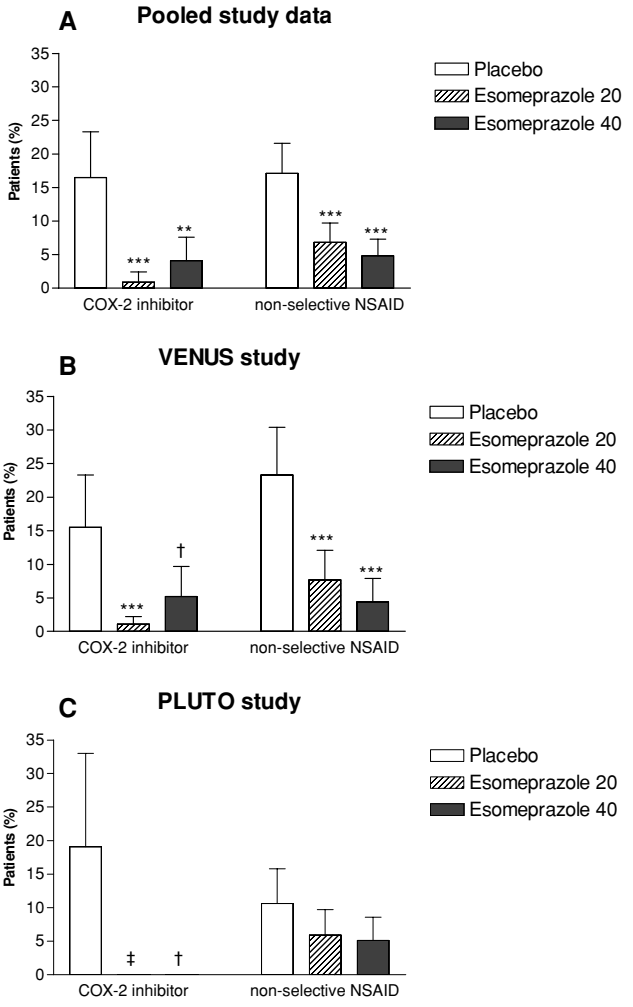

Figure 3. Cumulative proportion of patients developing a gastric ulcer (GU) or duodenal ulcer (DU) at 6 months, split by non-steroidal anti-inflammatory drug (NSAID) type for the (A) pooled study data, (B) VENUS study, and the (c) PLUTO study, based on life table estimates, intent-to-treat population. †$p = 0.02$, ‡$p = 0.03$, $^{**}p = 0.002$, $^{***}p < 0.001$, *versus* placebo (log rank test). 95% confidence intervals are shown.

NSAID group, although, there were significantly fewer low dose aspirin users in the COX-2 group. Some have argued (7, 21–23) that particularly high-risk patients may warrant concurrent use of both COX-2 inhibitors and PPIs. However, our studies do not establish whether, in patients taking a PPI, the use of a COX-2 inhibitor produces a lower risk of ulcer development than the use of a non-selective NSAID. This is an important question that warrants further investigation.

In both studies, esomeprazole 20 and 40 mg significantly improved NSAID-associated upper GI symptoms. The control of heartburn and acid regurgitation was more effective with esomeprazole 20 and 40 mg than with placebo and the use of rescue medication was lower in both esomeprazole groups. These results complement recent studies in lower-risk patients without ulcers who take long-term NSAIDs, including COX-2 inhibitors, which show that esomeprazole is effective in relieving upper GI symptoms and improving health-related quality of life (24).

Our data should prompt continued re-evaluation of the best therapeutic approach to use in patients who need to take NSAIDs, including COX-2 inhibitors.

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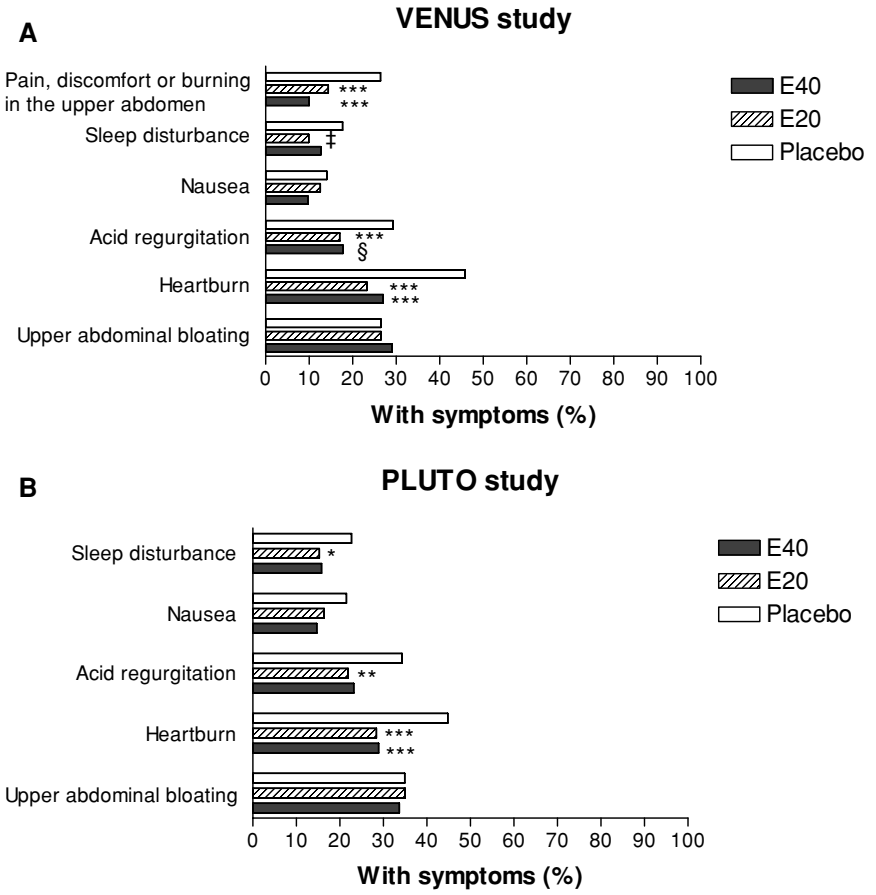

Figure 4. Proportion of patients with symptoms at month 1 in the (A) VENUS study, and the (B) PLUTO study, intent-to-treat population. $^{*}p = 0.03$, $^{**}p = 0.002$, $^{***}p < 0.001$, §$p = 0.001$, ‡$p = 0.007$ *versus* placebo (Cochran–Mantel-Haenszel test).

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