

Is age a predictor of endoscopic gastric ulcers in patients taking chronic NSAIDs? A pooled analysis including 854 patients from two Phase 3 studies comparing PN 400 and enteric-coated naproxen

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Introduction

- ▶ Advancing age is a recognised risk factor for major ulcer complications of nonsteroidal anti-inflammatory drug (NSAID) therapy, but its impact on endoscopic ulcer incidence remains controversial.
- ▶ A previously performed pooled analysis of 12 randomised controlled trials showed that the rate of NSAID-associated endoscopic ulcers increased with age, although these age-related effects were less pronounced than those reported for ulcer complications.¹
- ▶ Preventive therapy with proton pump inhibitors has been shown to be effective in patients at risk of NSAID-associated gastrointestinal toxicity due to their advanced age.²
- ▶ PN 400 is a fixed-dose combination tablet designed to provide delivery of immediate-release (IR) esomeprazole (20 mg) followed by delayed-release (DR) naproxen (500 mg).
- ▶ In each of two Phase 3 studies, PN 400 significantly reduced the incidence of gastric and duodenal ulcers in patients at risk for NSAID-associated ulcers compared with enteric-coated (EC) naproxen alone.³
- ▶ In this pooled analysis of the same two studies, we investigated the impact of age on the incidence of gastric ulcers in patients treated with PN 400 and EC naproxen.

Methods

Patients

- ▶ *Helicobacter pylori*-negative patients (as determined by stool antigen test) with osteoarthritis, rheumatoid arthritis, ankylosing spondylitis or any other condition requiring chronic NSAID therapy for ≥ 6 months were recruited.
- ▶ Eligible patients were either aged ≥ 50 years or were aged 18–49 years with a history of ulcer within the past 5 years.
- ▶ Exclusion criteria included the presence at baseline of gastric or duodenal ulcers (≥ 3 mm diameter with depth), as determined by endoscopy.

Study design and assessments

- ▶ These were two identical, randomised, double-blind, parallel-group, controlled, multicentre Phase 3 studies (Study 1 and Study 2; NCT00527787).
- ▶ Both studies were approved by the relevant ethics committees and were performed in accordance with the Declaration of Helsinki. All patients gave written, informed consent.
- ▶ Following baseline endoscopy, patients were randomised (1:1) to receive either PN 400 or EC naproxen (500 mg), both twice daily, stratified by low-dose aspirin (LDA, ≤ 325 mg). Study drugs were taken orally, 30–60 minutes before a meal in the morning and evening. Treatment was continued for 6 months or until gastric ulcer was detected by endoscopy (performed at 1, 3 and 6 months).

- ▶ In this subgroup analysis, the cumulative frequency of gastric ulcers at Months 1, 3 and 6 was calculated in patients aged < 60 years and ≥ 60 years. These data were calculated for the overall study population and for each treatment group (PN 400 and EC naproxen). Similar analyses at Month 6 were performed for the following age groups: < 50 years, 50–59 years, 60–69 years and ≥ 70 years.

Statistical analyses

- ▶ All analyses were performed in the intent-to-treat (ITT) population (patients who received ≥ 1 dose of study drug and had no ulcer at baseline).
- ▶ The influence of age on gastric ulcer risk was investigated using conditional logistic regression models that included treatment as a main effect, use of LDA as a stratum, and history of gastroduodenal ulcer within 5 years (yes/no) and age group (< 60 years/ ≥ 60 years) as covariates.
- ▶ Treatment-group differences in ulcer occurrence for each age group (< 50 years, 50–59 years, 60–69 years and ≥ 70 years) were assessed using a Cochran-Mantel-Haenszel test stratified by LDA use.

Results

Patients

- ▶ Overall, 854 patients were included in the combined ITT population (Figure 1). Of these, 433 patients (50.7%) were aged < 60 years and 421 (49.3%) were aged ≥ 60 years.
- ▶ Patient demographic and baseline characteristics were well balanced between treatment groups (Table 1).

Figure 1. Patient disposition

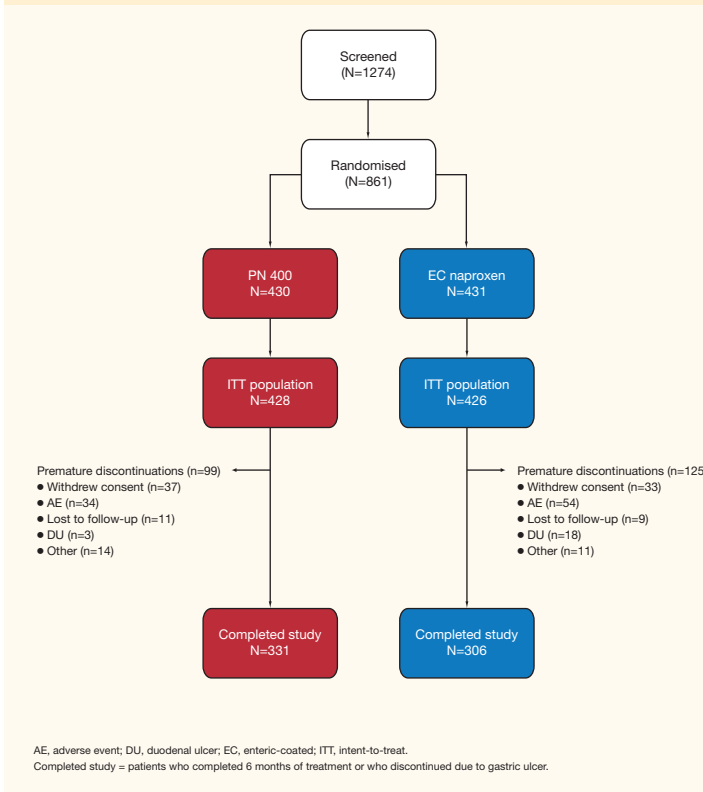


Table 1. Patient demographics and baseline characteristics (ITT population)

	PN 400 (N=428)	EC naproxen (N=426)
Gender, n (%)		
Female	282 (65.9)	291 (68.3)
Mean age, years (range)	60.2 (27–90)	60.6 (29–90)
Age group (years), n (%)		
<50	14 (3.3)	9 (2.1)
50–59	202 (47.2)	208 (48.8)
60–69	157 (36.7)	142 (33.3)
≥ 70	55 (12.9)	67 (15.7)
Race, n (%)		
White	367 (85.7)	371 (87.1)
Black	53 (12.4)	49 (11.5)
Other	8 (1.9)	6 (1.4)
Mean weight, kg (SD)	87.4 (20.5)	86.4 (19.6)
Mean height, cm (SD)	166.9 (9.2)	166.9 (9.9)
Smoker, n (%)	68 (15.9)	65 (15.3)
Low-dose aspirin use at randomisation, n (%)	99 (23.1)	102 (23.9)
Reason for NSAID use, n (%) ^a		
Osteoarthritis	345 (80.6)	352 (82.6)
Rheumatoid arthritis	33 (7.7)	17 (4.0)
Ankylosing spondylitis	3 (0.7)	2 (0.5)
Other	98 (22.9)	95 (22.3)
Ulcer history within previous 5 years, n (%)	33 (7.7)	36 (8.5)

^aPatients may have more than one indication for NSAID use. EC, enteric-coated; ITT, intent-to-treat; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.

Effects of age (< 60 years and ≥ 60 years) on gastric ulcer incidence

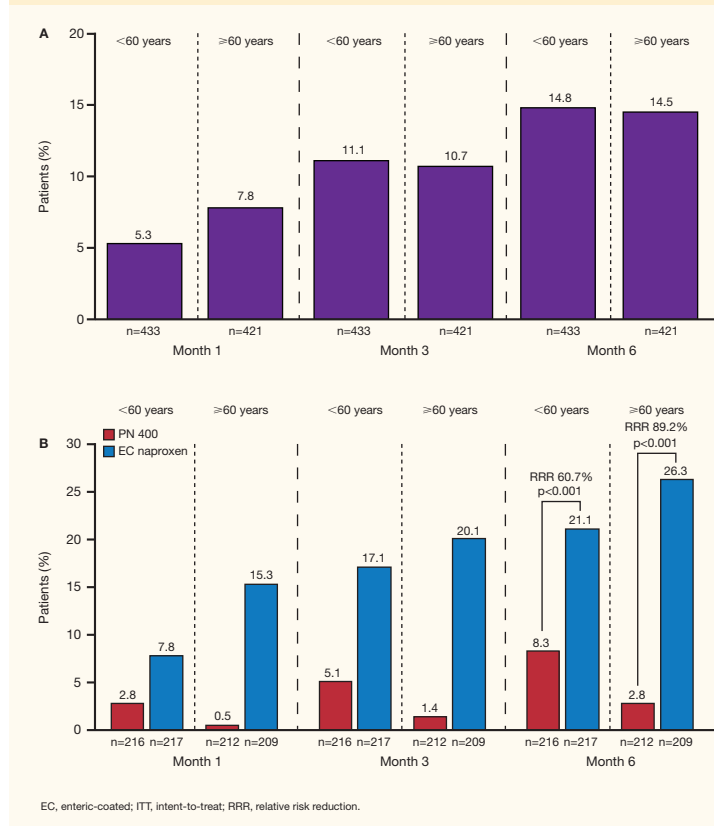
All randomised patients

- ▶ The cumulative incidence of gastric ulcers at Months 1, 3 and 6 for all patients aged < 60 years and ≥ 60 years, regardless of treatment, is shown in Figure 2A.
- At each time point, the incidence of gastric ulcers was similar in patients aged < 60 years and ≥ 60 years.
- Of the 125 patients who developed gastric ulcers by Month 6, 64 (51.2%) were aged < 60 years and 61 (48.8%) were aged ≥ 60 years.
- ▶ Conditional logistic regression models showed that age (≥ 60 years vs < 60 years) had no significant effect on the risk of developing gastric ulcers (Study 1: odds ratio [OR]=0.947, $p=0.854$; Study 2: OR=1.065, $p=0.824$).

PN 400 versus EC naproxen

- ▶ In patients aged < 60 years and those aged ≥ 60 years, PN 400 was associated with a significantly lower incidence of gastric ulcers than EC naproxen during 6 months of treatment ($p<0.001$; Figure 2B).
- ▶ The relative risk reduction for gastric ulcers in patients treated with PN 400 at Month 6 was 60.7% (95% confidence interval [CI]: 34.4%, 76.4%) in patients aged < 60 years and 89.2% (95% CI: 75.6%, 95.3%) in patients aged ≥ 60 years.

Figure 2. Cumulative incidence of gastric ulcers in patients aged < 60 years and ≥ 60 years for (A) the overall study population and (B) each treatment group (ITT population)



Effect of age subgroups (< 50 years, 50–59 years, 60–69 years and ≥ 70 years) on gastric ulcer incidence

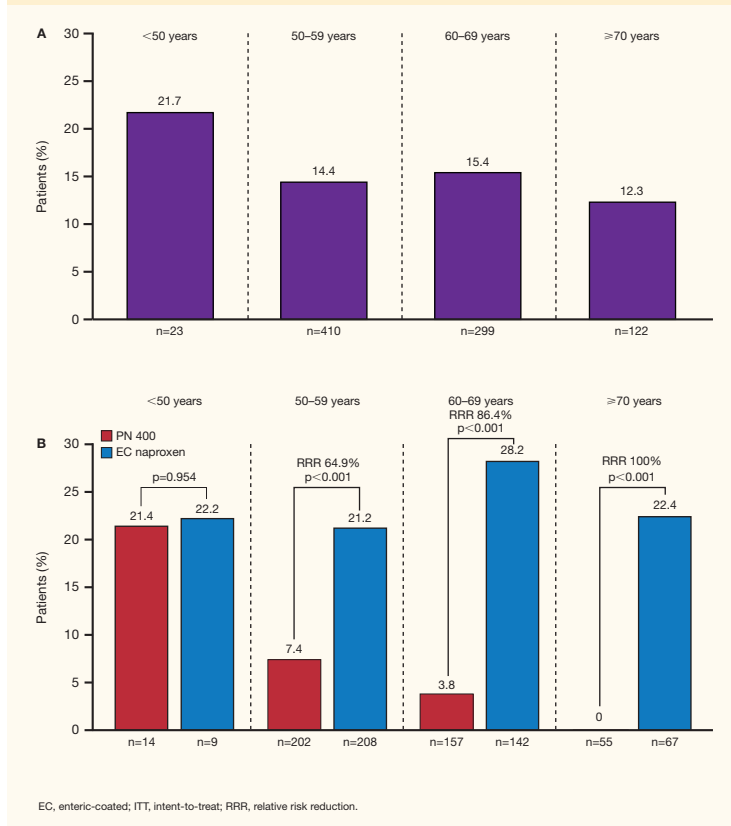
All randomised patients

- ▶ The cumulative incidence of gastric ulcers at Month 6 in patients aged < 50 years, 50–59 years, 60–69 years and ≥ 70 years, regardless of treatment, is shown in Figure 3A.
- The incidence of gastric ulcers at Month 6 was similar in all age subgroups.
- The number of patients aged < 50 years was too low to allow reliable assessment of gastric ulcer incidence in this age group.

PN 400 versus EC naproxen

- ▶ PN 400 was associated with a significantly lower incidence of gastric ulcers than EC naproxen at Month 6 for patients aged 50–59 years, 60–69 years and ≥ 70 years ($p<0.001$; Figure 3B).
- ▶ The relative risk reduction for gastric ulcers in patients treated with PN 400 at Month 6 was:
 - 64.9% (95% CI: 39.0%, 79.8%) in patients aged 50–59 years
 - 86.4% (95% CI: 69.0%, 94.1%) in patients aged 60–69 years
 - 100% in patients aged ≥ 70 years.
- ▶ Interestingly, within the PN 400 treatment group, the incidence of gastric ulcers was higher in patients aged 50–59 years than in those aged 60–69 and ≥ 70 years. In contrast, no effect of age on ulcer incidence was observed in the naproxen treatment group.

Figure 3. Cumulative incidence of gastric ulcers at Month 6 in patients aged < 50 years, 50–59 years, 60–69 years and ≥ 70 years for (A) the overall study population and (B) each treatment group (ITT population)



Conclusions

- ▶ In contrast with previous studies,¹ our results suggest that the risk of endoscopic ulcers in patients aged < 60 years receiving chronic NSAID therapy is not different from that in patients aged ≥ 60 years.
- ▶ PN 400, a fixed-dose combination of IR esomeprazole and DR naproxen, reduces the risk of endoscopic gastric ulcers regardless of age.

Acknowledgements

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