Clinical Study Report Synopsis

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The risk of uncomplicated peptic ulcer in a cohort of new aspirin users in secondary prevention

Study dates:	Retrospective observational cohort study covering the period January 2000 – December 2007
Phase of development:	Therapeutic use
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Study centre(s)
UK

Publications
None published at the time of writing this report.

Objectives
- To estimate the incidence of uncomplicated peptic ulcer (UPU) in a cohort receiving low-dose aspirin (ASA) for secondary prevention of vascular disease, and the relative risk of UPU associated with use and discontinuation of low-dose ASA
- To estimate the effect of proton pump inhibitors (PPI) on the occurrence of UPU among users of low-dose ASA for secondary prevention of vascular disease
- To evaluate the effect of other risk factors on the occurrence of UPU among users of low-dose ASA for secondary prevention of vascular disease

Study design
A retrospective, observational cohort study with nested case-control analysis performed using data from The Health Improvement Network (THIN) primary care database in the UK.

Study population
Individuals aged 50–84 years old who had a first prescription of low-dose ASA for secondary prevention of cardiovascular outcomes between January 2000 and December 2007 (N=38,975) were identified from the UK THIN database. Individuals had to have been enrolled with their primary care physician (PCP) for at least 2 years and had to have at least 1 year of computerized prescription history before the first prescription of ASA. Any patients aged 70 years or older who had a follow-up longer than 1 year, with less than 2 visits during the follow-up period, were excluded. Individuals with ASA use recorded in the database before the start of follow-up, as well as those with cancer or recorded alcohol abuse, were also excluded.

Case ascertainment
Individuals were followed from the date of first ASA prescription (start date) until the earliest occurrence of one of the following endpoints; first recorded diagnosis of UPU (index date), cancer, alcohol abuse or alcohol-related disease, reaching the age of 85 years old, death, date of practice last data collection or the end of the study period (30 September 2011).

Validation of UPU cases
There was a two-step validation process (free text review and PCP questionnaire review). The computerized profiles of potential UPU cases (n=555), including free-text comments, were

manually reviewed so that they could be classified as definite, possible or non-cases (including cases of complicated PU as non-cases). For a random sample of 100 patients among definite cases (n=96) and all possible cases (n=4) still alive and registered in a PCP practice willing to collaborate, a questionnaire was sent to the PCPs to confirm the diagnosis of UPU and request additional related information.

Statistical methods

The incidence rate of UPU was calculated overall and stratified by age, sex, year of start date, and previous history of PU disease at the start date. A Nelson–Aalen time-to-event analysis was performed to estimate the cumulative hazard function of developing UPU in patients with or without a previous history of PU disease. To assess the effect of age, sex and indication for ASA, hazard ratios (HR) for the risk of UPU and 95% confidence intervals (CIs) were calculated using Cox regression analysis adjusted for sex, age, calendar year, ASA indication, PPI use at the start date and prior history of PU.

A nested case-control analysis was also conducted to estimate the contribution of demographic and life style factors, comorbidity, and use of medications during follow-up to the development of UPU among ASA users. Control individuals (n=2000), frequency-matched to cases of uncomplicated PU by age, sex and time in study, were selected from the overall study cohort. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression models, adjusted for multiple potential confounding factors (Table 1). The effect of each of the following factors on development of UPU was analysed: body mass index (BMI), smoking, alcohol consumption, co-morbidity, as well as use of non-steroidal anti-inflammatory drugs (NSAIDs), low-dose ASA, steroids, and acid-suppressing drugs (PPIs and histamine 2 receptor antagonists [H_2RA]). Current use of a medication was defined as prescription active at the index date or ending in the 30 days before the index date.

Summary of results

Incidence of UPU

In total, 309 cases of UPU were confirmed. The overall incidence rate of UPU was 1.41 per 1000 person-years (95% CI: 1.26–1.58). The incidence in men was 1.30 per 1000 person-years (95% CI: 1.11–1.52), and 1.56 per 1000 person-years (95% CI: 1.33–1.83) in women. When stratified by age and sex, the incidence rate of UPU was higher in women than in men in the youngest age group (50–59 years old), but the opposite was observed in the oldest age group (80–85 years old). Patients with a prior history of PU had significantly greater probability of developing UPU, compared with those with no history ($p<0.0001$; Nelson–Aalen cumulative hazard estimate).The incidence of UPU was 3.03 per 1000-patient years

(95% CI: 2.26–4.08) in patients with a prior history of PU and 1.30 per 1000-patient years (95% CI: 1.15–1.46) in patients with no history.

Effect of PPIs on the occurrence of UPU

Among new users of low-dose ASA, the incidence of UPU was 1.84 per 1000 person-years (95% CI; 1.45–2.32) in patients who were receiving a PPI at the start date, compared with an incidence of 1.32 per 1000 person-years (95% CI; 1.16–1.50) in patients who were not.

In the nested case–control analysis, current use of PPI therapy was associated with an increased risk of UPU (adjusted OR: 1.68; 95% CI: 1.26–2.25), as was current use of H_2RAs (adjusted OR: 2.26; 95% CI: 1.34–3.82); this association was also observed among recent/past users. These findings may be due to confounding by indication; that is, an association may be observed because gastroprotective medications were initiated to treat PU symptoms. Two subgroups of patients who received PPIs were analysed to investigate this hypothesis further. Current PPI use initiated >30 days after the start date was associated with a greater than 2-fold increased risk of UPU (adjusted OR: 2.38; 95% CI 1.65–3.42), but patients who initiated PPI therapy before the start date (or within the 30 days after) did not have a significantly increased risk of UPU (OR: 1.25; 95% CI 0.86–1.80).

Risk factors for UPU

Cox regression analyses showed that advanced age at start date was a risk factor for UPU (adjusted HR: 1.69; 95% CI: 1.05–2.74 for age 80–85 years versus 50–59 years), but that sex, calendar year and indication for ASA did not significantly affect the risk.

Comorbidities and lifestyle factors that were found to be significant predictors of UPU in a nested case–control analysis are shown in Table 1. Smoking was an important predictor of UPU; smokers had a greater than 3-fold increased risk of uncomplicated duodenal ulcer, compared with non-smokers (adjusted OR: 3.40; 95% CI: 1.94–5.97). Lower socioeconomic status also increased the risk of UPU. Individuals living in rural areas were less likely to have a diagnosis of UPU (adjusted OR: 0.31; 95% CI: 0.14–0.68) than those living in urban areas. In addition, an increased risk of UPU was found among individuals with a prior history of anemia, stress or depression, and the presence of UPU-related symptoms during follow-up was associated with UPU.

In the nested case–control analysis, current use of the following medications was associated with an increased risk of developing UPU: NSAIDs (adjusted OR: 1.50; 95% CI: 1.06–2.13), coxibs (adjusted OR: 2.33; 95% CI: (1.13–4.79), paracetamol (adjusted OR: 1.45; 95% CI; 1.08–1.95) or oral steroids (adjusted OR: 1.88; 95% CI; 1.09–3.25). Current use of ASA was associated with an OR of 1.33 (95% CI: 0.87–2.04).

Table 1. Adjusted odds ratios for comorbidities and lifestyle factors identified as significant predictors of uncomplicated peptic ulcer in a nested case–control analysis

	UPU cases (n=309) n (%)	**Controls (n=2000) n (%)**	**Adjusted OR[a] (95% Cl)**
Smoking[b]	67 (21.7)	267 (13.4)	1.96 (1.37–2.80)
Townsend deprivation index of 5 (most deprived)[c]	54 (17.5)	216 (10.8)	1.56 (1.01–2.39)
Anemia[d]	70 (22.7)	177 (8.8)	2.53 (1.82–3.53)
Stress[d]	42 (13.6)	158 (7.9)	1.58 (1.06–2.33)
Depression[d]	103 (33.3)	474 (23.7)	1.38 (1.04–1.83)
UPU-related symptoms[e]	133 (43.0)	471 (23.5)	2.09 (1.56–2.81)

[a]Odds ratios were adjusted for age, sex, time in study, healthcare utilization (PCP visits and referrals), smoking and gastroprotective drugs, NSAIDs, ASA and paracetamol use during study period.
[b]Smokers compared with non-smokers.
[c]Compared with the least deprived segment according to the Townsend deprivation index.
[d]Any prior history before the index date (date of UPU diagnosis), compared with no history.
[e]Between first ASA prescription and the index date, compared with no symptoms in this time period.
ASA, acetylsalicylic acid; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio; PCP, primary care physician; UPU, uncomplicated peptic ulcer