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Suboptimal gastroprotective coverage of NSAID use and the risk of upper gastrointestinal bleeding and ulcers: an observational study using three European databases

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ABSTRACT

Background Gastro-protective agents (GPA) are co-prescribed with non-steroidal anti-inflammatory drugs (NSAID) to lower the risk of upper gastrointestinal (UGI) events. It is unknown to what extent the protective effect is influenced by therapy adherence.

Aim To study the association between GPA adherence and UGI events among non-selective (ns) NSAID users.

Methods The General Practice Research Database (UK 1998–2008), the Integrated Primary Care Information database (the Netherlands 1996–2007) and the Health Search/CSD Longitudinal Patient Database (Italy 2000–2007) were used. A nested case-control design was employed within a cohort of nsNSAID users aged ≥50 years, who also used a GPA. UGI event cases (UGI bleeding and/or symptomatic ulcer with/without obstruction/perforation) were matched to event-free members of the cohort for age, sex, database and calendar time. Adherence to GPA was calculated as the proportion of nsNSAID treatment days covered by a GPA prescription. Adjusted OR with 95% CI were calculated.

Results The cohort consisted of 618 684 NSAID users, generating 1 107 266 nsNSAID episodes. Of these, 117 307 (10.6%) were (partly) covered by GPA, 4.9% of which with a GPA coverage <20% (non-adherence), and 68.1% with a GPA coverage >80% (full adherence). 339 patients experienced an event. Among non-adherers, the OR was 2.39 (95% CI 1.66 to 3.44) for all UGI events and 1.89 (95% CI 1.09 to 3.28) for UGI bleeding alone, compared to full adherers.

Conclusions The risk of UGI events was significantly higher in nsNSAID users with GPA non-adherence. This underlines the importance of strategies to improve GPA adherence.

Significance of this study

What is already known about this subject?

- The use of non-selective non-steroidal anti-inflammatory drugs (nsNSAID) may lead to upper gastrointestinal (UGI) ulcers and bleeding.
- Gastroprotective agents (GPA) are recommended to reduce the risk of nsNSAID-related UGI events in patients with risk factors for developing nsNSAID-related UGI events.
- Previous studies have suggested that the preventive effect of GPA during nsNSAID use is compromised by suboptimal adherence, but the magnitude of this effect remains to be determined.

What are the new findings?

- GPA adherence differs between European countries.
- The risk of UGI bleeding and symptomatic UGI ulcers was increased in patients with low GPA adherence.
- The association between low GPA adherence and UGI events was present in patients with and without risk factors.

How might they impact on clinical practice in the foreseeable future?

- The results strongly highlight the importance of GPA adherence during nsNSAID use.
- Increasing adherence to GPA may reduce the risk of nsNSAID-related UGI events.

Non-steroidal anti-inflammatory drugs (NSAID) have analgesic and anti-inflammatory properties, and are indicated mainly for pain management in musculoskeletal injury, osteoarthritis and rheumatoid arthritis. The use of NSAID may lead to upper gastrointestinal (UGI) symptoms such as dyspepsia, and to more severe events such as gastroduodenal ulcers or UGI bleeding. The incidence of such clinically significant UGI events during NSAID use has been estimated at 1–2.5/100 person-years[1 2] and is associated with substantial mortality.[3] Non-selective (ns) NSAID inhibit the cyclooxygenase 1 enzyme more strongly than cyclooxygenase 2 selective inhibitors.[4] As cyclooxygenase 1 is involved in gastroprotection, nsNSAID are believed to increase the risk of UGI events to a higher degree than cyclooxygenase 2 inhibitors.[5]

To prevent UGI events during nsNSAID use, evidence-based guidelines recommend the concomitant use of gastroprotective agents (GPA),[6] mostly in nsNSAID users with one or more risk factors. The guidelines differ slightly in their definition of risk factors, but most consider advanced age, the history of a UGI event and the use of antiplatelet agents, anticoagulants or corticosteroids as risk factors.[7–9] Some guidelines also mention other factors, including the use of selective serotonin

reuptake inhibitors, infection with *Helicobacter pylori* or the presence of heart failure.[7–9]

The actual concomitant use of GPA with nsNSAID can be problematical for two reasons: suboptimal prescription by the physician and suboptimal use by the patient. Although the situation has recently been improving,[10] even recent observational studies estimated that 67–90% of the nsNSAID users with at least one risk factor did not receive GPA as recommended.[11–15] Two other studies showed that 25–50% of the patients did not use their GPA on a daily basis.[16 17]

Lack of adherence to concomitant GPA was shown to be associated with an increased risk of nsNSAID-induced UGI events, but the studies concerned were limited by lack of power, especially to detect an effect on the risk of UGI bleeding.[16 18] To investigate the extent of suboptimal GPA adherence during nsNSAID use and the consequences thereof, a case–control study nested within a cohort of nsNSAID plus GPA users aged 50 years or older drawn from three similar European population-based primary care research databases was conducted. Combining data from comparable medical record databases in different countries (UK, The Netherlands and Italy) enabled increased statistical power and expanded the inclusion to a wide variety of NSAID, resulting in increased generalisability.

METHODS

Data sources

Data for this study were obtained from three similar population-based primary care registries from the UK, The Netherlands and Italy. In the British, Dutch and Italian national healthcare systems, all citizens are registered with a primary care practice, which records all relevant medical information. Data recorded include demographics, symptoms and diagnoses, laboratory test results, drug prescriptions, specialist referrals, clinical diagnoses from outpatient visits and hospital discharge summaries. The databases comply with European Union guidelines on the use of medical data for medical research and have been demonstrated to be valid for pharmacoepidemiology research. In the EU–ADR project it was shown that primary care databases from Italy, The Netherlands and the UK were very similar in terms of UGI event rates.[19] The databases are briefly described below.

General practice research database (1998–2008)

The general practice research database (GPRD) is a dynamic longitudinal primary care research database from the UK that was established in 1987. Currently, there are more than 500 active practices and 4.4 million active patients who are demographically representative of the UK population. Symptoms and diagnoses are recorded using the thesaurus of clinical terms used in the UK (READ codes) and information on drug prescriptions is coded using the Multilex product dictionary and British National Formulary codes. When available, we requested additional information on hospitalisations from hospital episode statistics data including procedures coded according to the Office of Population, Censuses and Surveys: Classification of Interventions and Procedures, 4th revision and diagnoses coded according to the International Classification of Diseases, 10th revision.

Integrated primary care information database (1996–2007)

The integrated primary care information (IPCI) database is a dynamic longitudinal primary care research database from The Netherlands that was set up in 1992. The database covers approximately 800 000 patients from 150 active practices. Symptoms and diagnoses are recorded using the international classification for primary care[20] and free text; drug prescriptions are coded according to the anatomical therapeutic chemical (ATC)[21] classification.

Health search/CSD longitudinal patient database (2000–2007)

The health search/CSD longitudinal patient database (HSD) is a dynamic longitudinal primary care database from Italy that was established in 1998. The HSD currently contains data from over 900 general practitioners and covers approximately 1.6 million patients.[22] Symptoms and diagnoses are recorded using the International Classification of Diseases, 9th Revision, Clinical Modification. Information on drug prescriptions is coded according to the ATC classification.

The protocol of the present study was approved by the Scientific and ethical advisory board of each database.

Source population

For each database, patients were eligible for inclusion in the source population from the start of the study period, at 50 years of age or the date on which at least 1 year of valid enrollment data were obtained (whichever was latest). Eligibility ended at death, last data supply, transferring out of the practice, or end of the study period, whichever came first.

Study cohorts and exposure assessment

Two types of exposure cohorts were created: (1) NSAID cohort (nsNSAID plus cyclooxygenase 2 inhibitors) and (2) nsNSAID plus GPA subcohort, which was selected from the NSAID cohort. For each database, the NSAID cohort included all patients from the source population who received at least one NSAID prescription (ATC codes (or equivalent British National Formulary code) M01AA–M01AX, or ATC codes N02BA01, N02BA15 or N02BA51 at a dose >325 mg) during the eligibility period, and who did not receive any NSAID prescription during the 6 months previously. All identified new users of NSAID were followed from the start of NSAID therapy to the end of the eligibility period or the occurrence of the study outcome (whichever came earliest). Patients with a neoplasm of the gastrointestinal tract, alcohol abuse, chronic liver disease, Crohn's disease, ulcerative colitis or a coagulopathy recorded before or during follow-up were excluded from the cohort.

Within the NSAID cohort, episodes of NSAID use were defined as consecutive NSAID prescriptions with gaps not exceeding the duration of the previous NSAID prescription. For each prescription, duration was calculated by dividing the prescribed quantity by daily dose regimen (GPRD/IPCI) or the indication-specific defined daily dose (HSD). The end of an episode was defined as the end of the last NSAID prescription within that episode or the end of follow-up (whichever came earliest). There was no lower limit for consecutive NSAID use, in order to increase generalisability and to avoid the exclusion of events that occured with a first prescription. Patients could have more than one episode of NSAID use during follow-up, but eligible episodes were only those that had at least a 180-day NSAID-free period before the start of the episode.

From the NSAID cohort we selected the nsNSAID plus GPA subcohort, which comprised all nsNSAID users who received GPA for at least 1 day during an eligible nsNSAID episode. The beginning of the nsNSAID plus GPA episode was based on the beginning of the nsNSAID prescription; the GPA could have started earlier, on the same day or later during the episode. Patients could have more than one eligible episode of nsNSAID

plus GPA use and re-enter the cohort. All episodes that included Arthrotec (fixed combination of diclofenac with misoprostol; ATC code M01AB55) or cyclooxygenase 2 inhibitors (ATC code M01AH) or a combination of products (combination of nsNSAID, cyclooxygenase 2 inhibitors and/or Artrotec) were excluded (figure 1).

In this cohort, follow-up started at the beginning of the nsNSAID plus GPA episode and ended 60 days after the end of the last nsNSAID prescription in that episode (or the end of eligibility if earlier). This carry-over period was added because the nsNSAID-associated elevated risk of UGI events is believed to return to baseline approximately 2 months after stopping treatment.[23]

Among GPA we included proton pump inhibitors (PPI; ATC codes A02BC and A02BD), high-dosed histamine-$_2$ receptor antagonist (H_2RA; ATC code A02BA)[6] and misoprostol (ATC code A02BB01). The duration of GPA was calculated as described above for NSAID.

Adherence calculation

Within the nsNSAID plus GPA cohort, each particular nsNSAID day within an eligible episode was classified as being or as not being covered with a GPA prescription. Adherence estimates were created on the basis of the percentage of nsNSAID days covered (PDC) by a GPA. Adherence was expressed as both a continuous and a categorical variable: (1) non-adherence (PDC <20%); (2) moderate adherence (PDC 20–80%); and (3) full adherence (PDC >80%). This categorisation separates extremes and is based on previous studies on treatment adherence.[18 24]

Case and control definition

Cases were members from the nsNSAID plus GPA cohort who had an UGI event, which was defined as UGI bleeding and/or symptomatic UGI ulcer with or without perforation or obstruction, during follow-up. UGI events were identified by a sensitive electronic search and were subsequently manually (IPCI) or electronically (GPRD, HSD) validated considering all relevant information available in each database (ie, histology reports, specialist letters, endoscopy results, clinical notes as free text). Different systems for coding and recording clinical details prompted us to consider different search and validation algorithms for each database. In general, cases were classified as definite if: (1) an endoscopy record confirming the UGI event was available; (2) the event was mentioned together with the exact location (eg, 'acute duodenal ulcer with haemorrhage'); (3) there was a recording of a hospital admission or anaemia within 1 month of the event. Cases were classified as probable if the occurrence of a UGI event was mentioned, but was unconfirmed or non-specific (eg, 'blood in vomit'). Angiodysplasias, oesophageal varices and Mallory–Weiss syndrome were excluded as a case. The index date was defined as the start of the sign/symptom leading to the diagnosis of the UGI event, if present; otherwise it was defined as the date of diagnosis.

To each case we matched all eligible persons from the nsNSAID plus GPA cohort who were at the index date of the corresponding case: alive, at risk of an nsNSAID-related UGI event (ie, being in follow-up), of similar age (±3 years) and the same sex, and were present in the same database as the case. This matching method samples from person time rather than

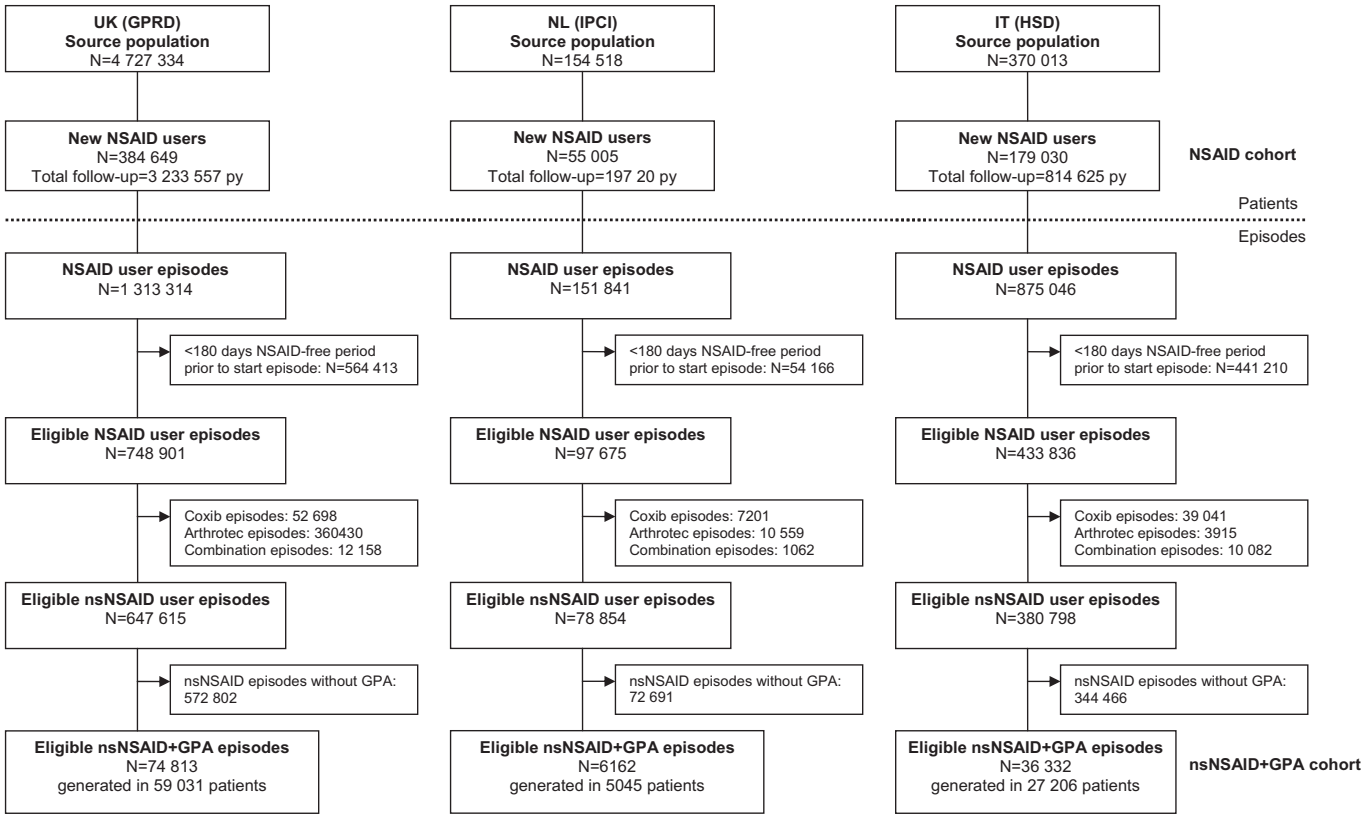

Figure 1 Cohort selection by database. GPA, gastroprotective agent; GPRD, general practice research database; HSD, health search/CSD longitudinal patient database; IPCI, integrated primary care information; IT, Italy; NSAID, non-steroidal anti-inflammatory drug; nsNSAID, non-selective non-steroidal anti-inflammatory drug; NL, The Netherlands.

persons and the controls should be regarded as person moments, similarly to a cohort approach. Adherence was calculated for the most recent episode of nsNSAID use (with censoring at the event) before the event.

Covariates

As covariates we evaluated the presence of risk factors for NSAID-related UGI events as commonly described in guidelines on the prevention of NSAID-related UGI events:[7–9] (1) age 65 years or greater; (2) history of UGI event; (3) concomitant use of antiplatelets; (4) concomitant use of anticoagulants; or (5) concomitant use of systemic steroids greater than 5 mg daily. In the nested case–control analysis, covariates were assessed before the index date. Concomitant use was defined as drug use overlapping the index date.

We additionally evaluated the presence of dyspepsia/gastro-oesophageal reflux in the year before the nsNSAID episode, (history of) smoking, presence of heart failure or diabetes, the concomitant use of serotonin reuptake inhibitors, spironolactone[25 26] or calcium antagonists, calendar year, the length of the NSAID episode and the density of NSAID use (number of NSAID prescription days divided by episode length) within the episode.

Statistical analyses

Baseline characteristics of the NSAID and nsNSAID plus GPA cohort were described by database. The database-specific and pooled crude incidence rates of UGI events within the NSAID cohort were estimated together with 95% CI based on the Poisson distribution, and expressed per 1000 NSAID user-years. Events that occurred during or within 60 days after an eligible NSAID episode were counted. In a subanalysis we calculated separately the incidence rate of UGI bleeding. Exposure time was censored at the occurrence of the outcome of interest.

GPA adherence in the nsNSAID plus GPA cohort was described by database and by the presence of the five major risk factors as described under 'Covariates'. To estimate the risk of nsNSAID-related UGI events and UGI bleeding according to GPA adherence we calculated pooled adjusted matched OR with 95% CI through conditional logistic regression analyses, while adjusting for all covariates that changed the estimated risk in any of the exposure categories by more than 10%. Statistical heterogeneity across databases was tested by using a Cochran's Q statistic, and no significant results were found.

The analyses were stratified by type of first used nsNSAID, duration of nsNSAID episode and the presence of the major risk factors (assessed at the index date). To test the robustness of our findings, sensitivity analyses were performed by restricting the analysis to definite cases only, to cases and controls using nsNSAID for at least 30 or 60 days or to only the first nsNSAID episode per patient.

We calculated the number needed to treat (NNT) within the nsNSAID plus GPA cohort based on the risk estimate in patients with full adherence compared with patients with non-adherence, and the UGI event rate in the non-adherent group. The NNT expresses the number of nsNSAID years during which patients need to be fully adherent to the GPA to prevent one UGI event.[27] This calculation was done separately for patients with no UGI risk factors and patients with at least one UGI risk factor.

All analyses were performed using SPSS 15.0 for Windows. A two-sided p-value of less than 0.05 was considered to be statistically significant.

RESULTS

NSAID cohort

Within the source population of 5 251 865 patients, we identified 618 684 patients who newly started on NSAID at least once

Table 1 Cohort characteristics for the NSAID cohort (at cohort entry) and for the nsNSAID plus GPA cohort (at start of each eligible episode) by database

	NSAID cohort			nsNSAID plus GPA cohort		
	UK n=384 649 n (%)	NL n=55 005 n (%)	IT n=179 030 n (%)	UK n=74 813 n (%)	NL n=6162 n (%)	IT n=36 332 n (%)
Age (mean±SD)	64.8±10.6	63.4±10.7	64.6±10.7	68.9±10.6	65.4±10.9	68.6±10.5
Male	157 881 (41.0)	23 897 (42.7)	74 571 (41.7)	28 047 (37.5)	2257 (36.6)	14 397 (39.6)
Individual UGI risk factors						
Age ≥65 years	177 975 (46.3)	22 845 (40.8)	83 174 (46.5)	45 807 (61.2)	2954 (47.9)	22 024 (60.6)
Previous UGI event	16 953 (4.4)	1134 (2.0)	7056 (3.9)	9040 (12.1)	385 (6.2)	3704 (10.2)
Use of antiplatelets	49 782 (12.9)	1682 (3.0)	13 629 (7.6)	20 043 (26.8)	853 (13.8)	6034 (16.6)
Use of anticoagulants	2809 (0.7)	334 (0.6)	1274 (0.7)	1191 (1.6)	148 (2.4)	553 (1.5)
Use of systemic steroids	4169 (1.1)	260 (0.5)	3797 (2.1)	2539 (3.4)	117 (1.9)	2302 (6.3)
No of UGI risk factors*						
0	186 188 (48.4)	32 029 (57.2)	86 331 (48.2)	21 080 (28.2)	2689 (43.6)	10 582 (29.1)
1	149 015 (38.7)	21 805 (38.9)	77 198 (43.1)	31 947 (42.7)	2556 (41.5)	17 595 (48.4)
2	45 762 (11.9)	2083 (3.7)	14 785 (8.3)	18 820 (25.2)	852 (13.8)	7460 (20.5)
3	3589 (0.9)	92 (0.2)	702 (0.4)	2834 (3.8)	63 (1.0)	6,78 (1.9)
≥4	95 (0.0)	2 (0.0)	14 (0.0)	132 (0.2)	2 (0.0)	17 (0.0)
Type of NSAID						
nsNSAID	353 036 (91.8)	46 778 (85.0)	158 093 (88.3)	74 813 (100.0)	6162 (100.0)	36 332 (100.0)
Cyclooxygenase 2 inhibitors	18 261 (4.7)	3266 (5.9)	18 411 (10.3)	Excluded	Excluded	Excluded
Arthrotec	12 581 (3.2)	4885 (8.9)	1725 (1.0)	Excluded	Excluded	Excluded
Combinations	771 (0.2)	76 (0.1)	801 (0.5)	Excluded	Excluded	Excluded

*Included in the count were previous UGI event (in any previous history), concomitant antiplatelet use, concomitant anticoagulant use, concomitant use of systemic steroids greater than 5 mg daily and age greater than 65 years.
GPA, gastroprotective agent; IT, Italy; NL, The Netherlands; NSAID, non-steroidal anti-inflammatory drug; nsNSAID, non-selective non-steroidal anti-inflammatory drug; UGI, upper gastrointestinal.

during the eligibility period (figure 1). The mean eligibility time per patient was 8.4 years in the UK, 3.6 years in The Netherlands and 4.6 years in Italy.

Table 1 shows the characteristics of the NSAID cohort by database. Most patients in the NSAID cohort started on nsNSAID (n=557 907; 90.2%). The most commonly prescribed nsNSAID were ibuprofen in the UK (69.8%), diclofenac in The Netherlands (38.6%) and nimesulide in Italy (28.5%). The mean age in the NSAID cohort was 64.6±10.7 years and 41.4% were men. Most patients had no (n=310 028; 50.1%) or one (n=259 668; 42.0%) risk factor for NSAID-induced UGI bleeding or ulcer. The most common risk factor was age of 65 years or greater (n=283 994; 45.9%).

During follow-up of the NSAID cohort, 2 340 201 NSAID user episodes were counted, 1 280 412 of which were eligible (ie, had at least a 180-day NSAID-free period before the start of the episode) (figure 1). The mean duration per NSAID episode was 27.5±71.5 days.

Incidence rates

In total, we identified 2056 patients with a UGI event (1182 UGI bleedings and 874 symptomatic ulcers), which occurred during or within 60 days of an eligible NSAID episode. The incidence rates are described in table 2. The incidence rate was 6.7 (95% CI 6.4 to 7.0) per 1000 NSAID user-years for UGI events and 3.8 (95% CI 3.5 to 4.1) per 1000 NSAID user-years for UGI bleedings.

Of all UGI events that occurred during an NSAID episode or within 60 days thereafter, 413 (20.1%) concerned an NSAID episode with concomitant GPA. For UGI bleeding, this

Table 2 Incidence rates of UGI events during eligible NSAID episodes in the NSAID cohort

	UGI events (UGI bleeding and ulcer)			UGI bleeding		
	n	NSAID user-years	Incidence* (95% CI)	n	NSAID user-years	Incidence* (95% CI)
Total	2056	306281.3	6.7 (6.4 to 7.0)	1182	307506.65	3.8 (3.5 to 4.1)
Age, years						
50–65	598	152902.6	3.9 (3.6 to 4.2)	272	153361.87	1.8 (1.6 to 2.0)
65–75	595	87061.3	6.8 (6.3 to 7.4)	330	87490.86	3.8 (3.4 to 4.2)
>75	863	66317.5	13.0 (12.2 to 13.9)	580	66653.92	8.7 (8.0 to 9.4)
Gender						
Male	967	120532.0	8.0 (7.5 to 8.5)	562	121092.25	4.6 (4.3 to 5.0)
Female	1089	185749.4	5.9 (5.5 to 6.2)	620	186414.40	3.3 (3.1 to 3.6)
Individual UGI risk factors						
Age ≥65 years	1458	153378.7	9.5 (9.0 to 10.0)	910	154144.78	5.9 (5.5 to 6.3)
Previous UGI event	209	12041.2	17.4 (15.1 to 19.8)	128	13121.10	9.8 (8.2 to 11.6)
Use of antiplatelets	537	41557.8	12.9 (11.9 to 14.1)	350	41781.33	8.4 (7.5 to 9.3)
Use of anticoagulants	40	2652.0	15.1 (10.9 to 20.3)	32	2667.36	12.0 (8.4 to 16.7)
Use of systemic steroids	58	4894.9	11.9 (9.1 to 15.2)	38	4930.46	7.7 (5.5 to 10.5)
No of UGI risk factors†						
0	464	135939.0	3.4 (3.1 to 3.7)	203	135988.33	1.5 (1.3 to 1.7)
1	960	128922.1	7.5 (7.0 to 7.9)	552	129341.65	4.3 (3.9 to 4.6)
2	557	38727.9	14.4 (13.2 to 15.6)	378	39304.89	9.6 (8.7 to 10.6)
3	72	2624.0	27.4 (21.6 to 34.3)	46	2794.67	16.5 (12.2 to 21.8)
4 or more	3	67.3	44.6 (12.3 to 118.9)	3	75.99	39.5 (10.9 to 105.3)
Type of first NSAID‡						
nsNSAID	1800	275695.0	6.5 (6.2 to 6.8)	1051	276703.0	3.8 (3.6 to 4.0)
Ibuprofen	721	121783.8	5.9 (5.5 to 6.4)	495	122052.4	4.1 (3.7 to 4.4)
Diclofenac	289	41418.3	7.0 (6.2 to 7.8)	159	41601.2	3.8 (3.3 to 4.5)
Naproxen	263	31191.9	8.4 (7.5 to 9.5)	182	31271.0	5.8 (5.0 to 6.7)
Nimesulide	129	26567.9	4.9 (4.1 to 5.8)	27	26739.8	1.0 (0.7 to 1.5)
Others/combinations	398	54733.1	7.3 (6.6 to 8.0)	188	55038.6	3.4 (3.0 to 3.9)
Cyclooxygenase 2 inhibitors	256	30586.3	8.4 (7.4 to 9.4)	131	30803.7	4.3 (3.6 to 5.0)
Celecoxib	99	13336.6	7.4 (6.1 to 9.0)	49	13434.8	3.7 (2.7 to 4.8)
Rofecoxib	115	12859.0	8.9 (7.4 to 10.7)	58	12933.0	4.5 (3.4 to 5.8)
Other/combinations	42	4390.7	9.6 (7.0 to 12.8)	24	4435.9	5.4 (3.6 to 7.9)
Origin of database						
UK	1392	198581.1	7.0 (6.7 to 7.4)	927	199162.7	4.7 (4.4 to 5.0)
The Netherlands	128	19341.2	6.6 (5.5 to 7.8)	92	19372.5	4.8 (3.9 to 5.8)
Italy	536	883593.0	6.1 (5.6 to 6.6)	163	88971.5	1.8 (1.6 to 2.1)
No GPA	1643	266886.6	6.2 (5.9 to 6.5)	965	267479.42	3.6 (3.4 to 3.8)
With GPA	413	39394.7	10.5 (9.5 to 11.5)	217	40027.23	5.4 (4.7 to 6.2)
GPA adherence						
PDC <20%	47	4125.7	11.4 (8.5 to 15.0)	19	4180.92	4.5 (2.8 to 7.0)
PDC 20–80%	120	11735.3	10.2 (8.5 to 12.2)	58	11909.43	4.9 (3.7 to 6.3)
PDC >80%	246	23533.81	10.5 (9.2 to 11.8)	140	23936.88	5.9 (4.9 to 6.9)

*Incidence per 1000 NSAID user-years.
†Included in the count were previous UGI event (in any previous history), concomitant antiplatelet use, concomitant anticoagulant use, concomitant use of systemic steroids greater than 5 mg daily and age greater than 65 years.
‡Episodes with Arthrotec use or with a combination of nsNSAID with cyclooxygenase 2 inhibitors were excluded.
GPA, gastroprotective agent; NSAID, non-steroidal anti-inflammatory drug; nsNSAID, non-selective non-steroidal anti-inflammatory drug; PDC, percentage of NSAID days covered with GPA; UGI, upper gastrointestinal.

percentage was similar (18.4%, n=217). The crude incidence rates of UGI events and UGI bleeding were significantly higher among GPA users than among non-GPA users (table 2). For UGI events, the crude incidence rates among cyclooxygenase 2 inhibitor users were significantly higher compared with nsNSAID users.

nsNSAID plus GPA cohort

After exclusion of episodes that included the use of cyclooxygenase 2 inhibitors (n=98 940) or Arthrotec (n=50 904) or a combination of products (n=23 302), 1 107 266 eligible nsNSAID episodes remained (figure 1). The mean number of eligible nsNSAID episodes per patient was 1.9. The mean length of the eligible nsNSAID episodes was 31.1 days (SD 73.5).

In 117 307 (10.6%) of the eligible nsNSAID episodes a GPA was prescribed (UK 11.6%; The Netherlands 7.8%, Italy 9.5%) and these episodes were the basis for the nsNSAID plus GPA cohort, comprising 91 282 patients (figure 1). The characteristics of this cohort are described in table 1.

Adherence to GPA in the eligible nsNSAID episodes is described in table 3. Overall, mean adherence was 0.81±0.28 (UK 0.83±0.27; The Netherlands 0.88±0.24; Italy 0.74±0.30), and 79 869 patients (68.1%) (UK 71.8%; The Netherlands 80.5%; Italy 58.3%) were fully adherent.

Nested case–control study

In the nsNSAID plus GPA cohort 339 UGI events occurred during follow-up, 187 of which were UGI bleeds. All patients with a UGI event during follow-up were included as cases and 71 380 controls were matched. The characteristics of the cases and controls at the index date are described in table 4.

The mean GPA adherence (PDC) of cases and controls was 0.74±0.33 and 0.82±0.28, respectively. The p value for the Cochran's Q statistic was 0.13, indicative of statistical homogeneity across databases. With every 10% decline in PDC, the risk of a UGI event increased by 9% (95% CI 5% to 13%) (table 5). NsNSAID users who were non-adherent to GPA had a 2.4-fold increased risk of UGI events (95% CI 1.7 to 3.4) compared with

Table 3 GPA adherence during nsNSAID use (in nsNSAID plus GPA cohort)

		GPA adherence (PDC)			
	n	Mean PDC† (SD)	<20% n (%)	20–80% n (%)	>80% n (%)
Total	117 307	0.81 (0.28)	5723 (4.9)	31 715 (27.0)	79 869 (68.1)
Age, years					
50–65	4522	0.80 (0.28)	2350 (5.1)	12 776 (27.5)	31 396 (67.5)
65–75	35 973	0.81 (0.28)	1785 (5.0)	9658 (26.8)	24 530 (68.2)
>75	34 812	0.81 (0.27)	1588 (4.6)	9281 (26.7)	23 943 (68.8)
Gender					
Male	44 701	0.81 (0.28)	2129 (4.8)	11 956 (26.7)	30 616 (68.5)
Female	72 606	0.81 (0.28)	3594 (5.0)	19 759 (27.2)	49 253 (67.8)
Individual UGI risk factors					
Age ≥65 years	70 785	0.81 (0.28)	3373 (4.8)	18 939 (26.8)	48 473 (68.5)
Previous UGI event	13 129	0.84 (0.25)	447 (3.4)	3002 (22.9)	9680 (73.7)
Use of antiplatelets	26 930	0.83 (0.26)	1092 (4.1)	6355 (23.6)	19 483 (72.3)
Use of anticoagulants	1892	0.85 (0.25)	64 (3.4)	423 (22.4)	1405 (74.3)
Use of systemic steroids	4958	0.82 (0.27)	238 (4.8)	1280 (25.8)	3440 (69.4)
No of UGI risk factors*					
0	34 351	0.79 (0.29)	1871 (5.4)	9869 (28.7)	22 611 (65.8)
1	52 098	0.80 (0.28)	2611 (5.0)	14 476 (27.8)	35 011 (67.2)
2	27 132	0.83 (0.27)	1122 (4.1)	6617 (24.4)	19 393 (71.5)
3	3575	0.86 (0.24)	117 (3.3)	723 (20.2)	2735 (76.5)
4 or more	151	0.89 (0.19)	2 (1.4)	30 (20.3)	119 (78.8)
Type of first NSAID					
Ibuprofen	47 782	0.83 (0.26)	2070 (4.3)	11 251 (23.5)	34 461 (72.1)
Diclofenac	19 936	0.81 (0.28)	876 (4.4)	5452 (27.3)	13 608 (68.3)
Nimesulide	8784	0.73 (0.31)	654 (7.4)	3012 (34.3)	5118 (58.3)
Naproxen	14 253	0.83 (0.26)	550 (3.9)	3517 (24.7)	10 186 (71.5)
Others/combinations	26 552	0.77 (0.29)	1573 (5.9)	8483 (31.9)	16 496 (62.1)
Type of GPA					
PPI	115 937	0.81 (0.28)	5645 (4.9)	31 286 (27.0)	79 006 (68.1)
H_2RA	3	0.94 (0.10)	0	0	3 (100)
Misoprostol	999	0.76 (0.30)	51 (5.1)	313 (31.3)	635 (63.6)
Combination of GPA	371	0.76 (0.30)	27 (7.3)	116 (31.3)	228 (61.5)
Duration of episode†					
<1 month	68 519 (58.4)	0.87 (0.24)	2086 (3.0)	13 659 (19.9)	52 774 (77.0)
1–6 months	43 843 (37.4)	0.73 (0.29)	2500 (5.7)	16 608 (37.9)	24 735 (56.4)
6–12 months	2599 (2.2)	0.65 (0.34)	473 (18.2)	826 (31.8)	1300 (50.0)
>12 months	2346 (2.0)	0.58 (0.38)	664 (28.3)	622 (26.5)	1060 (45.2)

*Included in the count were previous UGI event (in any previous history), concomitant antiplatelet use, concomitant anticoagulant use, concomitant use of systemic steroids greater than 5 mg daily and age greater than 65 years.
†p for trend=0.00.
GPA, gastroprotective agent; H_2RA, histamine$_2$ receptor antagonist; NSAID, non-steroidal anti-inflammatory drug; nsNSAID, non-selective non-steroidal anti-inflammatory drug; PDC, percentage of NSAID days covered with GPA; PPI, proton pump inhibitor; UGI, upper gastrointestinal.

Table 4 Association between patient characteristics and UGI events (nested case–control analysis in nsNSAID plus GPA cohort)

	Cases (n=339) N (%)	Controls (n=71 380) N (%)	$OR_{matched}$ (95% CI)
Age (mean±SD)*	71.6±10.7	71.0±9.0	–
Male gender*	137 (40.4)	21631 (30.3)	–
Type of first NSAID†			
Ibuprofen	89 (38.5)	25 768 (53.8)	1.0
Diclofenac	38 (16.5)	4421 (9.2)	1.87 (1.24 to 2.82)
Nimesulide	4 (1.7)	240 (0.5)	2.04 (0.60 to 6.90)
Naproxen	53 (22.9)	8772 (18.3)	2.00 (1.39 to 2.87)
Others/combinations	47 (20.3)	8683 (18.1)	1.32 (0.91 to 1.91)
UGI risk factors			
Previous UGI event	69 (20.4)	6340 (8.9)	2.19 (1.67 to 2.87)
Use of antiplatelets	92 (27.1)	18 924 (26.5)	1.04 (0.81 to 1.32)
Use of anticoagulants	16 (4.7)	1228 (1.7)	2.79 (1.68 to 4.63)
Use of systemic corticosteroids	23 (6.8)	2861 (4.0)	1.67 (1.09 to 2.55)
Dyspepsia/reflux before NSAID start	21 (6.2)	3335 (4.7)	1.24 (0.80 to 1.94)
Smoking	123 (36.3)	28 423 (39.8)	0.94 (0.74 to 1.18)
Chronic heart failure	32 (9.4)	3132 (4.4)	1.71 (1.17 to 2.50)
Diabetes mellitus	58 (17.1)	10 280 (14.4)	1.20 (0.90 to 1.59)
Use of SSRI	37 (10.9)	5053 (7.1)	1.79 (1.27 to 2.54)
Use of spironolactone	2 (0.6)	616 (0.9)	0.61 (0.16 to 2.62)
Use of calcium antagonists	57 (16.8)	11 879 (16.6)	1.11 (0.83 to 1.48)
No of UGI risk factors‡			
0	180 (53.1)	45 162 (63.3)	1.0
1	124 (36.6)	23 214 (32.5)	1.30 (1.03 to 1.65)
2	29 (8.6)	2874 (4.0)	2.29 (1.53 to 3.42)
3	6 (1.8)	129 (0.2)	10.39 (4.50 to 24.00)
4	0	1 (0.0)	–

*Matching variables.
†Adjusted for dose. Patients were only included when dose was available (67.7%).
‡Included in the count were previous UGI event (in any previous history), concomitant antiplatelet use, concomitant anticoagulant use and concomitant use of systemic steroids greater than 5 mg daily. Excluding age greater than 65 years because age was a matching variable. p for trend was 0.00.
GPA, gastroprotective agent; NSAID, non-steroidal anti-inflammatory drug; nsNSAID, non-selective non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; UGI, upper gastrointestinal.

patients who were fully adherent. Upon restriction to definite cases (n=91), the association became stronger; with every 10% decline in PDC, the risk of a UGI event increased by 16% (95% CI 9% to 25%). Upon restriction to patients with at least 30 (174 cases) or 60 (100 cases) days nsNSAID use during the episode or to only the first nsNSAID episode per patient, the results were similar to those of the original analysis (data not shown). Analyses stratified by the type of nsNSAID, duration of nsNSAID episode and the presence of risk factors are shown in table 6. No major heterogeneity was observed, with the exception of patients with the concomitant use of anticoagulants or corticosteroids, in whom the association between GPA adherence and nsNSAID-related UGI events was no longer present.

When analysing the subset of UGI bleeding cases, the mean adherence of the cases and the controls was 0.78±0.30 and 0.82±0.28, respectively. The p value for the Cochran's Q statistic was 0.62 for UGI bleeding, indicative of statistical homogeneity across databases. With every 10% decline in PDC,

Table 5 Association between adherence to gastroprotective agents during nsNSAID use and the risk of UGI events

	Cases	Controls	$OR_{matched}$ (95% CI)	$OR_{adjusted}$* (95% CI)	p for trend
UGI events (UGI bleeding and ulcer)					
Continuous: with every 10% decline in adherence	339	71 380	1.08 (1.04 to 1.12)	1.09 (1.05 to 1.13)	
Categorical:					0.00
Adherence PDC >0.8	205 (60.5)	50 309 (70.5)	1.00	1.00	
Adherence PDC 0.2–0.8	94 (27.7)	16 808 (23.5)	1.31 (1.02 to 1.67)	1.35 (1.05 to 1.73)	
Adherence PDC <0.2	40 (11.8)	4263 (6)	2.15 (1.53 to 3.03)	2.39 (1.66 to 3.44)	
UGI bleeding					
Continuous: with every 10% decline in adherence	187	39571	1.04 (0.99 to 1.10)	1.06 (1.01 to 1.12)	
Categorical					0.02
Adherence PDC >0.8	120 (64.2)	28 160 (71.2)	1.00	1.00	
Adherence PDC 0.2–0.8	51 (27.3)	9091 (23)	1.26 (0.91 to 1.75)	1.30 (0.93 to 1.82)	
Adherence PDC <0.2	16 (8.6)	2320 (5.9)	1.56 (0.93 to 2.64)	1.89 (1.09 to 3.28)	

*Adjusted for length of NSAID episode, density of NSAID use within episode.
GPA, gastroprotective agent; NSAID, non-steroidal anti-inflammatory drug; nsNSAID, non-selective non-steroidal anti-inflammatory drug; PDC, percentage of NSAID days covered with GPA; UGI, upper gastrointestinal.

Table 6 Risk of UGI events with every 10% decline in GPA adherence during nsNSAID use: stratified analyses

	Cases	Controls	$OR_{matched}$ (95% CI)	$OR_{adjusted}$* (95% CI)
Original	339	71 380	1.08 (1.04 to 1.12)	1.09 (1.05 to 1.13)
Type of first NSAID†				
Ibuprofen	89	25 768	1.02 (0.94 to 1.11)	1.04 (0.95 to 1.13)
Diclofenac	38	4421	1.20 (1.08 to 1.33)	1.19 (1.06 to 1.33)
Nimesulide	4	240	1.08 (0.71 to 1.63)	1.05 (0.66 to 1.69)
Naproxen	53	8772	1.08 (0.98 to 1.19)	1.10 (0.99 to 1.22)
Others/combinations	47	8683	1.11 (1.01 to 1.21)	1.15 (1.05 to 1.27)
Duration of NSAID episode‡				
<1 month	162	33 556	1.09 (1.02 to 1.16)	1.09 (1.02 to 1.16)
1–6 months	126	26 612	1.07 (1.00 to 1.14)	1.06 (1.00 to 1.13)
6–12 months	20	4440	1.17 (1.01 to 1.35)	1.20 (1.03 to 1.41)
>12 months	31	6772	1.07 (0.97 to 1.18)	1.07 (0.97 to 1.17)
Age, years				
50–65	95	19 047	1.10 (1.03 to 1.17)	1.11 (1.04 to 1.19)
65–75	107	27 321	1.08 (1.01 to 1.15)	1.08 (1.01 to 1.15)
>75	137	25 012	1.07 (1.01 to 1.13)	1.08 (1.02 to 1.15)
Risk level				
No UGI risk factors	65	14 246	1.11 (1.02 to 1.20)	1.12 (1.03 to 1.21)
≥1 UGI risk factor	274	57 134	1.07 (1.03 to 1.11)	1.08 (1.03 to 1.12)
Previous UGI event				
No	270	65 040	1.09 (1.05 to 1.13)	1.10 (1.06 to 1.15)
Yes	69	6340	1.07 (0.98 to 1.17)	1.07 (0.98 to 1.18)
Concomitant drug use				
Antiplatelets	92	18 924	1.03 (0.96 to 1.11)	1.04 (0.81 to 1.32)
Anticoagulants	16	1228	0.98 (0.80 to 1.20)	0.95 (0.75 to 1.20)
Corticosteroids	23	2861	1.00 (0.85 to 1.18)	0.99 (0.83 to 1.17)
SSRI	37	5053	1.08 (0.96 to 1.22)	1.09 (0.96 to 1.23)

*Adjusted for length of NSAID episode, density of NSAID use within episode.
†Additionally adjusted for dose. Patients were only included when dose was available (67.7%).
‡Only adjusted for density of NSAID use within episode.
GPA, gastroprotective agent; NSAID, non-steroidal anti-inflammatory drug; nsNSAID, non-selective non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; UGI, upper gastrointestinal.

the risk of developing a UGI bleed increased by 6% (95% CI 1% to 12%) (table 5). NsNSAID users who were non-adherent to their GPA had a 1.9-fold increased risk of UGI bleeding (95% CI 1.1 to 3.3) compared with patients who were fully adherent (table 5).

For calculation of the NNT, we calculated the nsNSAID-related UGI event rate in non-adherent patients with no UGI risk factor and with at least one UGI risk factor, being 7.7/1000 nsNSAID user-years (95% CI 3.8 to 14.0) and 18.9/1000 nsNSAID user-years (95% CI 3.7 to 25.5), respectively. In the patients with no risk factors, patients with full adherence were at a risk of 0.52 (95% CI 0.22 to 1.26) of developing a UGI event compared with non-adherers. In the patients with at least one risk factor, patients with full adherence were at a risk of 0.44 (95% CI 0.29 to 0.67) compared with non-adherers. Based on these numbers, we calculated that for patients with no risk factors, 274 nsNSAID user-years with GPA non-adherence needed to be covered with full GPA adherence to prevent one nsNSAID-related UGI event. For patients with at least one risk factor, this was 96 nsNSAID user-years.

DISCUSSION

This large, population-based, multidatabase study shows that, during nsNSAID use, non-adherence to GPA is associated with a 2.4-fold increased risk of UGI bleeding and ulcers and a 1.9-fold increased risk of UGI bleeding alone. With every 10% decrease in GPA adherence, the risk increased by 9% for UGI bleeding and ulcers and 6% for UGI bleeding alone. From the stratified analysis, it appears that full GPA adherence is important in both nsNSAID users with risk factors for developing a UGI event and nsNSAID users without any risk factor.

The results of this study are in line with two previous observational studies, one from USA[16] and one from Europe,[18] which also showed an increased risk of UGI events associated with low GPA adherence. As a result of the low use of GPA and the relatively rare incidence of serious UGI events, the impact of both studies was limited because of the small number of exposed cases. In the present study we were able to include more than 300 exposed cases as we combined together three large primary care databases. This allowed the conduction of several subanalyses. Randomised controlled trials on the subject are not available. This is understandable as in randomised controlled trials adherence to the study drug is often well controlled. To study the effects of drug adherence, real-world variability of use is needed.

In our study the overall incidence of UGI events was 6.7/1000 NSAID user-years. The incidence was higher among patients using GPA compared with patients who did not. This can be explained by channelling, ie, patients who are at higher risk of UGI events are more likely to be prescribed GPA or cyclooxygenase 2 inhibitors. To minimise channelling bias, we created the nsNSAID plus GPA cohort, excluding non-GPA users and cyclooxygenase 2 inhibitor users. Nevertheless, in nsNSAID plus GPA users only, it is conceivable that patients who are at higher risk of developing UGI events will be more adherent to their GPA. This is confirmed by the high crude incidence rate among full adherers compared with patients who were moderately adherent.

This study showed that mean GPA adherence is relatively high (0.81). Although the number of nsNSAID users who received a GPA prescription was lowest in The Netherlands, adherence was highest in this country. In this study (1996–2007), adherence in The Netherlands was slightly higher (0.88) than in a previous study (0.82) from the same database (1996–2002).[17] Lowest adherence was found in Italy.

The strength of this study is the large amount of data from three European countries. It describes real world prescription and patient behaviour in the general population. As with all observational database studies, however, selection bias, information bias and confounding need to be considered. Selection bias is limited because in the cohort we included all eligible patients available in the prospectively collected population-based data from the three databases. The data in these databases is collected for clinical use, irrespective of any research question.

Information bias includes misclassification of exposure and misclassification of outcome. With regard to misclassification of exposure, recall bias was avoided by using prescription data but precise information on actual dispensing and intake is not available. Also, over-the-counter (OTC) drug use is not recorded in the databases. In all three countries, OTC NSAID are available. OTC omeprazole (a PPI) is available in the UK (for short-term use). In all three countries only prescription NSAID and PPI are (partly) reimbursed. OTC NSAID and PPI are therefore usually for short-term use, but an underestimation of NSAID and PPI use in our study is conceivable. Low-dosed H_2RA are available OTC in all three countries, but it is unlikely that patients use doses that are high enough to classify as gastroprotection. Misclassification of the outcome was reduced by manual/electronic validation of the records after sensitive electronic searches based on both codes and key words in free text. A sensitivity analysis that included only definite cases strengthened the study findings. Heterogeneity was seen in the incidence of UGI bleeding, whereas there was homogeneity in the incidence of UGI events in the databases. The incidence of UGI bleeding was substantially lower in Italy than in The Netherlands and the UK. An explanation could be that the most frequently used nsNSAID in Italy is nimesulide, a drug that may lead to less UGI bleeding due to higher cyclooxygenase 2 specificity,[28] and also variations in coding systems or health-seeking behaviour may have contributed. The common case definition is, however, that all outcomes were symptomatic UGI events.

As a result of low numbers, the estimated risks differed between databases, but the conclusions were consistent across databases (data not shown) and heterogeneity was not significant.

Protopathic bias would be introduced if patients start the study drug (GPA) for the treatment of early symptoms of the outcome of interest (UGI events). In this particular study, this is an obvious threat to validity. Especially when GPA are started later in the nsNSAID episode, the association between low GPA adherence and UGI events would be overestimated. In order to avoid protopathic bias, we defined the index date as the start of symptoms leading to the diagnosis of the UGI event rather than the date of diagnosis, whenever possible, and determined the exposure before rather than at the index date.

Residual confounding might have been introduced by the *H pylori* status of patients, on which we had no information. If a positive *H pylori* status was to lead to a higher GPA adherence and to a higher risk of UGI events, this would lead to an underestimation of the true association between GPA adherence and UGI events.

As a result of the fact that the databases contain prescription data and no data on intake, we cannot make a distinction between physician-induced or patient-induced non-adherence. We calculated the risk associated with a suboptimal prescription pattern, irrespective of the cause. Most likely both prescriber and patient non-adherence play a role.

In conclusion, we observed a strong association between GPA adherence and the risk of nsNSAID-related UGI events. The results highlight the importance of GPA use during nsNSAID therapy and suggest that an improvement in GPA adherence could be beneficial in reducing the risk of nsNSAID-related UGI events.

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Competing interests MCJMS is head of a unit that occasionally conducts research for pharmaceutical companies. She has been consultant for Pfizer and Lundbeck in the recent past on issues not related to this study. MM has received grants from the SAEC consortium (collaboration of academia and industry), and from AstraZeneca and Pfizer. SHD works at the Pharmacoepidemiology Program at the Harvard School of Public Health which is partly supported by training grants from Pfizer, Novartis and Wyeth. She has consulted for pharmaceutical companies, some of which manufacture drugs discussed in this paper. JLG has received research and/or educational funding, consulting fees, contract payments and speaker's honoraria from AstraZeneca, Given, Horizon, Logical Therapeutics, Novartis, Pfizer, POZEN, Takeda and TAP. He has received consulting fees from Amgen, Astellas, GlaxoSmithKline, Merck, Novartis, PLX, Procter & Gamble and Wyeth. Grants have been awarded from Amgen, Novartis and GlaxoSmithKline and contract payments from Amgen and GlaxoSmithKline. EJK has served as a speaker and advisory board member for AstraZeneca. EMvS, VEV, GM, RS, GT and JPD declare no conflicts of interest.

Ethics approval This study was conducted with the approval of the scientific and ethical advisory board of each database.

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