

# Individual NSAIDs and Upper Gastrointestinal Complications

## A Systematic Review and Meta-Analysis of Observational Studies (the SOS Project)

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### Abstract

**Background:** The risk of upper gastrointestinal (GI) complications associated with the use of NSAIDs is a serious public health concern. The risk varies between individual NSAIDs; however, there is little information on the risk associated with some NSAIDs and on the impact of risk factors. These data are necessary to evaluate the benefit-risk of individual NSAIDs for clinical and health policy decision making. Within the European Community's Seventh Framework Programme, the Safety Of non-Steroidal anti-inflammatory drugs (NSAIDs) [SOS] project aims to develop decision models for regulatory and clinical use of individual NSAIDs according to their GI and cardiovascular safety.

**Objective:** The aim of this study was to conduct a systematic review and meta-analysis of observational studies to provide summary relative risks (RR) of upper GI complications (UGIC) associated with the use of individual NSAIDs, including selective cyclooxygenase-2 inhibitors.

**Methods:** We used the MEDLINE database to identify cohort and case-control studies published between 1 January 1980 and 31 May 2011, providing adjusted effect estimates for UGIC comparing individual NSAIDs with non-use of NSAIDs. We estimated pooled RR and 95% CIs of UGIC for individual NSAIDs overall and by dose using fixed- and random-effects methods. Subgroup analyses were conducted to evaluate methodological and clinical heterogeneity between studies.

**Results:** A total of 2984 articles were identified and 59 were selected for data abstraction. After review of the abstracted information, 28 studies met the

meta-analysis inclusion criteria. Pooled RR ranged from 1.43 (95% CI 0.65, 3.15) for aceclofenac to 18.45 (95% CI 10.99, 30.97) for azapropazone. RR was less than 2 for aceclofenac, celecoxib (RR 1.45; 95% CI 1.17, 1.81) and ibuprofen (RR 1.84; 95% CI 1.54, 2.20); 2 to less than 4 for rofecoxib (RR 2.32; 95% CI 1.89, 2.86), sulindac (RR 2.89; 95% CI 1.90, 4.42), diclofenac (RR 3.34; 95% CI 2.79, 3.99), meloxicam (RR 3.47; 95% CI 2.19, 5.50), nimesulide (RR 3.83; 95% CI 3.20, 4.60) and ketoprofen (RR 3.92; 95% CI 2.70, 5.69); 4–5 for tenoxicam (RR 4.10; 95% CI 2.16, 7.79), naproxen (RR 4.10; 95% CI 3.22, 5.23), indometacin (RR 4.14; 95% CI 2.91, 5.90) and diflunisal (RR 4.37; 95% CI 1.07, 17.81); and greater than 5 for piroxicam (RR 7.43; 95% CI 5.19, 10.63), ketorolac (RR 11.50; 95% CI 5.56, 23.78) and azapropazone. RRs for the use of high daily doses of NSAIDs versus non-use were 2–3 times higher than those associated with low daily doses.

**Conclusions:** We confirmed variability in the risk of UGIC among individual NSAIDs as used in clinical practice. Factors influencing findings across studies (e.g. definition and validation of UGIC, exposure assessment, analysis of new vs prevalent users) and the scarce data on the effect of dose and duration of use of NSAIDs and on concurrent use of other medications need to be addressed in future studies, including SOS.

## 1. Background

NSAIDs are widely used for the symptomatic treatment of acute pain and chronic inflammatory and degenerative joint diseases. However, their use is restricted by the occurrence of upper gastrointestinal (GI) complications (UGIC) such as peptic ulcer perforations, obstructions and bleeding. The use of NSAIDs has been associated with a 3- to 5-fold increase in the risk of UGIC.<sup>[1,2]</sup> Clinical trials and observational studies have shown that the use of selective cyclooxygenase (COX)-2 inhibitors is associated with a lower risk of UGIC;<sup>[3-5]</sup> however, they have been also associated with an increased risk of serious cardiovascular (CV) events.<sup>[6]</sup> Further data are necessary to quantify the risk of UGIC associated with many individual NSAIDs, including selective COX-2 inhibitors, and to evaluate the benefit-risk balance of the NSAIDs most often used in regular clinical practice, taking into account dose, duration and effect of other risk factors. These data can help clinicians select treatments for individual patients and help health policy regulators assess the public health impact of therapy.

Within the European Community's Seventh Framework Programme, the Safety Of non-Steroidal anti-inflammatory drugs (SOS) collaborative project started in 2008 with the goal of developing statistical and decision models to facilitate regulatory and treatment decisions based on the GI and CV safety of individual NSAIDs. One of the initial tasks of the SOS project was to summarize the data available on the risk of GI and CV events from observational studies. In this context, we conducted a systematic review and meta-analysis of published observational studies to provide pooled relative risks (RR) for UGIC associated with the use of individual NSAIDs versus non-use of NSAIDs. We followed the MOOSE guidelines for reporting meta-analyses of observational studies (<http://www.equator-network.org/resource-centre/>).

## 2. Materials and Methods

We performed a literature search in PubMed using medical subject headings (MeSH) and free-text terms for individual NSAIDs and selective

COX-2 inhibitors, GI disease, case-control studies and cohort studies. The search was restricted to observational studies published in the English language between 1 January 1980 and 31 May 2011. Details of the search strategy are available in the supplemental digital content (SDC; <http://links.adisonline.com/DSZ/A78>). Studies had to be (i) cohort, case-control or nested case-control studies; (ii) provide odds ratios or RRs of UGIC comparing individual NSAIDs with non-use of NSAIDs; and (iii) provide effect estimates adjusted at least for age and sex. All titles and/or abstracts of the articles identified were reviewed to select those potentially meeting the inclusion criteria. Data from these articles were abstracted in a standardized database that included information on source population, inclusion and exclusion criteria, study design, case definition and validation, selection of controls, exposure definition, confounding factors and statistical analysis. The accuracy of the abstracted data was reviewed independently by two of the authors (NR-G, JC). References from relevant studies and prior meta-analyses were also reviewed. Study authors were contacted when additional information was needed.<sup>[7]</sup>

The methodological quality of each study was evaluated using the Newcastle-Ottawa Scale (NOS).<sup>[8]</sup> The NOS involves a score system in which the study design is evaluated on three broad categories: (i) selection of the study groups; (ii) comparability between the study groups; and (iii) exposure/outcome ascertainment. For each study, the NOS was evaluated independently by two of the authors (NR-G and JC), and any differences were resolved by consensus.

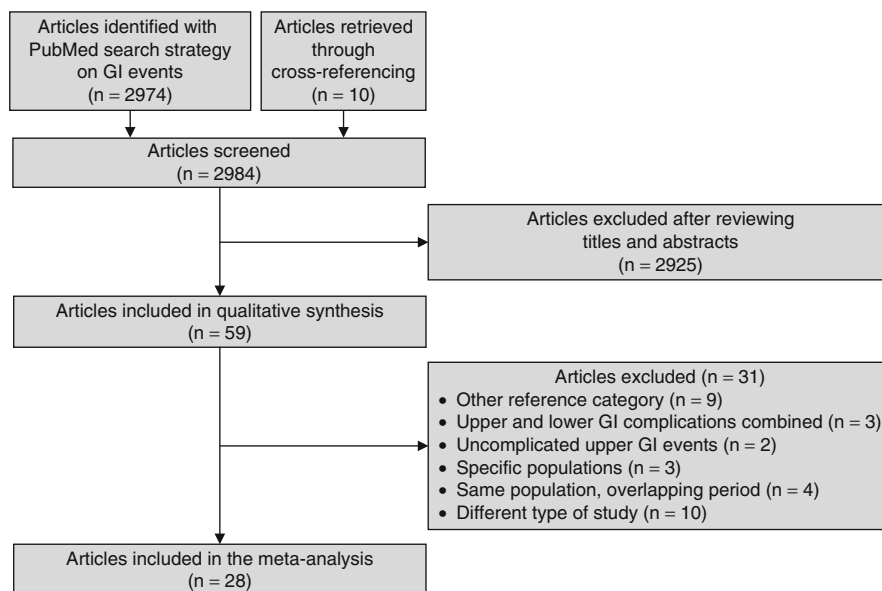
We estimated pooled RRs for those individual NSAIDs that had effect estimates reported in at least three different studies. Pooled RRs and 95% CIs were estimated using both the inverse-variance Lagrange fixed-effects method and the DerSimonian and Laird random-effects method.<sup>[9]</sup> We generated forest plots from the random-effects models. Heterogeneity between studies was assessed by graphical inspections of the forest plots and by Cochran's Chi-squared ( $\chi^2$ ) test of homogeneity, and subgroup analyses evaluating methodological and clinical heterogeneity between studies. Sub-

group analyses included stratification by study design, prior history of UGIC, bleeding complications, study period and dose of NSAIDs. Pooled estimates for dose were calculated according to the dose categorization used in each study. In the subgroup analyses, pooled RRs were also calculated for those NSAIDs with only two effect estimates available. The Higgins inconsistency  $I^2$  statistic was used to describe the percentage of the variability in effect estimates that is due to heterogeneity rather than chance.<sup>[10]</sup> The meta-analysis was conducted using Review Manager (RevMan), Version 5.0.22 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2009).

### 3. Results

A total of 2984 articles on NSAIDs and GI complications were identified. Of these, 2974 articles were identified in the PubMed search and ten additional articles were identified through the references of relevant studies (figure 1). The review of titles and abstracts of these studies led to select 59 articles for full data abstraction. After review of the abstracted information, 28 studies on the use of individual NSAIDs and the risk of UGIC met the inclusion criteria and were included in the meta-analysis.<sup>[7,11-35]</sup> The remaining 31 articles were excluded for the following reasons: the reference group was other than non-use of NSAIDs in nine studies;<sup>[36-44]</sup> the outcome was overall upper and lower GI complications in three studies;<sup>[45-47]</sup> the outcome was uncomplicated upper GI events in two studies;<sup>[48,49]</sup> the study population was restricted to users of specific drugs or to patients with specific diseases in three studies;<sup>[50-52]</sup> the study population and the study period overlapped in four studies;<sup>[53-56]</sup> and the study design did not meet the inclusion criteria in ten studies (i.e. different type of study or measures of association and exposure assessment).<sup>[57-66]</sup>

Selected characteristics of the 28 studies included in the meta-analysis are summarized in table I; 3 studies were cohort studies,<sup>[20,24,26]</sup> 10 were nested case-control studies,<sup>[7,11,17-19,23,25,33,35,67]</sup> and 15 were case-control studies.<sup>[12-16,21,22,27-32,34,68]</sup> Twelve studies, all case-control studies, were field studies



**Fig. 1.** Flow diagram for identification of studies on upper gastrointestinal complications and individual NSAIDs. **GI**=gastrointestinal.

collecting individual information by standardized questionnaires. The 16 remaining studies used information recorded in healthcare databases.

Cases were defined as hospitalization or referral to a specialist for upper GI bleeding in 13 studies,<sup>[12,15,16,19-22,27-30,33,34]</sup> and for bleeding and/or perforation in 15 other studies; four studies also included cases of uncomplicated peptic ulcer.<sup>[14,17,33,68]</sup> The site of complication was defined as gastric and/or duodenal in all studies, and two included oesophageal complications.<sup>[12,32]</sup> Most studies, both field and database studies, required information from endoscopy or other diagnostic procedures to confirm UGIC. Six studies conducted in healthcare databases did not conduct any validation of the cases identified.<sup>[14,17-20,68]</sup> Sixteen studies reported aggregate results for patients with and without a history of UGIC,<sup>[7,12-14,16,20-23,28,31-34,67,68]</sup> and 12 provided results for patients without a history of UGIC;<sup>[11,15,17-19,24-27,29,30,35]</sup> the remaining study was a case-crossover study.<sup>[14]</sup> Most studies excluded subjects with a history of a known cause of UGIC, including the use of gastrotoxic medications and life-threatening diseases (table II). Four studies did not have any exclusion criteria.<sup>[20,22,28,34]</sup>

Among the 14 case-control studies, seven included hospital controls;<sup>[12,13,16,21,29-31]</sup> five included both hospital and community controls;<sup>[22,27,28,32,34]</sup> one included community controls;<sup>[15]</sup> and two were case-crossover studies.<sup>[14,68]</sup> All case-control studies were matched on age, sex (except one study<sup>[16]</sup>), hospital or geographic area, and index date. Three of the case-control studies with hospital and community controls estimated separate results for each set of controls;<sup>[22,28,34]</sup> as results between the two sets were similar, we included in the meta-analysis results reported using hospital controls. In cohort studies, current use of NSAIDs was defined as the time covered by each prescription,<sup>[20,24]</sup> and one study extended the coverage by 15 days.<sup>[26]</sup> Most case-control studies defined current use of NSAIDs as any use ending at the index date or within 7 days before the index date. A few case-control studies considered current use as that ending up to 30 days<sup>[11,13,17,19,28,35]</sup> or 90 days<sup>[18]</sup> before the index date. Two cohort studies focused on new users of NSAIDs,<sup>[20,26]</sup> and one nested case-control study provided results for both new users and all users (incident and prevalent) of NSAIDs.<sup>[17]</sup> In addition to age and sex, the most frequent confounders considered were a history

**Table 1.** Description of observational studies on the risk of upper gastrointestinal complications associated with the use of individual NSAIDs

Study, y	Source population; study period	Study population (N); age (y)	Study design	Type of endpoint	Study endpoint	Case validation	Dose assessment	Exposure assessment	Definition of current use <sup>a</sup>
Mamdani et al., 2002 <sup>[20]</sup>	Ontario, Canada; 2000–1	143 969; >65	Cohort	All	Bleeding Site: gastric, duodenal Lesion: peptic ulcer, upper GI <sup>b</sup>	No	No	Dispensed prescriptions	Prescription coverage
Menniti-Ippolito et al., 1998 <sup>[24]</sup>	Umbria, Italy; 1993–4	201 357; 35–84	Cohort	Incident	Bleeding, perforation Site: gastric, duodenal Lesion: peptic ulcer, upper GI <sup>b</sup>	Review medical records	No	Dispensed prescriptions	Estimated prescription coverage
McMahon et al., 1997 <sup>[26]</sup>	Tayside, Scotland; 1989	156 398; All	Cohort	Incident	Bleeding, perforation Site: gastric, duodenal Lesion: upper GI <sup>b</sup>	Review medical records	No	Dispensed prescriptions	Prescription coverage plus 15 days
Helin-Salmivaara et al., 2007 <sup>[17]</sup>	Finland; 2000–4	50 971; All	Nested case-control	Incident	Bleeding, perforation, ulcer Site: gastric, duodenal Lesion: peptic ulcer	No	No	Dispensed prescriptions	0–30 days
Hippisley-Cox et al., 2005 <sup>[18]</sup>	OResearch, UK; 2000–4	98 274; 25+	Nested case-control	Incident	Bleeding, perforation Site: gastric, duodenal Lesion: peptic ulcer, upper GI <sup>b</sup>	No	No	Electronic prescriptions	0–90 days
Nergård et al., 2004 <sup>[19]</sup>	North Jutland, Denmark; 2000–2	3686; 18–90	Nested case-control	Incident	Bleeding Site: gastric, duodenal Lesion: peptic ulcer, gastritis, upper GI <sup>b</sup>	No	No	Dispensed prescriptions	0–30 days
Castellsague et al., 2009 <sup>[67]</sup>	Saskatchewan, Canada; 1999–2001	20 728; 20–89	Nested case-control	All	Bleeding, perforation Site: gastric, duodenal Lesion: peptic ulcer, upper GI <sup>b</sup>	Review medical records	Yes	Electronic prescriptions	0–7 days
García Rodríguez and Barreales, 2007 <sup>[7]</sup>	THIN, UK; 2000–5	11 561; 40–85	Nested case-control	All	Bleeding, perforation Site: gastric, duodenal Lesion: peptic ulcer, erosions, inflammation	Review computerized information and free text, and random sample medical records	Yes	Electronic prescriptions	0–7 days
García Rodríguez and Hernández-Díaz, 2001 <sup>[23]</sup>	GPRD, UK; 1993–8	13 605; 40–79	Nested case-control	All	Bleeding, perforation Site: gastric, duodenal Lesion: peptic ulcer, upper GI <sup>b</sup>	Review medical records	No	Electronic prescriptions	0–6 days
García Rodríguez et al., 1998 <sup>[25]</sup>	Friuli Venezia Giulia, Italy; 1991–5	21 505; 25–89	Nested case-control	Incident	Bleeding, perforation Site: gastric, duodenal Lesion: peptic ulcer, upper GI <sup>b</sup>	Review medical records	Yes	Dispensed prescriptions	0 days (on date of event)

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Table 1. Contd

Study, y	Source population; study period	Study population (N); age (y)	Study design	Type of endpoint	Study endpoint	Case validation	Dose assessment	Exposure assessment	Definition of current use <sup>a</sup>
García Rodríguez and Jick, 1994 <sup>(11)</sup>	GPRD, UK; 1990–3	9879; 25–77	Nested case-control	Incident	Bleeding, perforation Site: gastric, duodenal Lesion: peptic ulcer, upper GI <sup>b</sup>	Review random sample medical records	Yes	Electronic prescriptions	0–30 days
Griffin et al., 1991 <sup>(33)</sup>	Tennessee Medicaid, US; 1984–6	8478; 65+	Nested case-control	All	Bleeding, ulcer Site: gastric, duodenal Lesion: peptic ulcer, upper GI <sup>b</sup>	Review medical records	Yes	Dispensed prescriptions	0 days (on date of event)
Perez-Gutthann et al., 1997 <sup>(35)</sup>	Saskatchewan, Canada; 1982–6	11 377; All	Nested case-control	Incident	Bleeding, perforation Site: gastric, duodenal Lesion: peptic ulcer, upper GI <sup>b</sup>	Review medical records	Yes	Dispensed prescriptions	0–30 days
Chang et al., 2011 <sup>(68)</sup>	Taiwan; 2006	23 million; 20+	Case-crossover	All	Bleeding, perforation, ulcer Site: gastric, duodenal Lesion: peptic ulcer, gastritis, duodenitis, upper GI <sup>b</sup>	No	Yes	Electronic prescriptions	Prescription coverage
Sakamoto et al., 2006 <sup>(15)</sup>	Selected hospitals in Japan; 2002–4	522; 40+	Case-control	Incident	Bleeding Site: gastric, duodenal Lesion: peptic ulcer, gastritis	Field study. Endoscopy required	No	Questionnaire	0–7 days
Lanas et al., 2006 <sup>(16)</sup>	Selected hospitals in Spain; 2001–4	3353; 20–85	Case-control	All	Bleeding Site: gastric, duodenal Lesion: peptic ulcer	Field study. Endoscopy required	Yes	Questionnaire	0–7 days
Laporte et al., 2004 <sup>(21)</sup>	Selected hospitals in Spain and Italy; 1998–2001	10 006; >18	Case-control	All	Bleeding Site: gastric, duodenal Lesion: peptic ulcer, acute lesions of the gastric mucosa, erosive duodenitis, mixed lesions	Field study. Endoscopy required	Yes	Questionnaire	0–7 days
Biskupiak et al., 2006 <sup>(14)</sup>	Outpatient database, US; 1996–2004	60 212; All	Case-crossover	All	Bleeding, perforation, ulcer Site: gastric, duodenal Lesion: peptic ulcer, upper GI <sup>b</sup>	No	Low dose	Electronic prescriptions	90 days following prescription date

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Table 1. Contd

Study, y	Source population; study period	Study population (N); age (y)	Study design	Type of endpoint	Study endpoint	Case validation	Dose assessment	Exposure assessment	Definition of current use <sup>a</sup>
Lanas et al., 2003 <sup>[22]</sup>	Selected hospitals in Spain; 1995–8	8309; All	Case-control	All	Bleeding Site: gastric, duodenal Lesion: peptic ulcer, erosions, acute lesions of the gastric mucosa	Field study. Endoscopy required	No	Questionnaire	0–7 days
Matikainen and Kangas, 1996 <sup>[12]</sup>	Two hospitals in Finland; 1992–3	204; All	Case-control	All	Bleeding Site: oesophageal, gastric, duodenal Lesion: oesophagitis, peptic ulcer, erosions	Field study. Endoscopy required	No	Questionnaire	0–7 days
Moride and Abenthaim, 1994 <sup>[13]</sup>	Selected hospitals in Montreal, Canada; 1988–90	859; 68+	Case-control	All	Bleeding, perforation Site: gastric, duodenal Lesion: peptic ulcer, gastritis, duodenitis, upper GI <sup>b</sup>	Review medical records	No	Dispensed prescriptions	0–30 days
Kaufman et al., 1993 <sup>[27]</sup>	US, Sweden, Hungary; 1987–92	1733; 18–79	Case-control	Incident	Bleeding Site: gastric, duodenal Lesion: peptic ulcer, gastritis	Field study. Endoscopy required	No	Questionnaire	0–7 days
Langman et al., 1994 <sup>[28]</sup>	Selected hospitals in the UK; 1987–91	3259; 60+	Case-control	All	Bleeding Site: gastric, duodenal Lesion: peptic ulcer	Field study. Endoscopy required	No	Questionnaire	0–30 days
Nobili et al., 1992 <sup>[29]</sup>	Hospital in Northern Italy; 1987–8	1764; All	Case-control	Incident	Bleeding Site: gastric, duodenal Lesion: peptic ulcer, upper GI <sup>b</sup>	Field study. Endoscopy required	No	Questionnaire	0–7 days
Laporte et al., 1991 <sup>[30]</sup>	Selected hospitals in Spain; 1987–8	3557; All	Case-control	Incident	Bleeding Site: gastric, duodenal Lesion: peptic ulcer, acute lesions of the gastric mucosa, erosive duodenitis	Field study. Endoscopy required	No	Questionnaire	0–7 days
Savage et al., 1993 <sup>[31]</sup>	Selected hospitals in Christchurch, New Zealand; 1986	1466; All	Case-control	All	Bleeding, perforation Site: gastric, duodenal Lesion: peptic ulcer	Field study. Endoscopy required	No	Questionnaire	0–7 days

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Table 1. Contd

Study, y	Source population; study period	Study population (N); age (y)	Study design	Type of endpoint	Study endpoint	Case validation	Dose assessment	Exposure assessment	Definition of current use <sup>a</sup>
Henry et al., 1993 <sup>[32]</sup>	Selected hospitals in Newcastle, Australia; 1985–9	1912; All	Case-control	All	Bleeding, perforation Site: oesophageal, gastric, duodenal Lesion: peptic ulcer, erosions, inflammation, upper GI <sup>b</sup>	Field study. Endoscopy required	No	Questionnaire	0–7 days
Somerville et al., 1986 <sup>[34]</sup>	Nottingham University and City Hospitals, UK; 1983–5	667; 60+	Case-control	All	Bleeding Site: gastric, duodenal Lesion: peptic ulcer	Field study. Endoscopy required	No	Questionnaire	0 days (on date of event)

a Number of days before the index date if not defined otherwise.

b 'Upper GI' refers to diagnosis of melena, haematemesis or haemorrhage of the intestinal tract unspecified.

GI = gastrointestinal; GPRD = General Practice Research Database; THIN = The Health Improvement Network.

of peptic ulcer (21 studies),<sup>[7,11,15-31,35,67]</sup> smoking (13 studies),<sup>[7,11,15,18,20,21,23,27-32]</sup> alcohol use (9 studies),<sup>[7,15,19,21,27,28,30-32]</sup> use of proton-pump inhibitors and anti-ulcer medications (11 studies),<sup>[16-23,30,67,68]</sup> and concurrent use of medications increasing the risk of UGIC (16 studies).<sup>[7,11,15,16,19-21,23,27,29-31,33,35,67,68]</sup>

The quality of the studies measured with the NOS was, in general, very good: for the selection component, 12 studies had the maximum score of 4<sup>[7,11,15,22-25,32,33,35,67,68]</sup> and 13 studies had the next highest score of 3;<sup>[13,14,16-19,21,26,28,29,30,32,34]</sup> for comparability, 24 studies had the maximum score of 2;<sup>[7,11,14-19,21-33,35,67,68]</sup> and for the exposure/outcome component, 14 studies had the maximum score of 3<sup>[7,11,13,17-19,23-26,33,35,67,68]</sup> and 10 studies had the next highest score of 2.<sup>[12,14,16,20,21,28-30,32,34]</sup>

The studies included in the meta-analysis allowed us to estimate pooled RRs for the current use of 16 different NSAIDs (table III and figure 2). Forest plots for each individual NSAID are available in the SDC. Using random-effects models, pooled RRs ranged from 1.43 (95% CI 0.65, 3.15) for aceclofenac to 18.45 (95% CI 10.99, 30.97) for azapropazone. Pooled RR was less than 2 for aceclofenac, celecoxib and ibuprofen; between 2 and less than 4 for rofecoxib, sulindac, diclofenac, meloxicam, nimesulide and ketoprofen; between 4 and less than 5 for tenoxicam, naproxen, indometacin and diflunisal; and greater than 5 for piroxicam, ketorolac and azapropazone. Pooled RRs from studies providing results for patients without a history of UGIC were similar to those from the overall analysis except for naproxen (more than 10% change), 3.10 (95% CI 2.45, 3.91) and diclofenac, 3.76 (95% CI 2.71, 5.21). Data in patients with a history of peptic ulcer disease were available only for celecoxib (two studies) and rofecoxib (one study).<sup>[67,68]</sup> The pooled RR for celecoxib in this population was 1.50 (95% CI 1.16, 1.94).

Pooled RRs from case-control studies were higher than those from cohort studies for all NSAIDs except ibuprofen, ketorolac and sulindac. In general, pooled RRs from fixed-effects models were slightly lower than those from random-effects models. In general, there was significant heterogeneity between studies, which decreased in the subsequent subgroup analysis exploring methodological and clinical diversity.



**Table II.** Exclusions applied in observational studies on the risk of upper gastrointestinal complications<sup>a</sup>

Study, y	Prior peptic ulcer disease	Malignancy	Oesophageal varices	Mallory-Weiss syndrome	Alcohol-related disorders	Liver diseases	Coagulopathies	Use of anticoagulants	Nursing home residence	Other
Mandani et al., 2002 <sup>[20]</sup>	-	-	-	-	-	-	-	-	-	-
Menni-Ippolito et al., 1998 <sup>[24]</sup>	Excl.	Excl.	-	-	Excl.	Excl.	Excl.	-	-	-
McMahon et al., 1997 <sup>[26]</sup>	Excl.	-	-	-	-	-	-	-	-	Excl. <sup>b</sup>
Hein-Salmivaara et al., 2007 <sup>[17]</sup>	Excl.	Excl.	-	-	Excl.	-	-	-	Excl.	-
Hippisley-Cox et al., 2005 <sup>[18]</sup>	Excl.	-	-	-	-	-	-	-	-	-
Norgård et al., 2004 <sup>[19]</sup>	Excl.	-	-	-	-	-	-	-	-	-
Castellsague et al., 2011 <sup>[67]</sup>	-	Excl.	Excl.	Excl.	Excl.	Excl.	Excl.	-	-	Excl. <sup>c</sup>
García Rodríguez and Barreales, 2007 <sup>[7]</sup>	-	Excl.	Excl.	Excl.	Excl.	Excl.	Excl.	-	-	-
García Rodríguez and Hernández-Díaz, 2001 <sup>[23]</sup>	-	Excl.	Excl.	Excl.	Excl.	Excl.	Excl.	-	-	-
García Rodríguez et al., 1998 <sup>[25]</sup>	Excl.	Excl.	Excl.	Excl.	Excl.	Excl.	Excl.	-	-	Excl. <sup>d</sup>
García Rodríguez and Jick, 1994 <sup>[11]</sup>	Excl.	Excl.	Excl.	Excl.	Excl.	Excl.	Excl.	-	-	-
Griffin et al., 1991 <sup>[33]</sup>	-	Excl. <sup>e</sup>	Excl. <sup>e</sup>	-	-	-	-	-	-	-
Perez-Gutthann et al., 1997 <sup>[35]</sup>	Excl.	Excl.	Excl.	Excl.	Excl.	Excl.	-	Excl.	-	-
Chang et al., 2011 <sup>[68]</sup>	-	Excl.	-	-	-	-	Excl.	-	-	-
Sakamoto et al., 2006 <sup>[15]</sup>	Excl.	Excl.	Excl.	-	Excl.	-	-	Excl.	-	-
Lanas et al., 2006 <sup>[16]</sup>	-	Excl.	-	-	-	Excl.	Excl.	-	-	-
Laporte et al., 2004 <sup>[21]</sup>	-	Excl.	Excl.	-	-	Excl.	Excl.	Excl.	Excl.	-
Biskupiak et al., 2006 <sup>[14]</sup>	-	Excl.	-	-	-	-	-	Excl.	-	Excl. <sup>f</sup>
Lanas et al., 2003 <sup>[22]</sup>	-	-	-	-	-	-	-	-	-	-
Matikainen and Kangas, 1996 <sup>[12]</sup>	-	Excl.	Excl.	Excl.	-	-	-	-	-	Excl. <sup>g</sup>
Moride and Abenhaim, 1994 <sup>[13]</sup>	-	Excl.	Excl.	-	-	-	-	-	Excl.	-
Kaufman et al., 1993 <sup>[27]</sup>	Excl.	-	-	-	Excl.	Excl.	Excl.	Excl.	-	-
Langman et al., 1994 <sup>[28]</sup>	-	-	-	-	-	-	-	-	-	-
Nobili et al., 1992 <sup>[29]</sup>	Excl.	Excl.	Excl.	Excl.	Excl.	Excl.	Excl.	-	-	-

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Table II. Contd

Study, y	Prior peptic ulcer disease	Malignancy	Oesophageal varices	Mallory-Weiss syndrome	Alcohol-related disorders	Liver diseases	Coagulopathies	Use of anticoagulants	Nursing home residence	Other
Laporte et al., 1991 <sup>[30]</sup>	-	Excl.	Excl.	Excl.	Excl.	Excl.	Excl.	-	-	-
Savage et al., 1993 <sup>[31]</sup>	Excl. <sup>h</sup>	-	-	-	-	-	Excl.	Excl.	-	Excl. <sup>i</sup>
Henry et al., 1993 <sup>[32]</sup>	-	Excl. <sup>o</sup>	Excl. <sup>o</sup>	Excl. <sup>o</sup>	-	-	-	-	-	-
Somerville et al., 1986 <sup>[34]</sup>	-	-	-	-	-	-	-	-	-	-

a Exclusions are from the source population or from the study analysis.  
b History of endoscopy, use of antacids.  
c HIV infection, AIDS, organ transplant.  
d Regional enteritis, use of antacids.  
e Exclusion from cases only.  
f Enteritis, colitis, intestinal diverticula, infectious and parasitic disease, use of oral corticosteroids.  
g Upper GI vascular malformations.  
h Excl. from controls only.  
i Myocardial infarction among controls only.  
**Excl.** = excluded; **GI** = gastrointestinal; - represents that the criteria were not excluded.

Pooled RRs for the effect of daily dose were estimated for eight different NSAIDs. Cut-off values used in each study to define the daily dose of each NSAID are presented in table IV. Variations in cut-off values were, in general, small except for those used for ibuprofen (200 mg) and naproxen (220 mg) in one study,<sup>[14]</sup> and for ibuprofen (<2400 mg) in another study.<sup>[33]</sup> RRs for the use of high daily doses of NSAIDs were approximately 2- to 3-fold greater than RRs for low-medium doses (figure 3). The pooled RR for high daily dose of ibuprofen was similar to that for high daily dose of diclofenac. Exclusion of results from the studies with different cut-off values for ibuprofen<sup>[14,33]</sup> and naproxen<sup>[14]</sup> did not substantially change the pooled results for these individual NSAIDs. For ibuprofen, RRs were 2.15 (95% CI 1.66, 2.79) for low-medium dose and 4.22 (95% CI 1.76, 10.12) for high dose. For naproxen, the RR for low-medium daily dose was 3.62 (95% CI 2.62, 4.99) [the excluded study<sup>[14]</sup> did not provide data on high dose].

A total of 12 studies provided results specifically for upper GI bleeding for eight different NSAIDs; ten of these studies were case-control field studies. Pooled RRs were higher than those from all UGIC (bleeding, perforation and/or obstruction). Pooled RRs were 1.09 (95% CI 0.77, 1.53) for celecoxib; 1.43 (95% CI 0.65, 3.15) for aceclofenac; 1.88 (95% CI 1.00, 3.51) for ibuprofen; 2.25 (95% CI 1.56, 3.25) for rofecoxib; 4.20 (95% CI 3.03, 5.83) for diclofenac; 5.64 (95% CI 3.60, 8.83) for indometacin; 5.72 (95% CI 3.83, 8.53) for naproxen; and 13.36 (95% CI 9.62, 18.54) for piroxicam.

Pooled RRs from studies conducted from the year 2000 onward<sup>[7,15-18,21,67,68]</sup> were slightly higher than those from studies conducted before the year 2000 for ibuprofen, 2.13 (95% CI 1.66, 2.73) versus 1.50 (95% CI 1.12, 2.01); ketoprofen, 4.28 (95% CI 2.36, 7.76) versus 3.70 (95% CI 2.27, 6.05); and nimesulide, 3.89 (95% CI 3.18, 4.74) versus 3.50 (95% CI 2.03, 6.03); but lower for diclofenac, 3.08 (95% CI 2.47, 3.84) versus 3.63 (95% CI 2.81, 4.70).

Only one study provided information on the effect modification of gastroprotective agents.<sup>[18]</sup> In that study, RRs for all individual NSAIDs were lower among patients receiving ulcer-healing drugs than among those not receiving them.

**Table III.** Individual and pooled relative risks (95% CIs) of upper gastrointestinal complications associated with the use of individual NSAIDs

Study, y	NSAID					
	Ibuprofen	Naproxen	Diclofenac	Indometacin	Piroxicam	Ketoprofen
<b>Cohort and nested case-control studies</b>						
García Rodríguez et al., 1998 <sup>[25]</sup>	2.10 (0.62, 7.10)	4.30 (1.65, 11.21)	2.70 (1.51, 4.82)	5.50 (1.60, 18.91)	9.50 (6.52, 13.84)	3.20 (0.87, 11.78)
García Rodríguez and Hernández-Díaz, 2001 <sup>[23]</sup>	2.50 (1.87, 3.35)	4.00 (2.77, 5.78)	4.60 (3.63, 5.83)	5.20 (3.24, 8.34)	6.17 (3.75, 10.15)	3.30 (1.85, 5.89)
García Rodríguez and Barreales, 2007 <sup>[7]</sup>	2.00 (1.39, 2.88)	8.10 (5.20, 12.61)	3.69 (2.93, 4.64)	7.20 (3.79, 13.67)	NA	5.35 (1.73, 16.54)
Griffin et al., 1991 <sup>[33]</sup>	2.30 (1.77, 3.00)	4.30 (3.40, 5.44)	NA	3.80 (2.42, 5.96)	6.40 (4.85, 8.43)	NA
Helin-Salmivaara et al., 2007 <sup>[17]</sup>	1.90 (1.56, 2.31)	3.17 (2.46, 4.09)	4.16 (3.41, 5.08)	3.81 (2.10, 6.91)	6.32 (3.57, 11.18)	3.69 (2.69, 5.06)
Hippisley-Cox et al., 2005 <sup>[18]</sup>	1.58 (1.37, 1.83)	1.97 (1.48, 2.62)	2.07 (1.82, 2.35)	NA	NA	NA
Castellsague et al., 2009 <sup>[67]</sup>	1.71 (0.67, 4.39)	3.42 (1.76, 6.66)	2.10 (1.09, 4.06)	1.50 (0.64, 3.52)	NA	NA
McMahon et al., 1997 <sup>[26]</sup>	0.24 (0.05, 1.19)	4.49 (2.50, 8.06)	5.48 (3.20, 9.39)	2.42 (0.47, 12.44)	9.39 (5.02, 17.56)	NA
Menniti-Ippolito et al., 1998 <sup>[24]</sup>	NA	1.70 (0.52, 5.51)	3.20 (1.90, 5.39)	NA	4.80 (2.79, 8.26)	2.60 (0.93, 7.23)
Perez-Gutthann et al., 1997 <sup>[35]</sup>	2.10 (1.10, 4.00)	3.50 (2.56, 4.79)	3.10 (1.84, 5.22)	4.60 (3.48, 6.07)	4.50 (3.53, 5.74)	4.86 (2.43, 9.74)
<i>Pooled RR</i>						
Random effects	1.94 (1.62, 2.32)	3.67 (2.84, 4.75)	3.33 (2.51, 4.41)	4.27 (3.33, 5.48)	6.32 (4.99, 7.99)	3.72 (2.92, 4.72)
Fixed effects	1.85 (1.68, 2.03)	3.53 (3.15, 3.97)	2.96 (2.72, 3.22)	4.38 (3.65, 5.25)	5.99 (5.20, 6.89)	3.72 (2.92, 4.72)
Heterogeneity ( $\chi^2$ p-value)	0.02	<0.0001	<0.00001	0.18	0.03	0.89
Inconsistency I <sup>2</sup> (%)	56	75	88	32	57	0
<b>Case-control studies</b>						
Chang et al., 2011 <sup>[68]</sup>	1.59 (1.45, 1.74)	2.05 (1.76, 2.38)	2.24 (2.11, 2.38)	1.39 (1.14, 1.70)	2.29 (1.99, 2.64)	1.94 (1.60, 2.36)
Henry et al., 1993 <sup>[32]</sup>	0.70 (0.21, 2.35)	2.80 (1.81, 4.33)	1.70 (1.14, 2.54)	2.50 (1.51, 4.13)	4.80 (2.63, 8.74)	3.60 (1.97, 6.57)
Kaufman et al., 1993 <sup>[27]</sup>	1.00 (0.39, 2.55)	4.00 (1.48, 10.83)	0.90 (0.19, 4.19)	1.60 (0.42, 6.09)	NA	NA
Lanas et al., 2003 <sup>[22]</sup>	NA	4.20 (1.88, 9.36)	4.30 (2.40, 7.70)	NA	21.35 (8.24, 55.34)	NA
Lanas et al., 2006 <sup>[16]</sup>	4.08 (3.12, 5.32)	7.30 (4.69, 11.37)	3.10 (2.29, 4.19)	9.00 (3.91, 20.73)	12.60 (7.81, 20.33)	8.60 (2.53, 29.22)
Langman et al., 1994 <sup>[28]</sup>	1.50 (0.99, 2.27)	10.00 (5.64, 17.72)	3.70 (2.19, 6.26)	10.80 (5.50, 21.20)	13.60 (6.88, 26.90)	23.70 (7.57, 74.16)
Laporte et al., 1991 <sup>[30]</sup>	NA	6.50 (2.16, 19.60)	7.90 (4.29, 14.56)	4.90 (1.97, 12.17)	19.10 (8.24, 44.28)	NA
Laporte et al., 2004 <sup>[21]</sup>	3.10 (1.98, 4.85)	10.00 (5.69, 17.57)	3.70 (2.56, 5.35)	10.00 (4.42, 22.60)	15.50 (9.93, 24.19)	10.00 (3.87, 25.82)
Matikainen and Kangas, 1996 <sup>[12]</sup>	1.12 (0.45, 2.81)	NA	NA	0.66 (0.08, 5.77)	NA	0.40 (0.05, 3.25)
Moride and Abenheim, 1994 <sup>[13]</sup>	0.67 (0.22, 2.04)	NA	NA	3.03 (1.42, 6.47)	5.68 (2.42, 13.34)	NA
Nobili et al., 1992 <sup>[29]</sup>	NA	NA	4.90 (2.86, 8.40)	6.27 (2.44, 16.10)	4.90 (1.32, 18.23)	NA
Sakamoto et al., 2006 <sup>[15]</sup>	NA	NA	10.90 (2.45, 48.44)	NA	NA	NA
Savage et al., 1993 <sup>[31]</sup>	1.86 (0.53, 6.54)	5.10 (2.37, 11.00)	3.30 (1.59, 6.85)	13.90 (3.28, 58.82)	6.40 (2.77, 14.81)	2.40 (0.98, 5.88)
Somerville et al., 1986 <sup>[34]</sup>	1.02 (0.52, 2.00)	2.70 (1.21, 6.04)	NA	4.10 (1.95, 8.62)	6.46 (2.34, 17.85)	NA

Continued next page

Table III. Contd

Study, y	NSAID							
	Ibuprofen	Naproxen	Diclofenac	Indometacin	Piroxicam	Ketoprofen		
<i>Pooled RR</i>								
Random effects	1.60 (1.09, 2.33)	4.73 (2.92, 7.68)	3.37 (2.55, 4.46)	4.24 (2.42, 7.45)	8.32 (4.32, 16.03)	4.25 (2.06, 8.76)		
Fixed effects	1.74 (1.60, 1.88)	2.87 (2.54, 3.25)	2.36 (2.23, 2.50)	2.27 (1.94, 2.66)	3.62 (3.21, 4.07)	2.35 (1.97, 2.79)		
Heterogeneity ( $\chi^2$ p-value)	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001		
Inconsistency $I^2$ (%)	85	89	80	87	94	84		
<b>All studies (cohort, nested case-control and case-control)</b>								
<i>Pooled RR</i>								
Random effects	1.84 (1.54, 2.20)	4.10 (3.22, 5.23)	3.34 (2.79, 3.99)	4.14 (2.91, 5.90)	7.43 (5.19, 10.63)	3.92 (2.70, 5.69)		
Fixed effects	1.78 (1.68, 1.90)	3.21 (2.95, 3.49)	2.53 (2.42, 2.65)	3.00 (2.66, 3.38)	4.45 (4.07, 4.87)	2.75 (2.39, 3.16)		
Heterogeneity ( $\chi^2$ p-value)	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001		
Inconsistency $I^2$ (%)	77	84	86	85	91	75		
Ketorolac Meloxicam Sulindac Azapropazone Diflunisal Tenoxicam								
<b>Cohort and nested case-control studies</b>								
García Rodríguez et al., 1998 <sup>[25]</sup>	24.70 (9.60, 63.54)	NA	4.40 (2.51, 7.72)	NA	NA	NA	NA	4.30 (1.90, 9.72)
García Rodríguez and Hernández-Díaz, 2001 <sup>[23]</sup>	NA	3.80 (0.84, 17.19)	NA	NA	10.30 (3.52, 30.16)	NA	NA	3.40 (0.88, 13.10)
García Rodríguez and Barreales, 2007 <sup>[7]</sup>	NA	2.70 (1.51, 4.83)	NA	NA	NA	NA	NA	NA
Griffin et al., 1991 <sup>[33]</sup>	NA	NA	NA	4.20 (2.78, 6.34)	NA	NA	NA	NA
Helin-Salmivaara et al., 2007 <sup>[17]</sup>	NA	3.41 (2.57, 4.53)	4.00 (3.23, 4.96)	NA	NA	NA	NA	NA
McMahon et al., 1997 <sup>[26]</sup>	NA	NA	NA	NA	19.16 (9.63, 38.12)	14.60 (4.49, 47.48)	4.46 (0.87, 22.88)	NA
Menniti-Ippolito et al., 1998 <sup>[24]</sup>	5.90 (2.13, 16.32)	NA	2.50 (1.19, 5.25)	NA	NA	NA	NA	NA
Perez-Gutthann et al., 1997 <sup>[35]</sup>	NA	NA	NA	3.80 (2.38, 6.06)	NA	6.20 (3.43, 11.21)	NA	NA
<i>Pooled RR</i>								
Random effects	12.23 (3.01, 49.75)	3.27 (2.55, 4.21)	3.92 (3.23, 4.75)	4.02 (2.95, 5.47)	16.00 (8.96, 28.55)	8.12 (3.73, 17.71)	4.10 (2.16, 7.79)	
Fixed effects	12.73 (6.37, 25.43)	3.27 (2.55, 4.21)	3.92 (3.23, 4.75)	4.02 (2.95, 5.47)	16.00 (8.96, 28.55)	7.37 (4.34, 12.51)	4.10 (2.16, 7.79)	
Heterogeneity ( $\chi^2$ p-value)	0.04	0.76	0.45	0.75	0.34	0.20	0.95	
Inconsistency $I^2$ (%)	76	0	0	0	0	38	0	
<b>Case-control studies</b>								
Chang et al., 2011 <sup>[68]</sup>	5.76 (5.14, 6.45)	1.91 (1.66, 2.20)	NA	1.91 (1.61, 2.26)	NA	NA	NA	NA
Henry et al., 1993 <sup>[32]</sup>	NA	NA	NA	2.10 (1.09, 4.05)	NA	1.00 (0.41, 2.45)	NA	NA
Lanas et al., 2006 <sup>[16]</sup>	14.40 (5.20, 39.89)	9.80 (4.03, 23.81)	NA	NA	NA	NA	NA	NA

Continued next page

Table III. Contd

Study, y	NSAID						
	Ketorolac	Meloxicam	Nimesulide	Sulindac	Azapropazone	Diflunisal	Tenoxicam
Langman et al., 1994 <sup>[28]</sup>	NA	NA	NA	NA	31.53 (10.26, 96.94)	NA	NA
Laporte et al., 2004 <sup>[21]</sup>	24.70 (7.96, 76.68)	5.70 (2.18, 14.88)	3.21 (1.85, 5.58)	NA	NA	NA	NA
Savage et al., 1993 <sup>[31]</sup>	NA	NA	NA	3.60 (1.43, 9.08)	NA	NA	NA
<i>Pooled RR</i>							
Random effects	11.20 (4.28, 29.31)	4.44 (1.42, 13.84)	NA	1.96 (1.67, 2.30)	NA	NA	NA
Fixed effects	5.91 (5.28, 6.61)	2.03 (1.77, 2.33)	NA	1.96 (1.67, 2.30)	NA	NA	NA
Heterogeneity ( $\chi^2$ p-value)	0.01	0.0002	NA	0.41	NA	NA	NA
Inconsistency $I^2$ (%)	78	88	NA	0	NA	NA	NA
<b>All studies (cohort, nested case-control and case-control)</b>							
<i>Pooled RR</i>							
Random effects	11.50 (5.56, 23.78)	3.47 (2.19, 5.50)	3.83 (3.20, 4.60)	2.89 (1.90, 4.42)	18.45 (10.99, 30.97)	4.37 (1.07, 17.81)	4.10 (2.16, 7.79)
Fixed effects	6.03 (5.39, 6.73)	2.27 (2.01, 2.56)	3.83 (3.20, 4.60)	2.29 (1.98, 2.64)	18.45 (11.02, 30.87)	4.40 (2.79, 6.93)	4.10 (2.16, 7.79)
Heterogeneity ( $\chi^2$ p-value)	0.001	<0.00001	0.56	0.001	0.36	0.0004	0.95
Inconsistency $I^2$ (%)	78	82	0	78	1	87	0
<b>NSAID</b>							
<b>Cohort and nested case-control studies</b>							
Garcia Rodriguez and Barreales, 2007 <sup>[7]</sup>	NA	2.73 (1.67, 4.46)	2.30 (1.40, 3.79)				
Helin-Salmivaara et al., 2007 <sup>[17]</sup>	NA	2.11 (1.46, 3.04)	2.58 (1.98, 3.37)				
Hippisley-Cox et al., 2005 <sup>[18]</sup>	NA	1.25 (0.91, 1.72)	1.79 (1.42, 2.26)				
Castellsague et al., 2009 <sup>[67]</sup>	NA	1.10 (0.69, 1.76)	3.58 (2.24, 5.73)				
Mamdani et al., 2002 <sup>[20]</sup>	NA	1.01 (0.65, 1.57)	1.90 (1.29, 2.79)				
Norgård et al., 2004 <sup>[19]</sup>	NA	1.30 (0.65, 2.60)	2.10 (1.24, 3.53)				
<i>Pooled RR</i>							
Random effects	NA	1.49 (1.09, 2.04)	2.25 (1.84, 2.75)				
Fixed effects	NA	1.48 (1.25, 1.76)	2.19 (1.90, 2.51)				
Heterogeneity ( $\chi^2$ p-value)	NA	0.01	0.1				
Inconsistency $I^2$ (%)		67	45				
<b>Case-control studies</b>							
Chang et al., 2011 <sup>[68]</sup>	NA	1.52 (1.27, 1.82)	NA				
Lanas et al., 2003 <sup>[22]</sup>	0.7 (0.30, 1.60)	NA	NA				

Continued next page

Table III. Contd

Study, y	NSAID		
	Acetofenac	Celecoxib	Rofecoxib
Laporte et al., 2004 <sup>[21]</sup>	1.4 (0.60, 3.30)	NA	7.20 (2.28, 22.77)
Lanas et al., 2006 <sup>[16]</sup>	2.6 (1.50, 4.60)	0.97 (0.44, 2.13)	2.10 (1.10, 4.00)
<i>Pooled RR</i>			
Random effects	1.43 (0.65, 3.15)	1.44 (1.08, 1.92)	3.53 (1.07, 11.64)
Fixed effects	1.65 (1.10, 2.48)	1.49 (1.25, 1.77)	2.82 (1.61, 4.95)
Heterogeneity ( $\chi^2$ p-value)	0.03	0.27	0.07
Inconsistency $I^2$ (%)	70	16	70
<b>All studies (cohort, nested case-control and case-control)</b>			
<i>Pooled RR</i>			
Random effects	1.43 (0.65, 3.15)	1.45 (1.17, 1.81)	2.32 (1.89, 2.86)
Fixed effects	1.65 (1.10, 2.48)	1.48 (1.31, 1.68)	2.22 (1.94, 2.54)
Heterogeneity ( $\chi^2$ p-value)	0.03	0.02	0.07
Inconsistency $I^2$ (%)	70	57	47

$\chi^2$  = Chi-squared; NA = not available; RR = relative risk.

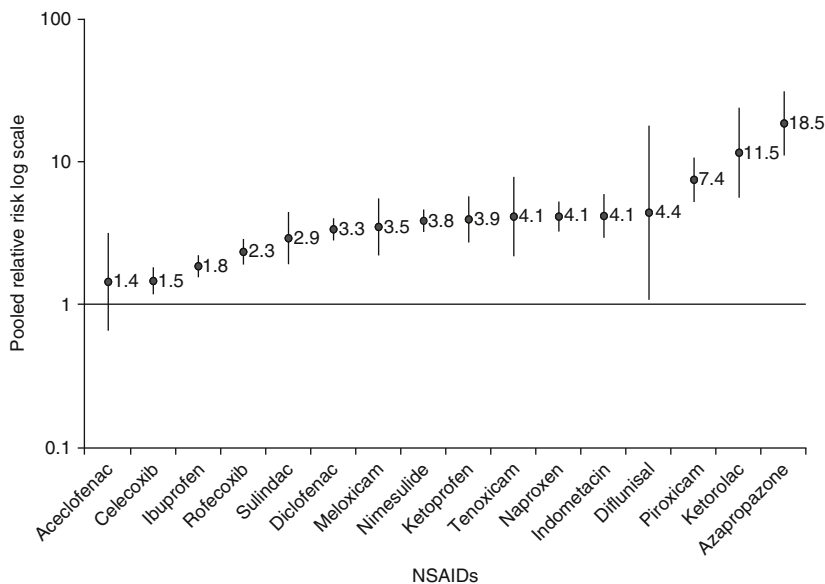
#### 4. Discussion

The results from this meta-analysis confirmed the variability of RRs among individual NSAIDs. The lowest RRs were observed for the use of acetofenac, celecoxib and ibuprofen, and the highest for the use of piroxicam, ketorolac and azapropazone. Intermediate RRs, between approximately 2 and 4, were observed for the rest of the NSAIDs for which at least three estimates were available: rofecoxib, sulindac, diclofenac, meloxicam, nimesulide, ketoprofen, tenoxicam, naproxen, indometacin and diflunisal.

The use of high daily doses of individual NSAIDs was associated with approximately a 2- to 3-fold increase of RRs for UGIC compared with the use of low-medium doses, except for celecoxib, for which we did not observe a dose-response relationship. For most NSAIDs, there were no major differences between studies restricted to patients without a history of peptic ulcer and those that included all patients, and between studies conducted before and after the year 2000. Data from the studies included in the meta-analysis were insufficient to estimate pooled RRs for the duration of use of individual NSAIDs and for the concurrent use of gastro-protective agents.

In general, there was significant heterogeneity among studies, although it improved or tended to disappear in the subgroup analysis conducted by study design, type of complication, history of peptic ulcer disease and dose of NSAIDs. However, the  $\chi^2$  test to detect heterogeneity is very sensitive to the number of studies (or sample size) included in the analysis. Meta-analysis of a small number of studies may be underpowered to detect heterogeneity. On the other hand, when the number of studies is large, the  $\chi^2$  test has a high power to detect a small amount of heterogeneity that may be clinically unimportant.

Most studies evaluated the role of confounding factors other than age and sex. One of the concerns in observational studies is the effect of confounding by indication. This is particularly relevant for selective COX-2 inhibitors as there is evidence that they have been preferentially prescribed to patients at high risk of UGIC.<sup>[20,46]</sup>



**Fig. 2.** Pooled relative risks and 95% CIs of upper gastrointestinal complications associated with the use of individual NSAIDs. Vertical bars denote 95% CIs.

Many studies attempted to minimize the effect of confounding by indication by adjusting for relevant comorbidity, including GI, CV and other chronic disease; concurrent use of medications; and prior use of healthcare services. Some studies also evaluated confounding by indication by conducting stratified analysis by markers of disease severity or restricted the study population to patients at high risk of UGIC.<sup>[7,19]</sup>

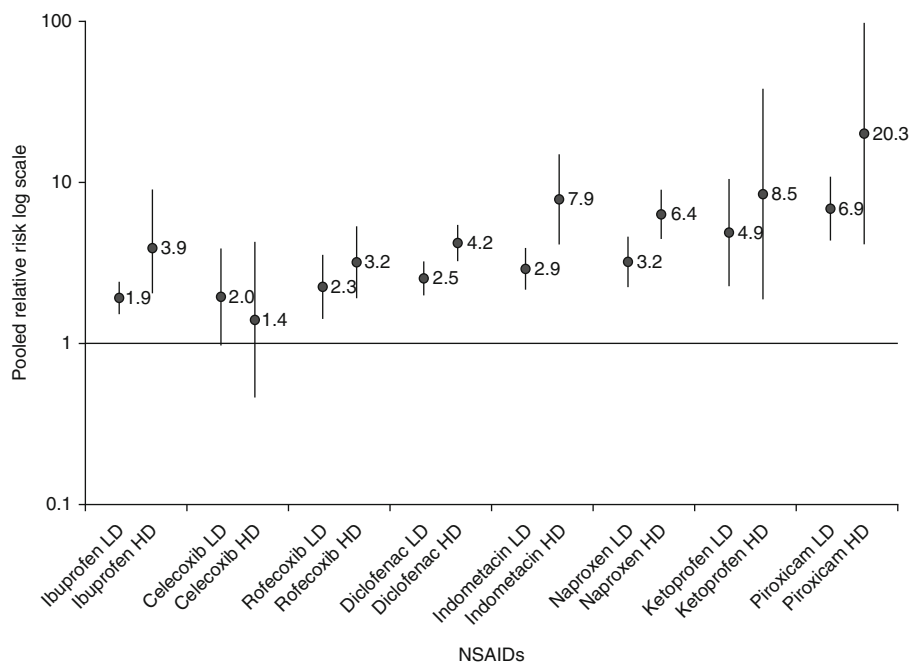
Pooled RRs from case-control studies were higher than those obtained from cohort studies, although CIs were wider. Most case-control studies were field studies restricted to upper GI bleeding. Thus, a more specific and strict definition of UGIC probably increased the internal validity of these studies. On the other hand, recall bias, leading to overestimation of effects, could be present in these case-control studies in which

**Table IV.** Cut-off values (mg) used to define daily dose<sup>a</sup> of NSAIDs in observational studies on the risk of upper gastrointestinal complications

Study, y	NSAID							
	Naproxen	Ibuprofen	Diclofenac	Indometacin	Piroxicam	Ketoprofen	Celecoxib	Rofecoxib
Castellsague et al., 2009 <sup>[67]</sup>	≤1200	≤1200	≤100	≤100	NA	NA	≤200	≤25
García Rodríguez and Barreales, 2007 <sup>[7]</sup>	≤750	≤1200	≤100	≤75	NA	≤150	≤200	≤25
García Rodríguez et al., 1998 <sup>[25]</sup>	≤500	NA	<75	NA	≤20	NA	NA	NA
García Rodríguez and Jick, 1994 <sup>[11]</sup>	≤750	≤1500	≤100	≤75	NA	NA	NA	NA
Griffin et al., 1991 <sup>[33]</sup>	<500	<2400	NA	<50	<20	NA	NA	NA
Perez-Gutthann et al., 1997 <sup>[35]</sup>	≤750	≤1500	≤100	≤75	≤20	≤150	NA	NA
Laporte et al., 2004 <sup>[21]</sup>	NA	<1800	<75	≤50	≤20	<200	NA	NA
Biskupiak et al., 2006 <sup>[14]</sup>	220	200	NA	NA	NA	NA	NA	NA

<sup>a</sup> Cut-off values are for the definition of low-medium vs high daily dose of NSAIDs.

NA = not applicable.



**Fig. 3.** Pooled relative risks and 95% CIs of upper gastrointestinal complications associated with the daily dose of individual NSAIDs. See table IV for cut-off values used in each study to define high dose and low-medium dose. Vertical bars denote 95% CIs. **HD**=high dose; **LD**=low-medium dose.

exposure to NSAIDs was assessed retrospectively by self-reported questionnaires.

Most studies included in this meta-analysis applied broad restrictions to the source population by excluding patients with major risk factors for peptic ulcer disease. Restriction results in more homogeneous study populations and increases the internal validity of studies.<sup>[69]</sup> On the other hand, absolute rates for UGIC obtained from studies conducted in restricted populations underestimated the rate of the disease.<sup>[24,26]</sup> This can impact public health policy, particularly when patients with risk factors for UGIC are excluded from studies estimating incidence rates.

Results for new users of NSAIDs were available for only three studies. The rest of the studies provided results for new and prevalent users overall. Inclusion of prevalent users of NSAIDs may result in an overrepresentation of the group of patients who tolerate the treatment (survivors). This is a selection process that may introduce bias if the risk varies with time since the beginning of treatment.

In the case of UGIC and the use of NSAIDs, some studies have shown that the risk is higher at the beginning of treatment because susceptible patients are affected early in therapy.<sup>[13]</sup> Restricting the study to new users of NSAIDs prevents bias from overrepresentation of long-term users who tolerate the treatment.<sup>[70,71]</sup>

Most studies confirmed cases of UGIC by requiring a positive endoscopy or other diagnostic or therapeutic procedure. However, some studies conducted in databases, which identified potential cases of UGIC by discharge codes, did not conduct any validation of the cases identified, thus introducing misclassification of the outcome.<sup>[72]</sup> Studies conducted in Canada and Italy show that the positive predictive values (PPVs) for specific discharge diagnoses (gastric ulcer and duodenal ulcer) range from 92% to 100%, whereas PPVs for other specific diagnoses (peptic ulcer and gastrojejunal ulcer) range from 81% to 84%, and those for the non-specific diagnoses (GI haemorrhage) range from 54% to 68%.<sup>[67,73,74]</sup> Overall, the results



from the studies included in this meta-analysis that did not confirm the cases identified may be biased towards the null, assuming non-differential outcome misclassification. Cohort studies estimating incidence rates of UGIC based on the cases identified through hospital discharge codes without performing any validation may overestimate absolute rates of UGIC by including non-cases or cases with uncertain clinical validity.<sup>[17,20,75]</sup>

The benefit-risk balance of individual NSAIDs is mainly driven by their GI and CV safety profile. Recent meta-analyses of observational studies on the CV risk associated with individual NSAIDs show that rofecoxib and diclofenac are associated with the highest RR and naproxen and ibuprofen with the lowest RR.<sup>[76,77]</sup> For cerebrovascular events, the increase in risk appears to be similar between naproxen, ibuprofen and diclofenac, and higher for rofecoxib.<sup>[78]</sup> In our study, ibuprofen was in the lowest range of pooled RRs for UGIC; rofecoxib and diclofenac were in the middle range; and naproxen was associated with a higher RR. However, estimates for individual NSAIDs varied by dose. The pooled RR of UGIC for high-dose ibuprofen was similar to the RR for high-dose rofecoxib and diclofenac, and the use of high-dose naproxen was associated with a higher RR.

## 5. Conclusions

We conclude that the results obtained in this meta-analysis are in line with those from other meta-analyses published in the last decade and confirm the variability of the risk of UGIC among individual NSAIDs as they are used in clinical practice.<sup>[1,2,5]</sup> Our meta-analysis provides pooled RRs for many individual NSAIDs, including, for the first time, nimesulide, tenoxicam and diflunisal. Aceclofenac, celecoxib and ibuprofen (analgesic and anti-inflammatory doses combined) were the NSAIDs with the lowest RR, whereas piroxicam, ketorolac and azapropazone were those with the highest RRs. Intermediate RRs were observed for the rest of the NSAIDs: rofecoxib, sulindac, diclofenac, meloxicam, nimesulide, ketoprofen, tenoxicam, naproxen, indometacin and diflunisal. The impact on the findings across studies related to varying study design approaches – including

choices in the definition and validation of UGIC, exposure assessment and analysis of new or prevalent users – should be taken into account when designing new studies. For individual NSAIDs, data on the effect of dose, duration of use and concurrent use of other medications are still scarce. These gaps need to be addressed in future studies, including those to be conducted in the ongoing SOS project (<http://www.sos-nsaids-project.org/>).

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Miriam Sturkenboom is coordinating the FP-7-funded SOS project. She is heading a research group at the Erasmus University that occasionally does drug safety studies for pharmaceutical companies such as AstraZeneca, Pfizer, Eli Lilly and Novartis. Most of these companies produce NSAIDs but they were not involved in this study.

Annie Fourier-Reglat and Federica Nicotra have no conflicts of interest that are directly relevant to the content of this study.

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