

The SOS Project: Cardiovascular and Gastrointestinal Safety of NSAIDs: Preliminary Results of a Systematic Review of Epidemiological Studies



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BACKGROUND

NSAIDs are widely used in medical practice for the symptomatic treatment of acute pain and chronic inflammatory diseases. The cardiovascular (CV) safety of nonsteroidal anti-inflammatory drugs (NSAIDs) has been the focus of attention since the introduction of cyclooxygenase-2 (COX-2) inhibitors, which offer a better gastrointestinal (GI) safety profile than the nonselective NSAIDs. Therefore, it is of clinical relevance to evaluate the CV and GI safety profile of the most frequently used individual NSAIDs. In 2008 the European Commission funded the Safety Of non-Steroidal anti-inflammatory drugs (SOS) collaborative project to develop a population-based decision model for treatment and regulatory decision-making regarding the use of NSAIDs. As part of this project, a systematic review of published epidemiological studies on the use of individual NSAIDs and the risk of CV and GI events is ongoing in order to identify gaps in research and to provide overall estimates of risks relative to non-use or remote use of NSAIDs.

OBJECTIVE

The objective of the present study is to summarize estimates for the risk of myocardial infarction (MI) or acute coronary syndrome (ACS) and upper GI complications associated with the use of selected individual NSAIDs versus non-use or remote use of NSAIDs.

METHODS

Studies were identified through a systematic literature search in the PubMed database using broad Medical Subject Headings and free-text search terms for NSAIDs, COX-2 inhibitors, and CV and GI endpoints. This search was supplemented with a manual search of the bibliographic references cited in relevant articles, including systematic reviews and meta-analyses.

The literature search was focused on studies on human subjects published in English between January 1, 1990, and November 30, 2008, for CV outcomes and between January 1, 1980, to November 30, 2008, for GI outcomes.

Inclusion Criteria

- Study Types
 - Observational, either cohort or case-control studies
 - Meta-analysis of observational studies

Measures

Studies were required to provide one of the following:

- Incidence rates
- Measures of association (e.g., odds ratios, relative risks [RR], rate ratios, hazard ratios) between the use of NSAIDs and prespecified CV or GI endpoints.

Exposures

Studies were required to provide results for exposure to any individual NSAID, including selective COX-2 inhibitors.

Endpoints

Selected endpoints were the following:

- CV: ACS, including MI, serious coronary heart disease, and unstable angina
- GI: upper GI complications, including peptic ulcer, upper GI bleeding, and perforation

Exclusion Criteria

- Clinical trials, case reports, case series, ecological studies and analysis of spontaneous reports, and studies based on voluntary reporting of events
- Studies published only in abstract form or letters to the editor
- Noncomparative studies or studies with external comparison groups
- Studies conducted in hospitalized or institutionalized patients
- Studies evaluating the risk of CV or GI with the use of NSAIDs only as a group

Two members of the RTI Health Solutions study team, in consultation with other team members, reviewed the titles and abstracts of all articles identified in the literature search and selected for full-text review those articles that potentially met the inclusion criteria. Full-text articles for these selected studies were obtained and reviewed independently by two reviewers to identify eligible articles. If a publication was selected as eligible by only one of the two reviewers, a consensus was reached by consultation with a third reviewer.

Meta-analysis

We conducted a meta-analysis of new individual studies not included in prior meta-analysis. Summary RRs for ACS and upper GI complications associated with ibuprofen, diclofenac, naproxen, celecoxib, and rofecoxib were estimated using random effect models.^{1,2}

RESULTS

Table 1 presents the results of the literature for ACS or MI and upper GI complications related to the use of individual NSAIDs.

Table 1. CV Events and Upper GI Complications Associated With the Use of Individual NSAIDs vs. Non-Use or Remote Use

Study Type	Cardiovascular Studies			Upper GI Complications		
	Studies Excluded	Studies Included	Total	Studies Excluded	Studies Included	Total
Individual studies						
Literature search	-	3,193	3,193	-	2,667	2,667
Review title and abstract	3,128	65	65	2,560	107	107
Cross-referencing	-	10	75	-	13	120
Review full-text article	20	55	55	63	57	57
ACS events or upper GI complications and use of individual NSAIDs vs. non-use or remote use	25	30	30	32	25	25
New studies not included in past meta-analyses	23	7	7	14	11	11
Meta-analyses						
MI or GI complications	-	4	4	-	9	9
MI or upper GI complications	1	3	3	1	8	8
Data on individual NSAIDs vs. non-use or remote use	-	3	3	5	3	3
Good methodological quality	1	2	2	-	3	3

Cardiovascular Complications

Individual Studies

The search in PubMed identified 3,128 studies, of which 55 met the inclusion criteria. Endpoints included the following:

- ACS (n = 36)
- Recurrent MI events (n = 2)
- Cerebrovascular events (n = 8)
- Heart failure (n = 6)
- Mortality (n = 2)
- Composite endpoint (n = 8)
- Data on several endpoints (n = 7).

From the 36 articles that reported data on ACS, 13 were new studies not included in past meta-analyses. After excluding those articles that included reference categories other than non-use or remote use, a total of seven studies were considered.

Meta-analyses

A total of four meta-analyses investigating the risk of MI due to individual NSAID use were found; out of these, two meta-analyses were considered.

Upper Gastrointestinal Complications

Individual Studies

From 2,667 studies identified in the PubMed search, 57 studies met our inclusion criteria. Out of these, 25 reported results for upper GI complications associated with the use of individual NSAIDs vs. non-use or remote use of NSAIDs. A total of 11 of these studies were new studies not included in prior meta-analyses and were included in the current analysis.

Meta-analyses

We identified nine meta-analyses assessing the risk of GI complications associated with the use of NSAIDs. Three of these meta-analyses provided results for upper GI complications and the use of individual NSAIDs.

Effect of Individual NSAIDs

Figures 1 and 2 report the RRs and 95% confidence intervals (CIs) for CV events (MI and ACS) and upper GI complications, respectively, and the following NSAIDs: ibuprofen, diclofenac, naproxen, celecoxib, and rofecoxib. The random effects model was used to calculate the pooled estimate.

Figure 1 displays the relative risks RRs estimated by pooling studies published before 2006 and included in the two most recent published meta-analysis and the estimates for each of the seven published studies that were not included in the prior meta-analyses. The pooled RR estimated from the new studies was consistent with those previously obtained from the meta-analyses for ibuprofen, diclofenac, naproxen, celecoxib, and rofecoxib. Results of the individual studies were homogeneous across the studies for ibuprofen and diclofenac, but heterogeneous for naproxen, celecoxib, and rofecoxib.

Figure 2 shows the 11 individual studies and three meta-analyses included in the analysis. All three of the meta-analyses included ibuprofen, and two of them included diclofenac and naproxen. None of the meta-analyses reported a selective NSAID. The pooled estimates for the new studies including information from ibuprofen, diclofenac, and naproxen were in line with previous meta-analyses. There are six studies for upper GI complications and use of celecoxib, and seven for rofecoxib. The pooled RR for upper GI complications was 1.38 (95% CI: 0.97-1.96) for celecoxib, and 2.01 (95% CI: 1.64-2.66) for rofecoxib. A visual exam of the heterogeneity showed that celecoxib had the most homogeneous results across studies, followed by rofecoxib and diclofenac, while the results from diclofenac and naproxen were more homogeneous.

Figure 1. ACS or MI Events and Use of Individual NSAIDs vs. Non-Use or Remote Use

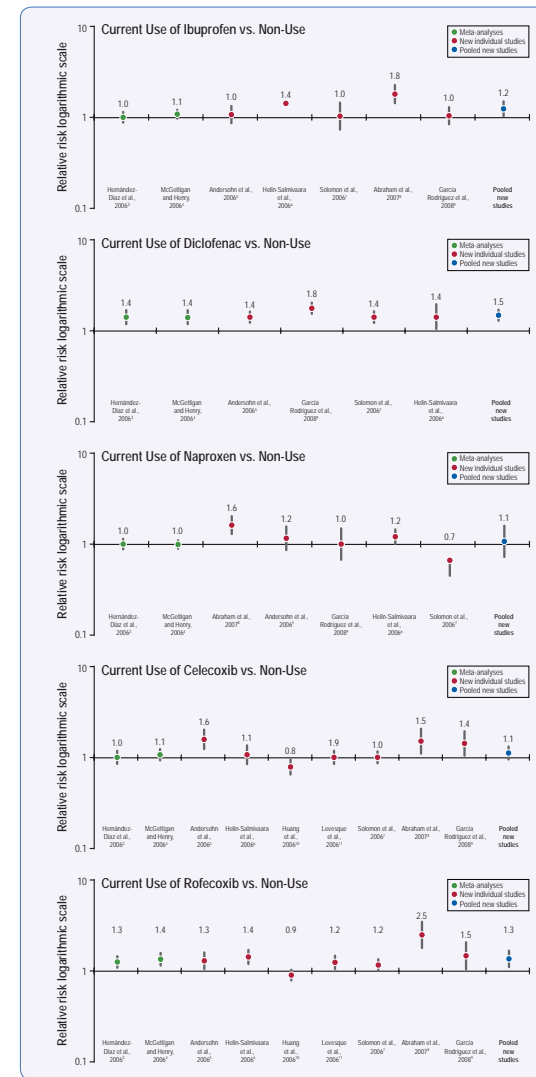
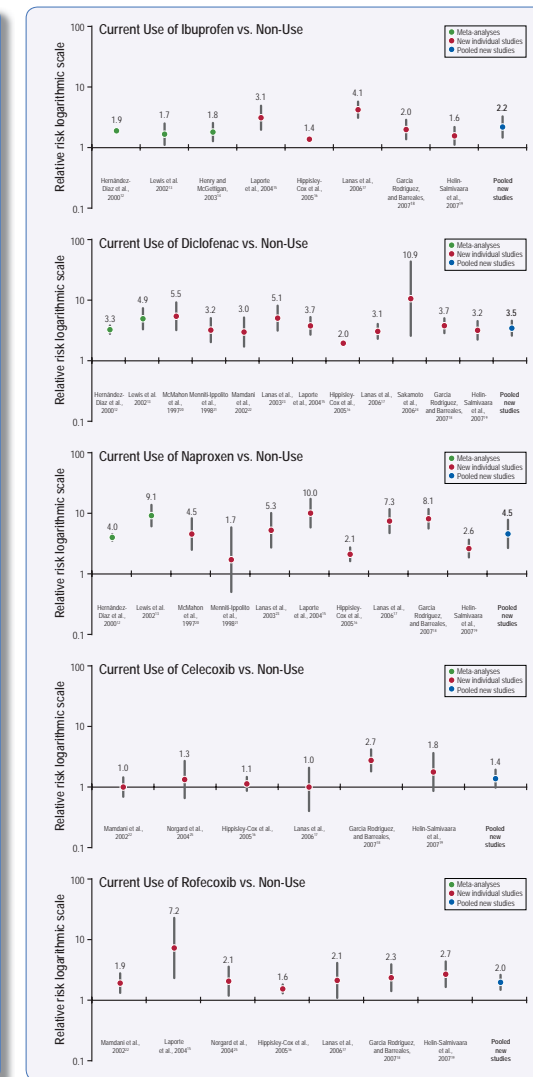


Figure 2. Upper GI Complications and Use of Individual NSAIDs vs. Non-Use or Remote Use



CONCLUSIONS

- Since the most recent published meta-analysis:
 - 13 new studies have been published assessing the risk of ACS events associated with individual NSAID use.
 - 11 studies have been published assessing the risk of upper GI complications and the use of individual NSAIDs.
- The pooled RRs estimated for the new studies were consistent with those previously obtained from prior meta-analyses for:
 - ACS: ibuprofen, diclofenac, naproxen, celecoxib, and rofecoxib
 - Upper GI complications: ibuprofen, diclofenac, and naproxen
 - Pooled estimate for upper GI complications was 1.38 (95% CI: 0.97-1.96) for celecoxib and 2.01 (95% CI: 1.64-2.66) for rofecoxib. Neither of these two selective NSAIDs were included in prior meta-analyses.
- Prior meta-analyses did not estimate the effect of dose and duration of each individual NSAID on the risk of ACS. There are limited data on the effect of dose and duration of each individual NSAID on the risk of GI complications.
- These results support the need for further studies and meta-analyses to assess the CV and GI safety of individual NSAIDs. The meta-analysis of observational studies is ongoing.

REFERENCES

Provided on the handout.

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August 16-19, 2009
Providence, RI, United States

