

# The SOS project (Safety of NSAIDs): Preliminary results of published meta-analyses review



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## Background

After rofecoxib withdrawal, a debate on cardiovascular (CV) and gastrointestinal (GI) safety of non-steroidal anti-inflammatory drugs (NSAIDs) was raised. To date, there are insufficient data to conclude on thrombotic risk related to every individual NSAID, both traditional or selective. Therefore, an increased risk cannot be excluded for many individual products and should be further explored (e.g. exact magnitude, timing of risk, effect of dose). In 2008 the European Commission funded the Safety Of non-Steroidal anti-inflammatory drugs (SOS) project. This project, conducted by a consortium of 11 research groups, is aiming to develop a decision model for treatment and regulatory decision-making regarding NSAIDs. The first part of SOS was aimed to define knowledge gaps in terms of safety data retrieved from clinical studies. The most relevant randomized clinical trials (RCTs) will be identified using the results of a systematic review of published meta-analyses (MAs) of RCTs focused on NSAID safety, particularly GI or CV safety. The latter is described here.

## Objectives

The main objective of this study was to identify MAs of RCTs reporting CV or GI safety data of NSAIDs. As a secondary aim, potential knowledge gaps in terms of GI and CV events were to be identified.

## Methods

There is no standardized method to perform a systematic review of MAs. The MeSH database was used to identify terms for MAs and RCTs; other terms were also added through expertise (e.g. pooled analysis). The MeSH database was also used to identify terms related to SOS adverse reaction of interest: gastrointestinal complication (upper and lower bleeding, perforation), myocardial infarction, heart failure, stroke. A wide number of terms were also included (e.g. cardiovascular or gastrointestinal). All individual NSAIDs (including aspirin 100 mg/d) were included. A literature search was performed using 4 different online databases of medical literature: Medline, ISI-Web of Science, Cochrane and SCOPUS, and it was limited to articles in English published between 1983 and 2008. Four pharmacoepidemiologists participated in the selection process, with a final cross-validation stage.

## Results (1)

After running the initial search for MAs in Medline, ISI, Scopus and Cochrane, 1,865 references were identified. After screening titles and abstracts of the corresponding articles and elimination of duplicates, 1,710 were excluded and 155 were retained for retrieval and examination of the full-text version. These examinations led to exclusion of 24 other references (14 were not quantitative pooled analysis of RCTs, 6 were Cochrane systematic reviews for which a more recent update was available and 3 focused on other products than those of interest) (figure 1). Thus, a total of 131 were eligible for the identification of the RCTs.

## Results (2)

Figure 1. Meta-analysis selection process.

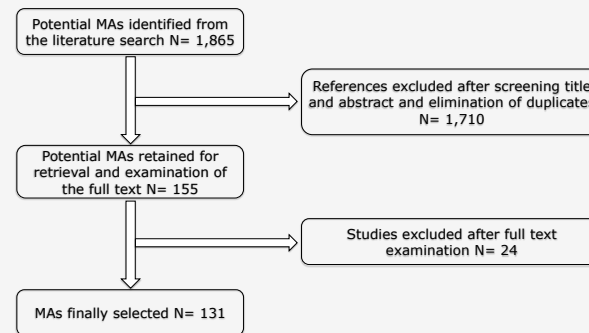


Table 1. Meta-analyses per drug.

Drugs	Number of MAs*
Amitolmetin	2
Aspirin	8
Celecoxib	16
Dexibuprofen	1
Diclofenac	7
Etodolac	2
Etoricoxib	6
Flurbiprofen	2
Ibuprofen	7
Indomethacin	10
Lumiracoxib	4
Meloxicam	6
Nabumetone	1
Naproxen	4
Nimesulide	3
Parecoxib	1
Piroxicam	2
Rofecoxib	14
Valdecoxib	6
COXIB §	16
Traditional NSAIDs §	37

\*The same MA could examine more than one drug.  
§ globally considered

As shown in Table 1, celecoxib (16 MAs), rofecoxib (14), and indomethacin (10) were the most frequently individually studied NSAIDs. Only one MA was performed on dexibuprofen, etodolac, nabumetone or piroxicam. Moreover, 48 NSAIDs, among which some widely used ones, were never the subject of a MA that reported on safety aspects (e.g. ketoprofen, mefenamic acid, or ketorolac). Among the 62 MAs having specific safety outcomes, 30 regarded COXIBs, 20 traditional NSAIDs, and 12 both classes. A total of 26 MAs specifically investigated CV safety, 20 concerning COXIB, 2 traditional NSAIDs, and 4 both classes. A total of 24 MAs specifically investigated GI safety, 9 concerning COXIBs, 7 traditional NSAIDs and 8 both classes. Only one MA investigated specifically both the GI and CV safety of a traditional NSAID (meloxicam). Celecoxib (7 MAs), rofecoxib (3 MAs), and valdecoxib (3 MAs) were the most studied drugs in terms of CV safety. Among traditional NSAIDs, only diclofenac and meloxicam were specifically studied for their CV safety (one MA each). Meloxicam (4 MAs), celecoxib (3 MAs), diclofenac, rofecoxib and valdecoxib (2 MAs each) were the most meta-analyzed drugs in terms of GI safety. Finally, 5 efficacy MAs (1 nimesulide, 4 traditional NSAIDs) were performed on paediatric patients, 12 in preterm infants (8 indomethacin, 3 ibuprofen, 1 traditional NSAIDs).

## Conclusions

As a quantitative analysis of published MAs, this study allows certain conclusions: 1) around half of marketed NSAIDs have never been the subject of a MA that reported on safety aspects, maybe because the available RCT data are not sufficient to be informative on their safety profile; 2) CV safety of NSAIDs is confirmed as an important topic, but the information retrievable from MAs concerns almost exclusively the selective COX-2 inhibitors; 3) safety of NSAIDs in children were never considered as primary topic among the retrieved MAs.

