Non-steroidal anti-inflammatory drugs and cardiovascular risk

Summary

Objetive. To review the data available on cardiovascular risk of traditional non-steroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 agents. **Material and methods.** A search of observational studies, clinical trials and systematic reviews in MEDLINE was performed to evaluate cardiovascular risk among different NSAIDs and to compare the intake of such agents to no treatment as well. Practical guidelines were also searched for in MEDLINE and recommendations on the management of such risk published on the online web pages of the European Medicines Agency (EMEA) and the U.S. Food and Drug Administration. Where a systematic review is found that synthesizes the data from various studies, then only the results of this review will be presented. **Results and conclusions.** The distinction between traditional NSAIDs and coxibs makes no sense, given that some of the first possess a similar COX-2 selectivity as the latter. The coxibs are associated with greater cardiovascular risk, and thus should not be employed in patients with a high cardiovascular risk. Ibuprofen in doses of up to 1,200 mg daily and naproxen are the anti-inflammatory agents with the most available information on safety with regard to cardiovascular risk. Diclofenac seems to carry a greater risk. The use of safer agents should be considered, and the NSAIDs should be employed in low doses and for the shortest period possible. The use of NSAIDs in patients with heart failure and those under treatment with aspirin should be avoided as far as possible.

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Introduction

In 2004 rofecoxib was withdrawn from the market due to increasing reports of cardiovascular events observed in clinical trials. This fact, complicated by a lamentable falsification in the communication of adverse effects[1], brought about reasonable alarm that obliged a new reflection on the cardio-vascular safety of both traditional NSAIDs and the selective inhibitors of cyclooxygenase-2, known as COX-2 inhibitors or coxibs. From this moment, studies have been published with the aim of clarifying and studying the safety profile of this class of NSAIDs. The European Medicines Agency (EMEA) has issued several warnings on the matter, modified technical drug information of these products by introducing new contraindications and precautions. In addition the EMEA has elaborated a detailed report based on data from both clinical trials and epidemiological studies that are published or not[2].

NSAIDs are a class of drugs that are widely used. In an attempt to study the situation in Navarre, it is known that 16,200 patients undergo prolonged treatment. This accounts for 3% of the population. Of these, 14% are also treated with antiplatelet agents or anticoagulants*.

In table 1, it is surprising to note the high percentage of patients with cardiovascular risk who are under treatment with coxibs.

Traditional NSAIDs and coxibs. Are they really different?

Although many studies differentiate between traditional NSAIDs and coxibs, in reality some of the first traditional NSAIDs, like diclofenac and meloxicam present a high selectivity for COX-2 in the same order as any coxib[3,4] (figure 1). This is important when comparing the cardiovascular risk of different drugs, given that this risk is usually associated with COX-2 selectivity (figure 2). To augment the confusion, the classification of drugs in function of their selectivity to COX-2 is not uniform in different studies. A recent guideline recommends abandoning the distinction between coxibs and traditional NSAIDs and referring to all these agents as NSAIDs while being aware of the different selectivity profiles and the adverse effects of each drug[5].

Why does cardiovascular risk increase?

Various mechanisms have been proposed to explain the increased cardiovascular risk of NSAIDs. The most obvious is the increase in blood pressure and the liquid retention associated with traditional NSAIDs and coxibs.

The implication of the selectivity of COX-2 inhibitors in cardiovascular risk can be based on the imbalance between the production of prostacyclin

Table 1. NSAIDs prescription profile in Navarre, Spain, in 2008.

INDICATOR	MEDIAN	INTERQUARTILE RANGE
% chronic patients[a] taking NSAIDs older than 70 years	49%	41% to 57%
% chronic patients[a] taking NSAIDs diagnosed with cardiovascular disease[b]	23%	20% to 28%
% patients taking coxibs who have cardiovascular disease[b]	11%	10% to 14%

(a) Long-term use of NSAIDs registered in the computerised clinical record.

(b) Ischemia, myocardial infarction, heart failure, stroke, cerebrovascular disease, peripheral vascular disease.

(*) Data from prescriptions registered during may-july 2008. Patients who received more than 30 defined daily doses during the study period were included.
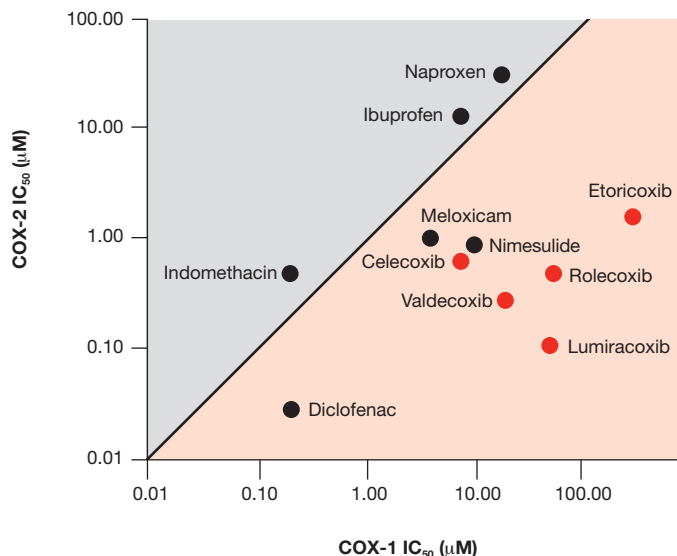
Figure 1. Selectivity for COX-1 or COX-2 inhibition. The diagonal line indicates equivalent COX-1 and COX-2 inhibition. Drugs plotted below the line are more COX-2 selective than drugs plotted above the line. The distance to the line is a measure of selectivity. For example, lumiracoxib is the compound with the highest degree of selectivity for COX-2 as its distance to the line is the largest. Celecoxib and diclofenac have similar degrees of selectivity for COX-2, as their distances to the line are similar; however, diclofenac is active at lower concentrations and thus located more to the left[4].
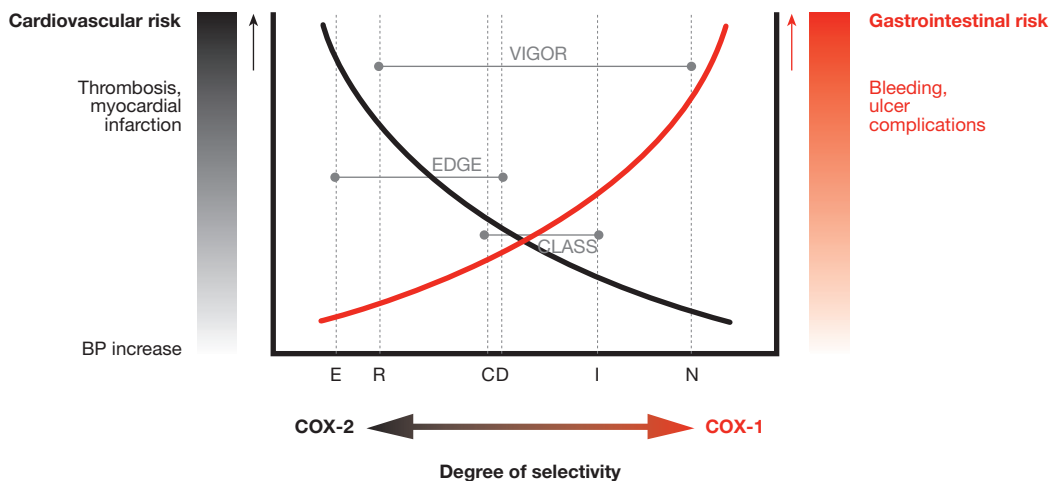
E: Etoricoxib. **R:** Rofecoxib. **C:** Celecoxib. **D:** Diclofenac. **I:** Ibuprofen. **N:** Naproxen.

Figure 2. Implication of the relative degrees of selectivity. Increasing degrees of selectivity for COX-2 are associated with augmented cardiovascular risk while increasing degrees of selectivity for COX-1 are associated with augmented gastrointestinal risk (adapted from reference 4).

> *Coxibs are NSAIDs with the most cardiovascular risk.*

and thromboxane. Platelets only possess COX-1, that produces thromboxane, a potent proaggregant and vasoconstrictor. On the contrary, endothelial cells produce prostacyclin, through COX-2, with vasodilator and antiaggregant properties. The excess of thromboxane not compensated by prostacyclin could be responsible for the increased thrombotic risk[4,6].

What is the quality of the data available on cardiovascular risk?

The information available proceeds from different sources, each with its own limitations. Clinical trials from which data is available were not properly designed to measure cardiovascular risk, so that most data obtained was a posteriori. Moreover, the strict criteria in the inclusion of patients could not make them representative of the general population.

On the other hand, observational studies can present some bias, for example, confusion by indication o severity (the more sick a patient is, the more probable the prescription of drugs).

What is the cardiovascular risk of NSAIDs?
Clinical trials of coxibs versus placebo or traditional NSAIDs

A meta-analysis that evaluated the number of severe vascular events (myocardial infarction, stroke, or cardiovascular death) of coxibs and traditional NSAIDs found that in patients treated with coxibs, there was a relative increase of 42% in the incidence (principally myocardial infarction) with respect to placebo (1.2% per year with coxibs versus 0.9% with placebo). This risk could mean that, in the population as a whole, there would be 3 more cases (CI 95% 1-5) of severe atherothrombotic events per 1,000 patients-year. To make a comparison, with the employment of statins in primary prevention, 4 major coronary events are avoided per 1,000 patients-year[7]. The increase in absolute risk is much greater in patients with a personal history of cardiovascular disease. The coxibs present greater risk than naproxen, especially with regard to myocardial infarction (table 2)[8].

Clinical trials with celecoxib

After the withdrawal of rofecoxib, several trials including the APC (Adenoma Prevention with Celecoxib), the PreSAP (Prevention of Spontaneous Adenomatous Polyps) and ADAPT (Alzheimer's Disease Anti-inflammatory Prevention Trial) were interrupted prematurely given the increase in cardiovascular risk observed with the former agent. Table 3 shows the data from the most important clinical trials and meta-analyses that evaluate the cardiovascular risk of this drug.

Table 2. Outcomes of the treatment with coxibs vs placebo or other NSAIDs[8].

	COXIB vs PLACEBO	COXIB vs OTHER NSAIDs	COXIB vs NAPROXEN	COXIB vs OTHER NSAIDs DIFFERENT FROM NAPROXEN
Vascular events				
%/Year	1.2% vs 0.9%	1.0% vs 0.9%	1.1% vs 0.7%	0.9% vs 1.1%
Rate Ratio (CI95%)	1.42 (1.13 to 1.78)	1.16 (0.97 to 1.38)	1.57 (1.21 to 2.03)	0.88 (0.69 to 1.12)
Myocardial infarction				
%/ Year	0.6% vs 0.3%	0.6% vs 0.4%	0.6% vs 0.3%	0.5% vs 0.4%
Rate Ratio (CI95%)	1.86 (1.33 to 2.59)	1.53 (1.19 to 1.97)	2.04 (1.41 to 2.96)	1.20 (0.85 to 1.68)
Stroke				
%/ Year	0.4% vs 0.4%	0.3% vs 0.4%	0.4% vs 0.4%	0.2% vs 0.4%
Rate Ratio (CI95%)	1.02 (0.71 to 1.47)	0.83 (0.62 to 1.12)	1.10 (0.73 to 1.65)	0.62 (0.41 to 0.95)
Vascular death				
%/Year	0.3% vs 0.2%	0.3% vs 0.3%	0.3% vs 0.2%	0.2% vs 0.3%
Rate Ratio (CI95%)	1.49 (0.97 to 2.29)	0.97 (0.69 to 1.35)	1.47 (0.90 to 2.40)	0.67 (0.43 to 1.06)

Table 3. Clinical trials and meta-analyses evaluating cardiovascular events associated with celecoxib use.

TRIAL / PATIENTS	ENDPOINT	TREATMENT / OUTCOMES
CLASS (Celecoxib Long-Term Arthritis Safety Study)[9] 8,059 patients with osteoarthritis or rheumatoid arthritis Length: 6 to 9 months (median)	Incidence of thromboembolic events	Celecoxib 400 mg/12h: 1.3% Ibuprofen 800 mg/8h: 1.1% Diclofenac 75 mg/12h: 1.4% No statistically significant differences Celecoxib vs ibuprofeno+diclofenaco, RR = 1.1 (CI 95% 0.7 to 1.6)
APC and PreSAP[10] 3,596 patients in the prevention of recurrent colorectal adenomas Foreseen follow up: 37 months It was reached by 77% patients in the APC trial and 54% in the PreSAP trial	Composite endpoint: cardiovascular death, myocardial infarction, stroke or heart failure	Celecoxib 400-800 mg /daily vs placebo HR = 1.9 (CI 95% 1.1 to 3.1)
Meta-analysis by Kearney et al[8] 41 clinical trials with a minimum duration of 4 months 13,929 patients-year	Severe vascular events (myocardial infarction, stroke or vascular death)	Celecoxib: 0.9%/year Placebo: 0.6%/year
Meta-analysis by Caldwell et al[11] Double-blind clinical trials with a minimum duration of 6 weeks Versus placebo: 4 trials, 4,422 patients Versus placebo, acetaminophen, other NSAIDs: 5 trials, 12,780 patients	Myocardial infarction	Celecoxib vs placebo, OR = 2.26 (CI 95% 1.0 to 5.1) Celecoxib vs placebo, acetaminophen, other NSAIDs, OR = 1.88 (CI 95% 1.15 to 3.08) No statistically significant differences were found in stroke, nor cardiovascular death nor in the composite endpoint
Meta-analysis by Chen et al[12] Double-blind clinical trials with a minimum duration of 4 weeks Versus placebo: 8 trials, 8,183 patients Versus other NSAIDs: 13 trials, 29,568 patients	Myocardial infarction	Celecoxib vs placebo, OR = 1.68 (CI 95% 0.82 to 3.42) Celecoxib vs other NSAIDs, OR = 1.51 (CI 95% 0.93 to 2.45)
ADAPT[13] 2,528 patients older than 70 years with family history of Alzheimer's disease 4,660 patients-year	Composite endpoint: cardiovascular death, myocardial infarction, stroke, heart failure or transient ischemic attack	Celecoxib 200 mg/12h: 5.54% Naproxen 220 mg/12h: 8.25% Placebo: 5.68% Celecoxib vs placebo: HR = 1.10 (CI 95% 0.67 to 1.79) Naproxen vs placebo: HR = 1.63 (CI 95% 1.04 to 2.55)
Metanálisis de Solomon et al[14] Clinical trials with a minimum duration of 3 years in other diseases than osteoarthritis or rheumatoid arthritis 6 trials, 16,070 patients-year	Composite endpoint: cardiovascular death, myocardial infarction, stroke, heart failure or thromboembolic event	Celecoxib vs placebo: All doses, HR = 1.6 (CI 95%:1.1 to 2.3) Celecoxib 400 mg/24h, HR = 1.1 (CI 95% 0.6 to 2.0) Celecoxib 200 mg/12h, HR = 1.8 (CI 95% 1.1 to 3.1) Celecoxib 400 mg/12h, HR = 3.1 (CI 95% 1.5 to 6.1) For patients at higher baseline risk, relative risk was also higher

Clinical trials with etoricoxib

The information available on this drug is derived fundamentally from the MEDAL programme, in which the incidence of thrombotic cardiovascular events was analysed (myocardial infarction, thrombotic stroke, cerebrovascular thrombosis, transient ischemic attacks, deep vein thrombosis, pulmonary embolism, peripheral arterial thrombosis, sudden death or unexplained death) in trials that compared etoricoxib at doses of 60 or 90 mg daily vs diclofenac at 150 mg daily. This study included 34,701 patients with osteoarthritis or rheumatoid arthritis who were followed for an average of 18 months.

No differences were found between etoricoxib and diclofenac in the incidence of thrombotic events as a whole [1.25 per 100 patients-year with etoricoxib vs 1.19 with diclofenac, HR = 1.03 (CI 95%, 0.89 to 1.18)]. Nor were there any differences observed in the composite endpoint of myocardial infarction, stroke or vascular death. However, discontinuations due to oedema or increments in blood pressure were higher in patients with etoricoxib[15]. One of the problems of this study, as we shall see was that diclofenac is associated with a higher cardiovascular risk than most NSAIDs and therefore it was not the most adequate comparator[6].

Use of NSAIDs in patients with a history of infarction or heart failure increases mortality risk.

Box 1. Coxibs contraindications and cardiovascular precautions[17,18,19].

Coxibs are contraindicated in:

· Congestive heart failure (NYHA II-IV)
· Ischemic heart disease
· Peripheral vascular disease
· Cerebrovascular disease

Etoricoxib is also contraindicated if uncontrolled hypertension (>140/90 mmHg). Blood pressure should be monitored before initiating treatment, two weeks afterwards and then periodically.

Patients with relevant cardiovascular risk factors such as hypertension, diabetes, or smoking should only be treated with coxibs after a careful consideration.

Etoricoxib has not been approved in the USA after an internal document of the FDA showed increased risk with respect to naproxen (table 4)[16].

The EMEA issued a report warning of the risk of increased blood pressure values with etoricoxib. It affirms that etoricoxib should not be prescribed in those patients with persistent values of blood pressure above 140/90 mmHg. Blood pressure should be measured before initiating treatment, after two weeks of treatment and periodically thereafter[17].

Observational studies

Most of the information available is recollected in a meta-analysis of cohort and case-control studies that included 24 trials (one trial was added after submission of the study). The studies evaluated the risk of severe cardiovascular events (especially myocardial infarction and sudden death of cardiovascular origin) in consumers of NSAIDs with respect to non-consumers. The following RR were observed: celecoxib, 1.06 (CI 95% 0.92 1.22); diclofenac, 1.40 (CI 95% 1.19 - 1.65); ibuprofen, 1.09 (CI 95% 0.99 - 1.2); naproxen, 0.99 (CI 95% 0.89 - 1.09); meloxicam, 1.24 (CI 95% 1.06-1.45); piroxicam, 1.16 (CI 95% 0.86 - 1.56); indometacin, 1.36 (CI 95% 1.15 - 1.61)[20].

A retrospective study of a cohort of 11,930 patients over 35 years of age for a two-year follow up period compared the cardiovascular risk (myocardial infarction, death due to cardiac ischemia, stroke) of various NSAIDs with respect to ibuprofen. Long-term use of celecoxib (over 180 days) was associated with a higher risk [HR = 3.64 (CI 95% 1.36 – 9.70)]; etodolac and naproxen did not present any differences in risk with ibuprofen. In short-term consumption, none of the drugs under evaluation showed differences when compared to ibuprofen[21].

Another retrospective study of cohorts limited to patients over 65 years of age followed 384,322 patients for three years. Here NSAIDs were divided into highly COX-2 selective (rofecoxib, valdecoxib), moderately selective (celecoxib, etodolac, meloxicam, nabumetone) and low selective (naproxen, ibuprofen). The incidence of myocardial infarction and stroke was evaluated (table 5) and it was found that high COX-2 selectivity was associated with increased risk for both pathologies. Any NSAID can increase risk when compared to non-consumption[22].

A posterior study evaluated the relation between the consumption of NSAIDs and the risk of stroke in a cohort of 70,063 patients-year. NSAIDs were classified in three groups: COX-1 selective (indometacin, piroxicam, ketoprofen, flurbiprofen, aza-

Table 4. Cardiovascular risk of etoricoxib vs naproxen.

DRUG	N	CARDIOVASCULAR EVENTS/ 100 PATIENTS-YEAR (CI95%)	RELATIVE RISK vs NAPROXEN (CI95%)
Etoricoxib	1,960	1.09 (0.72 to 1.58)	2.72 (1.18 to 6.27)
Naproxen	1,497	0.41 (0.16 to 0.83)	

Source: FDA, presentation by Shibuya R. Available at: www.fda.gov/ohrms/dockets/ac/07/slides/2007-4290s1-01-02-FDA-Shibuya.ppt [Last accessed 11/11/2008]

propazone; non-selective (diclofenac, naproxen, ibuprofen, nabumetone, sulindac) and COX-2 selective NSAIDs (rofecoxib, celecoxib, meloxicam, etoricoxib, valdecoxib). The use of COX-1 selective NSAIDs was not associated with an increase in the risk for stroke when compared to not using NSAIDs, HR = 1.10 (CI 95% 0.41 – 2.97). On the other hand, an increased risk was observed among non-selective NSAIDs (HR = 1.72; CI 95% 1.22 – 2.44) and the COX-2 selective NSAIDs (HR = 2,75; CI 95% 1.28 - 5.95). By individual drugs the risk ratios were as follows: rofecoxib (HR = 3.38; CI 95% 1.48 – 7.74); naproxen (HR = 2.63 CI 95% 1.47 – 4.72); diclofenac (HR = 1.60; CI 95% 1.00 – 2.57); ibuprofen (HR = 1.47 CI 95% 0.73 – 3.00); celecoxib (HR = 3.79 CI 95% 0.52 – 27.6). If the analysis was limited to ischemic stroke, then the risk ratios were of the same order[23].

A recent analysis using the British General Practice Research Database, the primary care data base, followed a cohort of 630,044 patients-year between 40 and 84 years taking NSAIDs up to first myocardial infarction. The study found that there was an increase in risk among recent consumers of coxibs: HR = 2.11 (CI 95% 1.04 to 4.26); and COX-2 selective NSAIDs (meloxicam, diclofenac and etodolac): HR = 2.24 (CI 95% 1.13 to 4.42); but not for the rest of the traditional NSAIDs: HR = 1.33 (CI 95% 0.79 to 2.24) with respect to distant consumption of NSAIDs[24].

What is the risk of using a NSAID in a patient who has suffered from myocardial infarction?

A cohort study evaluated the risk of death or new admission to hospital due to myocardial infarction associated with the consumption of coxibs or traditional NSAIDs. These patients were compared with non-consumers of NSAIDs. All patients had previously suffered from myocardial infarction. The cohort included 58,432 patients of which 9,773 were admitted to hospital and 16,573 died. The results are shown in table 6.

An important dose-effect relationship can be appreciated among all the drugs. Evidence of increased risk is observed for celecoxib, both at high and low doses (under 200 mg daily); as for ibuprofen (at doses >1,200 mg daily) and for diclofenac at ≥ 100 mg daily.

Another case-control study evaluated the modification of the risk profile to suffer a new myocardial infarction in patients with a history of myocardial infarction. The rate ratios (RT) of re-infarction in

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Box 2. What about traditional NSAIDs?

Systematic reviews of both clinical trials[8] and observational studies[20] show that traditional NSAIDs could be associated, to a different degree, with a moderate increase of cardiovascular risk, mainly myocardial infarction, especially at high doses and in long-term use. Individual drugs may differ in their risk profile[2].

Naproxen: presents a lower cardiovascular risk than coxibs and an association with increased cardiovascular risk has not been shown, although a small risk cannot be excluded.

Ibuprofen: at high doses (2,400 mg daily) it is associated with increased atherothrombotic risk. At lower doses (<1,200 mg daily) no risk increase has been found.

Diclofenac: is associated with increased atherothrombotic risk at doses over 150 mg daily.

With regard to the rest of traditional NSAIDs there is not enough evidence available.

The figure bellow shows the estimated risks of three different NSAIDs versus placebo or non-treatment obtained from the main meta-analyses of both clinical trials and observational studies[6].
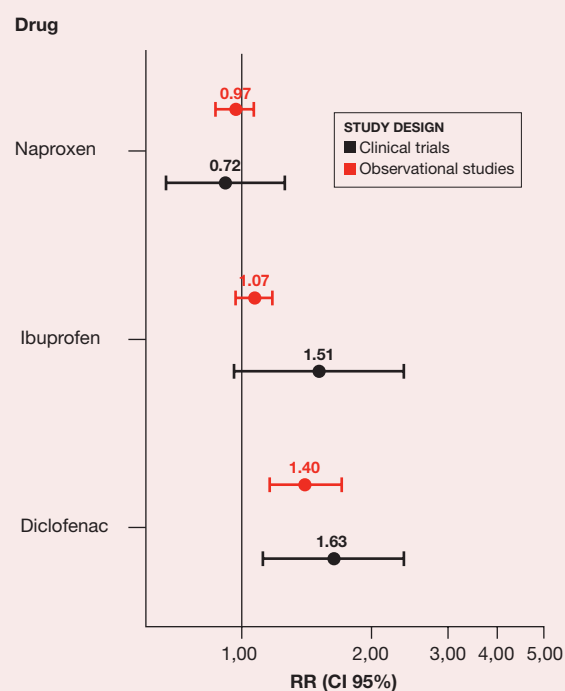
Table 5. Multivariate analysis of cardiovascular risk, HR (IC95%)[22].

	MYOCARDIAL INFARCTION	STROKE
COX-2 selectivity		
No NSAID	0.7 (0.5 to 0.8)	0.6 (0.5 to 0.7)
Low	Reference	
Moderate	1.0 (0.8 to 1.1)	1.2 (0.9 to 1.4)
High	1.5 (1.1 to 1.9)	1.6 (1.2 to 2.2)
According to drug		
No NSAID	Reference	
Rofecoxib	2.5 (1.8 to 3.4)	3.0 (2.0 to 4.4)
Celecoxib	1.5 (1.1 to 2.1)	1.7 (1.1 to 2.5)
Etodolaco	1.6 (1.2 to 2.3)	2.7 (1.8 to 3.9)
Nabumetone	1.8 (1.0 to 3.2)	1.8 (0.8 to 4.1)
Ibuprofen	1.8 (1.4 to 2.3)	1.7 (1.2 to 2.3)
Naproxen	1.6 (1.3 to 2.1)	2.0 (1.5 to 2.7)

Table 6. Risk of death or recurrent myocardial infarction associated with the use of NSAIDs[25].

DRUG	DEATH HR (CI 95%)	NNH* (CI 95%)	RECURRENT MYOCARDIAL INFARCTION (CI 95%)
Rofecoxib	2.80 (2.41 to 3.25)	13 (10 to 20)	1.63 (1.27 to 2.10)
Celecoxib	2.57 (2.15 to 3.08)	14 (10 to 24)	1.50 (1.10 to 2.05)
Ibuprofen	1.50 (1.36 to 1.67)	45 (29 to 102)	1.25 (1.07 to 1.46)
Diclofenac	2.40 (2.09 to 2.80)	24 (16 to 45)	1.54 (1.23 to 1.93)
Other NSAIDs	1.29 (1.16 to 1.43)	143 (58 to 315)	1.27 (1.09 to 1.47)

(*) Number needed to treat with NSAIDs during one year to have an additional death.

consumers of NSAIDs versus non-consumers indicated an increase in risk for rofecoxib (1.59; CI 95% 1.15 to 2.18) and for celecoxib (1.40; CI 95% 1.06 to 1.84). In the case of naproxen (1.56; CI 95% 0.68 to 3.58) and for other NSAIDs (0.95; CI 95% 0.44 to 2.04) no increase in risk was shown[26].

Box 3. When do cardiovascular events appear?

Several studies show that there is evidence of risk from the first month of treatment[20,24].

What occurs when a patient is under treatment with aspirin for cardiovascular prevention?

As seen in the box 1, most of the indications of aspirin are contraindications for coxibs. Moreover, no significant differences have been shown as far as gastrointestinal safety among coxib + aspirin when compared to NSAIDs + aspirin in long term clinical trials. Some clinical pharmacological studies suggest that ibuprofen can interfere with the antiplatelet effect of aspirin, although in epidemiological studies no increase in risk was observed. In clinical trials a small increment in risk was found in doses of 2,400 mg daily[2].

Box 4. Concomitant use of NSAIDs and aspirin.

Treatment with NSAIDs in patients taking aspirin should be avoided whenever possible because:

· NSAIDs increase cardiovascular risk, which is the outcome we precisely try to prevent by taking aspirin.
· Concomitant use of NSAIDs and aspirin provide a synergetic increase in gastrointestinal risk.
· Some NSAIDs, such as ibuprofen, could interact with aspirin and reduce its efficacy.

And if the patient suffers from heart failure?

A cohort study of patients who had been admitted to hospital for cardiac failure evaluated the risk of taking NSAIDs with respect to non-consumers. There were 107,092 patients included in the study, of which 60,974 died, while 8,970 patients were

Tabla 7. Risk of death and hospital admission in patients diagnosed with heart failure taking NSAIDs[28].

DRUG	DEATH HR (CI 95%)	NNH* HR (CI 95%)	HOSPITAL ADMISSION DUE TO HEART FAILURE HR (CI 95%)	HOSPITAL ADMISSION DUE TO MYOCARDIAL INFARCTION HR (CI 95%)
Rofecoxib	1.70 (1.58 to 1.82)	9 (8 to 11)	1.40 (1.26 to 1.55)	1.30 (1.07 to 1.59)
Celecoxib	1.75 (1.63 to 1.88)	14 (11 to 19)	1.24 (1.12 to 1.39)	1.38 (1.13 to 1.69)
Ibuprofen	1.31 (1.25 to 1.37)	53 (36 to 100)	1.16 (1.10 to 1.23)	1.33 (1.19 to 1.50)
Diclofenac	2.08 (1.95 to 2.21)	11 (9 to 13)	1.35 (1.24 to 1.48)	1.36 (1.12 to 1.64)
Naproxen	1.22 (1.07 to 1.39)	51 (22 to 158)	1.18 (1.00 to 1.40)	1.52 (1.11 to 2.06)
Other NSAIDs	1.28 (1.21 to 1.35)	43 (29 to 78)	1.27 (1.18 to 1.36)	1.32 (1.13 to 1.54)

(*) Number needed to treat with NSAIDs during one year to have an additional death.

Box 5. NSAIDs use in heart failure.

NSAIDs should be avoided in patients diagnosed with heart failure because[27]:
· Sodium retention and peripheral vasoconstriction can appear.
· The efficacy of diuretics, ACE inhibitors and angiotensin II receptor blockers (ARB) is reduced.
· The toxicity of diuretics, ACE inhibitors and ARBs which in turn can contribute to the risk of renal impairment.
· With concomitant use of aldosterone antagonists, the risk of hyperkalemia and adrenal deterioration is increased.
· In a recent observational study an increase in both cardiac morbidity and mortality was observed.

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admitted to hospital due to myocardial infarction and another 29,984 admitted due to heart failure. Table 7 shows the results of the study.

The use of any NSAID is associated with an increase in mortality where a dose-effect relationship is also found. Evidence of this risk is observed in the coxibs and diclofenac at any dose, while for ibuprofen at >1,200 mg daily, and naproxen at >500 mg daily.

Should we make a choice between cardiovascular and gastrointestinal risk?

The picture obtained from the data available is that COX-1 selectivity is associated with a higher gastrointestinal risk while COX-2 selectivity is associated with a higher cardiovascular risk (figure 2).

Although coxibs are associated with a lower gastrointestinal risk than traditional NSAIDs, the reduction in risk is only seen in less severe complications[2]. There is no evidence that on using coxibs, the risk is less than when using a traditional NSAID with gastroprotection[29,30]. It is not clear if the advantage of gastrointestinal risk of the coxibs over traditional NSAIDs still exists when both are associated with gastroprotection.

It is important to recall that high cardiovascular risk, especially if treated with aspirin, is an indication for gastroprotection[6].

Uncertainties

The strict distinction between traditional NSAIDs and coxibs is not justified by either clinical or laboratory data, even though many epidemiological studies have used this classification. This has led to considerable problems in the interpretation of results. The information available from clinical trials are limited to the most recent drugs and their comparators. The clinician should reflect on several questions which as yet have not been definitively clarified:

· In what measure do celecoxib and etoricoxib share the profile of cardiovascular effects that obliged the withdrawal of rofecoxib?

· Do the coxibs present advantages in terms of gastrointestinal safety with respect to the rest of the NSAIDs when both are associated with gastroprotection (which is a usual practice)?

· Should the same precautions and contraindications of the coxibs be applied to diclofenac in relation to cardiovascular risk?

· What is the cardiovascular risk of those NSAIDs of which no data is available as yet?

Conclusions

The use of acetaminophen or topical NSAIDs should be considered habitually as a first option instead of oral NSAIDs.

When necessary, NSAIDs should be prescribed at the lowest effective doses and for the shortest possible period.

Coxibs are associated with greater cardiovascular risk and thus should not be used in patients with a high risk profile.

An adequate choice of NSAIDs should be made taking into account the cardiovascular and gastrointestinal risk profile of each patient. In patients with high cardiovascular risk, ibuprofen at low doses (maximum 1,200 mg daily) and naproxen are the options with the best safety profile available. Their association with a proton pump inhibitor is recommended to reduce gastrointestinal risk.

The use of NSAIDs in patients under treatment with aspirin for antiplatelet therapy should be avoided whenever possible.

When long-term NSAIDs are required in elderly patients with high vascular risk or kidney failure, the following aspects of management should be revised periodically:
· Need to continue therapy.
· Blood pressure.
· Kidney function.
· Presence of oedema.
· Signs of gastrointestinal bleeding.

Besides the proven efficacy of NSAIDs in the treatment of pain and inflammatory processes these drugs can present severe adverse effects, thus careful consideration must be taken when indicated.

References

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