Cardiovascular Risk of Cyclooxigenase Selective Inhibitors

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Introduction

Ever since the appearance of aspirin more than 100 years ago, the advantages of using this medication for the control of different pathological states has been demonstrated. Years later, non-steroidal anti-inflammatory drugs (NSAIDs) have become safer and conserve their anti-inflammatory capacity. In spite of this, gastrointestinal complications related to NSAIDs have limited noticeably their use, especially in the population over 65 years of age, due to gastrointestinal risk factors which impedes their carefree prescription in this group of patients, in who some rheumatic diseases, such as osteoarthritis, are more common. This led to the development of a group of anti-inflammatory drugs labeled selective inhibitors of cyclooxigenase 2, which have proven a greater gastrointestinal security and maintain the same anti-inflammatory capacity.

Cardiovascular Safety

Rofecoxib

Starting in 1999 when the first selective inhibitors of cyclooxigenase (coxib) in the market appeared, several clinical trials made it evident that these new molecules could have different effects from those of NSAIDs regarding their safety profile. This was notorious when the results of the VIGOR (Vioxx and Gastrointestinal Outcomes Research) study[1] appeared, in which a dose of 50 mg of rofecoxib/day against 500 mg/12 h of naproxen were compared in a population of about 8000 persons with rheumatoid arthritis, who were not allowed to use anti-aggregation doses of aspirin, in spite of the fact that a percentage of this population had cardiovascular risk factors.

The primary objective of the study was to evaluate the gastrointestinal safety of the drug compared with naproxen. A fact that must not go by unnoticed is that the double of the dose (50 mg) commonly employed in the clinical practice was used, and that patients with rheumatoid arthritis have a greater cardiovascular morbidity and mortality than the general population. The results of the study showed that the dose of rofecoxib led to a reduction in 54% of upper gastrointestinal adverse events. However, it was also demonstrated that naproxen was associated to a significant number of cardiovascular adverse events (non-fatal myocardial infarction and sudden death) when compared to rofecoxib (0.8% for rofecoxib vs 0.4% for naproxen; $P<.05$); this difference was mainly attributed to an elevated incidence of myocardial infarction in the group of patients receiving rofecoxib. The relative risk (RR) for a cardiovascular event was 2.38 (95% confidence interval [CI], 1.39-4; $P<.0001$) (Table 1).

Celecoxib

The CLASS (Celecoxib Long-term Arthritis Safety Study)[2] clinical trial, designed to analyze the gastrointestinal safety of celecoxib as compared to 2 non-selective NSAIDs, included an approximately similar amount of subjects than the VIGOR study; however, this population was composed by patients with osteoarthritis and rheumatoid arthritis, the first of which has a reduced cardiovascular risk when compared to the second disease and, on the other hand, this trial did allow the use of low-dose aspirin as an anti-aggregation agent. The results showed that celecoxib had a gastrointestinal safety profile similar to the other 2 NSAIDs employed for comparison and, in relation to cardiovascular safety, it was shown that there was no significant difference between celecoxib, diclofenac, and ibuprophen (Table 2).

Nonetheless, this trial reported the data of approximately half of the time of the duration of the study (6 of the 12 months programmed) and, when the data was complete, it was evident that there was no clear difference in the

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TABLE 1. Vascular Events and Mortality in the VIGOR Trial

	Acute Myocardial Infarction		Cardiovascular Mortality, %	Cerebrovascular Events, %	General Mortality, %
	Patients	Events, %			
Rofecoxib	45	46 (0.4)[a]	0.2	0.2	0.5
Naproxen	20	20 (0.1)	0.2	0.2	0.4

[a]Relative risk = 2.38 (95% confidence interval, 1.39-4; *P*<.001).

final points regarding gastrointestinal safety between celecoxib and the NSAIDs with which it had been compared.[3]

On the other hand, when reviewing the annual average of myocardial infarction andd comparing the results of the VIGOR trial and the CLASS study, it was observed that the quantities were similar (0.74% and 0.80%, respectively).[4]

After the publication of the VlGOR and CLASS studies, several types of trials appeared that analyzed, in a different manner and in different populations, the cardiovascular safety of coxib's, with results that only fueled the fire of controversy. In this sense, the work by Konstam et al,[5] a grouped analysis of 23 phase IIb to V studies with rofecoxib, which included 28 000 patients and whose outcome was the established by the Antiplatelet Trialists' Collaboration (APTC), which includes death of cardiovascular or unknown origin, non-fatal myocardial infarction, or non-fatal cerebrovascular disease, demonstrated that the relative risk of reaching the outcome was 0.84 (95% CI, 0.51-1.38) when comparing rofecoxib with placebo, in the case of rofecoxib versus NSAID (but not naproxen) the RR was 0.79 (95% CI, 0.040-1.55), although this comparison was done only in patients with osteoarthritis, and 1.69 (95% CI, 1.07-2.69) when comparing rofecoxib to naproxeno. In this way it was concluded that there was no cardiovascular risk when using rofecoxib compared to placebo and with a non-naproxen NSAID and that the observed difference was mainly due to the anti-platelet effect of naproxen. However, it did not exclude the possibility that the elevated risk with rofecoxib were due to the fact that aspirin was not used in the population with rheumatoid arthritis with a high cardiovascular risk.[6]

Diverse evidence was published contrary to this posture, confirming the elevated cardiovascular risk with rofecoxib and, in this sense, a case-control study of 54 475 patients who were over 65 years of age which demonstrated that the current use (taking the pill at the moment of carrying out the trial) of rofecoxib was associated with an elevated RR for myocardial infarction compared to celecoxib (odds ratio [OR] = 1.24; 95% CI, 1.05-1.46; *P*=.011) and with other drugs different from NSAIDs (OR=1.14; 95% CI, 1.00-1.31; *P*=.054), and in the same way it was demonstrated that the RR was elevated when using doses of rofecoxib over 25 mg/day, and that this elevation of the RR occurred mainly in the first 90 days of treatment.[7]

TABLE 2. Vascular Adverse Events in the CLASS Trial[a]

	Acute Myocardial Infarction	Chest Pain	Cerebrovascular Event
Celecoxib	10 (0.3)	24 (0.6)	5 (0.1)
NSAIDs	11 (0.3)	22 (0.6)	10 (0.3)

[a]NSAIDs indicates non-steroidal anti-inflammatory drugs.
Data represented as No. (%).

This controversy ended on September 30, 2004 when Merck announced that it was withdrawing rofecoxib from the market because of its elevated cardiovascular risk, based on the results of the APPROVE study which, at the time, was ongoing in 2568 patients with colorectal adenomas and in which 25 mg of rofecoxib were compared with placebo, with the objective of preventing recurrence of neoplasic colon polyps. The exclusion criteria of this trial were uncontrolled hypertension (>165/95 mm Hg) and chronic heart failure; however, patients with elevated cardiovascular risk were included (having a history of myocardial infarction) and the use of low-dose aspirin was allowed in 20% of the study population, with a 3-year follow-up.

The study was suspended due to safety concerns that arose after observing, in a preliminary analysis, that the patients who were receiving rofecoxib had double the risk of a cardiovascular event than those assigned to placebo (RR=1.96; 95% CI, 1.20-3.19; *P*=.007). The relative risk for a final point of the APTC was 2.25 (95% CI, 1.24-4.08; *P*=.008). There were 25 cardiovascular events in 3315 patients/year in the placebo group (0.75 events per 100 patients-year) and 45 in 3041 patients/year taking rofecoxib (1.48 events per 100 patients/year). The results reflect a lack of balance in the presence of myocardial infarction and cerebrovascular ischemia; however, these differences were observed after 18 months of treatment. It must be pointed out that the use of baseline low-dose aspirin, or during more than half of

TABLE 3. Risk of Cascular Disease With Celecoxib in the APC Study

Adverse Event	Placebo, No. (%) (n=679)	Celecoxib 200 mg/12 h, No. (%) (n=685)	Celecoxib 400 mg/12 h, No. (%) (n=671)	Both doses of celecoxib, No. (%) (n=1356)
Cardiovascular death	1 (0.1)	3 (0.4)	6 (0.9)	9 (0.7)
Myocardial infarction	3 (0.4)	9 (1.3)	9 (1.3)	18 (1.3)
Cerebrovascular disease	3 (0.4)	3 (0.4)	5 (0.7)	8 (0.6)

TABLE 4. Vascular Adverse Events in the APPROVe Trial[a]

	Rofecoxib		Placebo		Risk Relation (95% CI)
Adverse Event	No. (%)	Mean 100 Patients-Year	No. (%)	Mean 100 Patients-Year	
Cardiac event	31 (2.4)	101	12 (0.9)	0.36	2.80 (1.44-5.45)
Myocardial infarction	21		3		
Cerebrovascular event	15 (1.2)	0.49	7 (0.5)	0.21	2.32 (0.89-6.74)
Cerebral ischemia	11		6		

[a]CI indicates confidence interval.

the follow-up period, did not demonstrate a significant interaction between serious thrombotic events and the subgroup analysis.[8] Table 3 shows the confirmed severe thrombotic events. A very similar situation occurred with celecoxib.

The APC (adenoma prevention with celecoxib) study included 2035 patients who underwent an endoscopic polypectomy with the objective of comparing the reduction in adenomatous polyps in the colon and rectum, 1 and 3 years after the procedure, comparing celecoxib 200 and 400 mg twice a day versus placebo, allowing for the use of aspirin for cardiovascular prevention. After a mean follow-up of 2.8 to 3.1 years, the patients who received 200 mg twice a day had a risk relation of 2.3 (95% CI, 0.9-5.5) for death of a cardiovascular origin, myocardial infarction, cerebrovascular disease, or heart failure, and in those who took 400 mg twice a day, the risk relation was 3.4 (95% CI, 1.4-7.8). The annual incidence of death due tpot he same compound objective was 7.8 events per 1000 patients-year in the 200 mg of celecoxib twice a day group and of 11.4 events per 1000 patients-year in those who received 400 mg twice a day. As happened in the APPROVe study, the patients who in their baseline conditions had an increased cardiovascular risk presented a larger number of thrombotic adverse events, independent of the use of aspirin. This data lent more credibility to the concept that the COX-2 inhibitors could increase the risk of severe cardiovascular events and med to the suspension of the trial.[9] Table 4 shows the individual components of the study's compound objective.

Etoricoxib

Etoricoxib is also a COX-2[10] inhibitor molecule that has demonstrated a favorable analgesic capacity in different experimental models. The studies in healthy humans showed that it did not inhibit platelet aggregation, nor did it prolong bleeding time, having a half-life of 22 hours which facilitated its administration every 24 hours and, on the other hand, different clinical studies showed that it was as effective as indomethacin in the treatment of an acute crisis of gout[11] and equally effective in osteoarthritis[12] and rheumatoid arthritis.[13]

The EDGE trial,[14] designed to analyze gastrointestinal tolerance for etoricoxib in osteoarthritis, showed a better digestive safety profile than diclofenac and no cardiovascular complications. This 1-year trial included 7111 patients with a mean age of 64 years, of which approximately 4% had a history of an upper gastrointestinal event, 28% took aspirin since before inclusion, 45% suffered hypertension, and 37% were considered as high risk for cardiovascular disease. All of these patients were treated with 90 mg/day of etoricoxib or diclofenac 50 mg 3 times a day.

No differences in the cardiovascular events means were found between etoricoxib and diclofenac during the development of the study, and 14 days after ceasing to

TABLE 5. Vascular Adverse Events in the CABG Study[a]

Adverse Event	Plac (n=548)	Plac+Val (n=544)	Par+Val (n=544)	Both COX-2 Inhibitors (n=1088)	Plac Versus Plac+Val, RR (95% CI); *P*	Plac Versus Par+Val, RR (95% CI); *P*	Plac Versus Noth COX-2 Inhibitors, RR (95% CI); *P*
Cardiovascular events	3 (0.5)	6 (1.1)	11 (2.0)[b]	17 (1.6)	2 (0.5-8.1); .31	3.7 (1-13.5); .03	2,9 (0,8-9,9); .08
AMI	0	1 (0.2)	1 (0.2)	2 (0.2)			

[a]AMI indicates acute myocardial infarction; CI, confidence interval; Par, parecoxib; Plac, placebo; RR, relative risk; Val, valdecoxib.
[b]*P*=.03

take the drug the relative risk for a cardiovascular event was 1.07 (95% CI, 0.65-1.74) and 1.02 (95% CI, 0.64-1.62) at 28 days. In the case of cerebrovascular disease, a mean of 0.15 was seen in the population receiving etoricoxib and 0.23 in those treated with diclofenac. The means for myocardial infarction (100 patients-year) were 0.68 for etoricoxib and 0.42 for diclofenac.[15,16]

Valdecoxib and parecoxib

Valdecoxib, as well as parecoxib, its pro-drug, belongs to the sulphonamide group; a dose of 5-10 mg once a day has the same efficacy as traditional NSAIDs for the treatment of symptomatic osteoarthritis of the knee and hip.[16] In 10 randomized and controlled clinical trials it proved to be more effective than placebo in the treatment of osteoarthritis, rheumatoid arthritis, dysmenorrhea, and postsurgical analgesia. In the same manner, it was well tolerated and had the same incidence of adverse events as placebo.

In a phase III, double blind, randomized, placebo, and parallel group controlled trial done in 462 patients who underwent coronary surgery, upon comparing parecoxib/valdecoxib versus ordinary analgesic care, the observation was made that the experimental group received a lesser dose of morphine or its equivalent than patients in the control group and had a significant improvement in 6 of the 8 domains evaluated with the Brief Pain Inventory questionnaire. No differences were observed in adverse events in general; however, serious adverse events were twice as frequent in the parecoxib/valdecoxib group (19%; 59/311 patients) than in controls (9.9%; 15/151 patients; *P*=.015). The main serious adverse event observed was a greater incidence of sternal surgical wound infection in the experimental group (10 [3.2%]) vs the control group (0 [0%]) (*P*=.035). Other serious adverse events, among which cerebrovascular complications, myocardial infarction, and renal dysfunction were found were proportionally more frequent in the experimental group but did not show a statistically significant difference.[17]

The Coronary-Artery Bypass Grafting (CABG) trial included 1671 patients who had previously undergone a cardiopulmonary bypass in a selective manner and who in the 3 moths prior to the study did not present cerebrovascular accidents, transient ischemic attacks, deep venous thrombosis, or pulmonary embolisms.

Patients who in the 7 days prior to study entry suffered a myocardial infarction were also excluded. Patients were randomized to 3 groups in order to receive: intravenous parecoxib, 3 days, followed by oral valdecoxib up until day 10; intravenous placebo followed by oral valdecoxib, or placebo for 10 days. The results evidenced a higher, statistically significant frequency of cardiovascular events in the group that received parecoxib /valdecoxib than in the placebo group (2% vs 0.5%; risk relation, 3.7; 95% CI, 1.0-13.5; *P*=.03). Taking into account these results it is recommended that these drugs are avoided in the population who is scheduled to undergo cardiopulmonary bypass because the risk of treatment with valdecoxib/parecoxib surpass the benefits in this population.[18] Table 5 summarizes the cardiovascular events and the acute myocardial infarction that occurred during the CABG trial.

Lumiracoxib

The TARGET (Therapeutic Arthritis Research and Gastrointestinal Event Trial) study included 18 325 patients over 50 years of age, with osteoarthritis, who were randomized to treatment with lumiracoxib 400 mg/day (9156), naproxen 500 mg twice a day (4754), or ibuprophen 800 mg 3 times a day (4415). Patients with high cardiovascular risk were allowed to employ low dose aspirin (75-100 mg/day) as primary or secondary cardiovascular prophylaxis (24% of the population; n=4326). The primary objective of the trial was to determine the risk o developing upper ulcer complications and, secondarily, to analyze cardiovascular morbidity and mortality.

The results showed that lumiracoxib reduces 3-4 times the possibility of presenting ulcer complications, when compared to NSAIDs.[19]

With regard to the cardiovascular security, the group that compared lumiracoxib versus naproxen included a larger amount of patients with a history of cardiovascular risk (12%) that in the lumiracoxib versus ibuprophen group (8%). The total number of patients did not show differences regarding the number of myocardial infarcts between lumiracoxib and both NSAIDs; however, patients who received naproxen without prophylactic aspirin had less myocardial infarction (4 events; 0.11%) than the lumiracoxib group (10 events; 0.28%; *P*=.1454). In patients who did take low-dose aspirin the incidence was similar.[20] The authors explained these facts through 2 mechanisms, first, the influence of chance and, second, the antithrombotic role of naproxen, without forgetting that under baseline conditions the group that compared lumiracoxib against naproxen had a larger history of cardiovascular risk (12%).

Probable Reasons for a Higher Cardiovascular Mortality

After the introduction of the coxibs in the clinical practice, FitzGerald et al[21] called to attention their effect in the synthesis of endothelial eicosanoids, by demonstrating the reduction in urinary prostacyclin metabolites (PGI-2), without affecting the excretion of thromboxane A2 (TXA-2) or platelet aggregation. These results indicated that when suppressing the endothelial production of PGI-2, the unopposed activity of platelet COX-1 was allowed, leading to the synthesis of TXA-2 and a probable prothrombotic effect; this situation was reinforced by the results of the VIGOR study[1] and the posterior meta-analysis which generated conflicting results, as mentioned above. When trying to explain these conflicting results, FitzGerald et al[22] propose 3, non-exclusive explanations, the prothrombotic capacity of rofecoxib, the platelet anti-aggregation activity of naproxen, and the probable effect of chance.

Was Rofecoxib Thrombogenic?

Vascular endothelium-produced PGI-2 represents one of the most important molecules involved in platelet anti-aggregation; however, it is not the only one capable of this effect. Due to its anti-aggregating and vasodilating nature antagonizes the effects of TXA-2 which stimulates platelet aggregation and produces vasoconstriction.[23] Rofecoxib only inhibits COX-2 through which it produces PGI2 without an effect on platelet COX-1 that produces TXA-2, and probably generates disequilibrium in favor of prothrombotic forces.

However, in rats it was demonstrated that it is necessary to inhibit COX-1 and COX-2 in order to generate gastric damage,[24] probably because COX-2 can substitute COX-1 as a producer of cytoprotective prostaglandins and, on the other hand, COX-1 can also produce PGI.[25] These conditions, plus the fact that there are other molecules capable of neutralizing the activating/platelet anti-aggregating effects of TXA-2, such as nitric oxide, CD39/ecto-ADPase,[26] and platelet-endothelial cell molecule 1,[27] would lead to the assumption that there are several anti-aggregating mechanisms that remain operant in spite if the inhibition of endothelial PGI-2; this, in time, would lead us to think that the sole inhibition of PGI-2 on the part of rofecoxib is not potent enough as to unleash a thrombotic event.

Are Other Coxibs Thrombogenic?

The CLASS[2] study reported that the cardiovascular adverse events were similar between celecoxib and NSAIDs used for comparison (ibuprophen and diclofenac); heart failure was observed (9 and 9 cases, respectively), myocardial infarction (10 and 10 events, respectively), and coronary disease (9 and 7 episodes, respectively).

In a posterior analysis[28] the annualized myocardial infarction means were calculated for the VIGOR and CLASS study and it was observed that, in both cases, the mean was larger for both the coxib compared to placebo: 0.74% (*P*=.04) for rofecoxib and 0.80% (*P*=.02) for celecoxib. In the same way, a retrospective study also demonstrated an increase in the cardiovascular risk with celecoxib.[29] Certainly this evidence needs to be interpreted carefully, taking into account that in the type of studies that generated them there could be important bias and variables which could not be controlled or the effect of these on other outcomes, in such a way that this leads to conclusions which are not concordant with reality. It has been previously mentioned that a study projected to analyze the analgesic capacity of parecoxib/valdecoxib in patients who underwent coronary bypass surgery demonstrated that the incidence of severe adverse events was twice as frequent in the group who received parecoxib/valdecoxib (19.0%; 59/311 patients) than in the control group (9.9%; 15/151 patients; *P*=.015), finding, in first place, sternal surgical wound infection. Other serious adverse events were cerebrovascular complications, acute myocardial infarction, and renal dysfunction, and although the latter were proportionally higher in the group which received the coxib, it did not show a a statistically significant difference; these facts, as we have seen, were confirmed in a posterior study that demonstrated a higher frequency of cardiovascular events in patients undergoing elective cardiopulmonary bypass and postoperatively treated with.[18]

An analysis of 40 patients with essential hypertension demonstrated a selective COX-2 inhibition with parecoxib, a pro-drug of valdecoxib, capable of reducing acetylcholine-induced vasodilation in the forearm circulation, something that did not occur with acetylsalycilate-lysine, a COX-2

unspecific inhibitor.[30] These findings may explain in some manner the cardiovascular complications in persons who have previous cardiovascular risk factors, which are enhanced by the coxib mechanism of action.

In relation with the cardiovascular events unleashed by etoricoxib, previously mentioned in the study by Matsumoto et al[13] in 816 patients with rheumatoid arthritis who were treated with etoricoxib or naproxen and where 2 cardiovascular events were confirmed in patients who took etoricoxib, plus one transient ischemic attack and a non-Q wave myocardial infarction. Another, very similar, study confirmed 3 cardiovascular thrombotic events, chest pain and pulmonary embolism in 2 patients taking etoricoxib and an episode of thrombophlebitis in only 1 patient of the placebo group.[31]

However, in the EDGE trial, which included a much larger population with a 52 month follow-up, the incidence of cardiovascular events was not different between etoricoxib and diclofenac. The means for myocardial infarction (per 100 patients-year) were 0.68 for etoricoxib and 0.42 for diclofenac. In the case of cerebrovascular disease a mean of 0.15 was seen in the population who received etoricoxib and 0.23 in those treated with diclofenac.[14]

It has previously mentioned that the TARGET[20] trial, which analyzed the gastrointestinal safety of lumiracoxib, showed a higher incidence of acute myocardial infarction in the subgroup that compared lumiracoxib versus naproxen who did not take cardiovascular prophylaxis with aspirin (4 events [0.11%] vs 10 events [0.28%], respectively; *P*=.1454).

This evidence leads us to think that coxib different from rofecoxib are not exempt of a higher cardiovascular risk when compared to placebo or naproxen in a population with prior cardiovascular risk factors. Therefore, these effects common to coxib would allow for speculation on the fact that the adverse cardiovascular events, which have been documented by different clinical trials could be explained mainly by a class effect and not to the mechanism of action of a particular molecule.

Does Naproxen Have an Antiaggregation Effect?

This question has generated an important amount of trials that have set the objective of analyzing the anti-aggregating capacity of this NSAID. The evidence for one or the other has been widely published; however, because of the design of these studies, it has not been possible to reach an unimpeachable consensus on its aggregating effect.

When naproxen is used at a 500-mg/12 h dose in regular form, it leads to the inhibition of more than 90% of platelet TXA-2 during the ingestion of the drug.[32]

Several case-control studies have demonstrated the platelet anti-aggregation capacity of naproxen. In this sense, the study by Rahme et al[33] concluded that the concurrent chronic use of naproxen has a lower incidence of acute myocardial infarction with an OR of 0.64 (95% CI, 0.48-0.86) compared with the concurrent users of other NSAIDs and maintains that naproxen is a more potent inhibitor of COX-1 than ibuprophen or diclofenac. The study by Watson et al[34] in patients with rheumatoid arthritis found that the risk of a cardiovascular thromboembolic event during the use of naproxen, versus that of other NSAIDs different from naproxen, had an OR of 0.65 (95% CI, 0.34-1.24) and the risk of myocardial infarction with the current use of naproxen compared to the use of another NSAID different from naproxen was 0.40 (95% CI, 0.13-1.20). This indicates that patients with rheumatoid arthritis used concomitantly with naproxen have a reduced risk of cardiovascular thromboembolic events, included acute myocardial infarction, than those patients who had not used naproxen.

Another case-control study[35] demonstrated that the use of naproxen produced a 16% reduction in the risk of acute myocardial infarction (OR=0.84; 95% CI, 0.72-0.98; *P*=.03) and indicates that the patients who take non-selective NSAIDs seem to have a reduced risk for cardiovascular events, facts that coincide with the protective effect of naproxen.

In the opposed sense, Ray et al[36] did not find a protective effect of naproxen or other NSAIDs in the risk for coronary disease. The RR for current and previous NSAID users was 1.05 (95% CI, 0.97-1.14) and 1.02 (95% CI, 0.97-1.08), respectively, and in a naproxen-specific manner was 0.95 (95% CI, 0.82-1.09); for ibuprophen, 1.15 (95% CI, 1.02-1.28); and NSAIDs, 1.03 (95% CI, 0.92-1.16). When comparing naproxen versus ibuprophen, the RR with current use was 0.83 (95% CI, 0.69-0.98).

An observational, retrospective trial,[37] in Canadian population, found that naproxen does not diminish the risk of acute myocardial infarction in the short term and presents relative risks which are very similar between naproxen (RR=1.0; 95% CI, 0.6-1.7), non-selective NSAIDs different from naproxen (RR=1.2; 95% CI, 0.9-1.4), celecoxib (RR=0.9; 95% CI, 0.7-1.2), and rofecoxib (RR=1.0; 95% CI, 0.8-1.4).

It is difficult to reach a valid conclusion with the abovementioned results when taking into account the limitations inherent to these designs an the lack of a randomized, controlled trial that should analyze the platelet anti-aggregation effect of naproxen versus aspirin, coxib, and other non-specific NSAIDs different from naproxen. It is known that naproxen administered at a dose of 500 mg/12 h has a good anti-aggregation effect during this dosing interval,[32] in such a way that a study as the one pointed out could clear up in a more exact manner some aspects such as dose-response, response duration, and temporal relationships.

It is very probable that we are not yet faced with a completely defined situation regarding the potential risk of the coxib, taking into account that we do not have

randomized, controlled, double blind trials in populations without cardiovascular risk, or with a low or high risk, in order to determine the adequate dose for each drug, the level of risk of each, the time frame in which a negative outcome is more likely to occur and in which patients the benefits are larger than the potential adverse events.

In conclusion we can think that, by doing a balance of all of the trials known to date, that the cardiovascular profile of coxib seems to be more a class effect and less probably molecule-related as was suggested when the first adverse events with rofecoxib appeared, in such a manner that we need to undertake a complete analysis of each patient, of the potential benefits and the risks that they would face when using a coxib.

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