Cardiovascular risk associated with the use of selective COX-2 inhibitors: a systematic review

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ABSTRACT

Introduction: Selective inhibitors of the enzyme cyclooxygenase-2 were developed to reduce the gastrointestinal toxicity of conventional nonsteroidal anti-inflammatory drugs. However, this class of drugs decreases prostacyclin production and can disrupt endothelial homeostatic balance, leading to a prothrombotic state that offsets potential gastrointestinal benefits.
Methods: A systematic review of all study publications linking cyclooxygenase-2 inhibitor nonsteroidal anti-inflammatory drugs and related cardiovascular events was performed.
Results: The highest overall risks were seen with rofecoxib, 1.45 (95% CI 1.33 to 1.59), and diclofenac, 1.40 (1.27 to 1.55). The lowest risks recorded were with ibuprofen, 1.18 (1.11, 1.25), and naproxen, 1.09 (1.02, 1.16). The risk of VTE increased with diclofenac [OR 1.63 (95% CI: 1.53, 1.74)], ibuprofen [OR = 1.49 (95% CI: 1.38, 1.62)], meloxicam [OR = 1.29 (95% CI: 1.11, 1.50)] and coxibs [celecoxib, OR= 1.30 (95% CI: 1.11, 1.51); rofecoxib, OR= 1.44 (95% CI: 1.18, 1.76)]. Naproxen did not increase the risk of VTE [OR = 1.00 (95% CI: 0.89, 1.12)]. Furthermore, there is a significant association with atrial fibrillation for etoricoxib (HR 1.35; 95% CI 1.19–1.54).
Conclusion: This review suggests that the risk of these adverse effects is greater in patients with an earlier history of cardiovascular disease or at considerable risk for developing it. Evidence shows that among the widely used NSAIDs, low-dose naproxen and ibuprofen are less likely to increase cardiovascular risk. Data for etoricoxib were sparse, but in pairwise comparisons this drug had a significantly higher relative risk than either naproxen or ibuprofen. Indomethacin is an older drug that is also toxic to the gastrointestinal system, and evidence of cardiovascular risk casts doubt on its continued clinical use.

KEYWORDS

Cyclooxygenase-2 inhibitors, NSAIDS, Risk Factors, Thrombosis, Acute Myocardial Infarction.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used medications for the treatment of pain and osteoarticular diseases. (1) Its mechanism of action consists of inhibiting the enzyme cyclooxygenase (COX), responsible for the metabolism of arachidonic acid, which leads to the synthesis of prostaglandins and thromboxane. (2)

Due to the relative scarcity of COX-2 enzyme expression in the gastrointestinal tract and its high expression in inflammatory tissues, selective COX-2 inhibitors were developed and introduced into therapeutics in 1999, designated COXIBs, with the aim of minimizing the gastrointestinal toxicity of non-selective NSAIDs. [3]
COXIBs are as or more effective than non-selective NSAIDs for the treatment of inflammation and associated symptoms. However, as platelets primarily express COX-1, these drugs do not have antithrombotic properties, thus proposing that the most important consequence of selective COX-2 inhibition in relation to the cardiovascular system is propensity for thrombosis., due to the deviation of the prothrombotic/antithrombotic balance on the endothelial surface, in addition to the loss of the protective effect of COX-2 upregulation in myocardial ischemia and acute myocardial infarction. [4,5]
The evidence on the increased cardiovascular risk with the use of NSAIDs is still incomplete, due to the lack of randomized controlled trials with power to assess relevant cardiovascular outcomes. However, the results of prospective clinical studies and meta-analyses show that COXIBs exert important adverse cardiovascular effects, including increased risk of myocardial infarction, stroke, heart failure, renal failure, and arterial hypertension. [6]
Although the most frequent adverse effects are related to the selective inhibition of COX-2, the lack of selectivity for this isoenzyme does not drop the risk of cardiovascular events, so all drugs from the broad spectrum of NSAIDs should be prescribed only after consideration of the risk/benefit balance. [6,7]
The aim of this study is to analyze the cardiovascular safety of COXIBs and to discover the advantages and limitations of this group of drugs.

METHODS

A synthesis of the available evidence on the association between cyclooxygease-2 inhibitors and cardiovascular risk was carried out through a systematic review study. The NCBI Pubmed, Google Scholar and Cochrane pages were used as search sources. As a bibliographic search strategy, the following terms were used:

- (“Cyclooxygenase 2 Inhibitors” [Mesh]) AND (“Thrombosis” [Mesh]) with the “humans” filter. 67 results were obtained.
- (“Cyclooxygenase 2 Inhibitors”[Mesh]) AND “adverse effects” [Subheading]” with the filters “clinical trials” and “humans”. 377 results were obtained.

Study Population: Patients older than 18 years of age who have received selective inhibitors of the enzyme cyclooxygenase-2 to treat osteoarticular diseases.
Inclusion Criteria: Systematic reviews and retrospective case-control studies that have correlated cyclooxygenase-2 inhibitor drugs and cardiovascular events such as venous thromboembolism and acute myocardial infarction were included.
Exclusion Criteria: Animal studies were excluded.

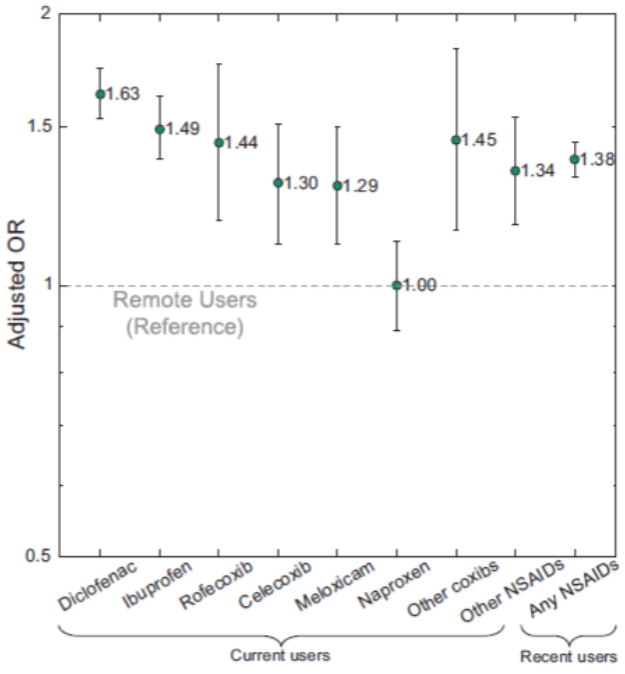
RESULTS

University of Pennsylvania, USA – Risk of acute myocardial infarction:
Thirty case-control studies included 184,946 cardiovascular events and 21 cohort studies described outcomes in 2.7 million exposed people. Of the widely studied drugs (10 or more studies), the highest cardiovascular risk was seen with rofecoxib, 1.45 (95% CI 1.33 to 1.59), and diclofenac, 1.40 (1.27 to 1.55). The NSAIDs that presented the lowest cardiovascular risks were ibuprofen, 1.18 (1.11, 1.25), and naproxen, 1.09 (1.02, 1.16), respectively.
In a subset of studies, the risk was increased with low dose rofecoxib, 1.37 (1.20, 1.57), celecoxib, 1.26 (1.09, 1.47), and diclofenac, 1.22 (1.12, 1.33), and increased in each case with higher doses. The risk of ibuprofen was seen only at higher doses. Naproxen was risk neutral in all doses.
Of the least studied drugs: etoricoxib, 2.05 (1.45, 2.88), etodolac, 1.55 (1.28, 1.87) and indomethacin, 1.30

(1.19, 1.41), showed the highest cardiovascular risks.
In pairwise comparisons, etoricoxib had a higher RR than ibuprofen, RR = 1.68 (99% CI: 1.14, 2.49), and naproxen, RR = 1.75 (1.16, 2.64); Etodolac was not significantly different from naproxen and ibuprofen. Naproxen had a significantly lower cardiovascular risk than ibuprofen, RR = 0.92 (0.87, 0.99). RR estimates were consistent across diverse backgrounds of cardiovascular disease risk and increased early during treatment. [12]

British Society of Rheumatology - Risk of Venous Thromboembolism:
Among rheumatoid arthritis patients with at least one NSAID prescription, 4,020 incident cases of VTE and 20,059 matched controls were found.
The adjusted odd ratios (Odds Ratio) for remote users were 1.38 (95% CI: 1.32, 1.44) for recent users and 1.43 (95% CI: 1.36, 1.49 for recent users)) for current users. Among current NSAID users, the risk of VTE was increased with diclofenac [OR 1.63 (95% CI: 1.53, 1.74)], ibuprofen [OR = 1.49 (95% CI: 1.38, 1.62)], meloxicam [OR = 1.29 (95% CI: 1.11, 1.50)] and coxibs [celecoxib, OR= 1.30 (95% CI: 1.11, 1.51); rofecoxib, OR= 1.44 (95% CI: 1.18, 1.76)]. Naproxen did not increase the risk of VTE [OR = 1.00 (95% CI: 0.89, 1.12)]. However, the effects of diclofenac, ibuprofen, meloxicam, and celecoxib are greater in subjects younger than 70 years. [8]

Fig. 1 Risk of VTE with usage of specific NSAIDs after adjustment



VTE: venous thromboembolism.

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The relationship between acute coronary syndrome and the use of anti-inflammatories was positive (RR 3.64; 95% CI 2.94 to 4.52; p<0.001). Cardiovascular risk was higher in alkanones (nabumetone) (RR 18; 95% CI 2.53 to 127; p=0.004), followed by propionic agents such as ibuprofen (RR 2.58; 95% CI 2.16 to 3.69; p< 0.001). In third place are the arylacetics (diclofenac) (RR 1.88; 95% CI 1.6 to 2.22; p<0.001) and finally the coxibs (RR 1.55; 95% CI 1.25 to 1.92).; p<0.001), which did not increase their cardiovascular risk with time of consumption. Propionic acid derivatives, such as ibuprofen, which are the most consumed anti-inflammatory drugs in Spain, are the only ones that increased cardiovascular risk with time of use. [11]

Riesgos relativos de padecer síndrome coronario agudo asociados al consumode antinflamatorios no esteroideos. Modelo de Poisson			
Antiinflamatorios no esteroideos		Riesgo relativo (IC95%)	p
Arilacéticos	No	1	
	Sí	1,88 (1,60 – 2,22)	<0,001
Tiempo arilacéticos (incremento 1 mes)		1,012 (0,997 – 1,028)	0,12
Propiónicos	No	1	
	Sí	2,58 (2,16 – 3,09)	<0,001
Tiempo propiónicos (incremento1 mes)		1,025 (1,016 – 1,034)	<0,001
Coxibs	No	1	
	Sí	1,55 (1,25 – 1,92)	<0,001
Tiempo coxibs (incremento 1 mes)		0,997 (0,972 – 1,024)	0,84
Indolacéticos	No	1	
	Sí	1,27 (0,82 – 1,99)	0,29
Tiempo indolacéticos (incremento 1 mes)		1,017 (0,983 – 1,052)	0,34
Oxicams	No	1	
	Sí	1,27 (0,96 – 1,68)	0,10
Tiempo oxicams (incremento 1 mes)		0,996 (0,962 – 1,031)	0,81
Pirazolonas	No	1	
	Sí	18,0 (2,53 – 127)	0,004
Tiempo pirazolonas (incremento 1 mes)		1,125 (0,614 – 2,061)	0,70
Otros AINE	No	1	
	Sí	0,69 (0,10 – 4,91)	0,71
Tiempo otros AINE (incremento 1 mes)		1,052 (0,947 – 1,170)	0,34
IC95%: Intervalo de confianza del 95%. Todas las estimaciones fueron ajustadas por edad y sexo.			

European Society of Cardiology - Karolinska Institute (Stockholm – Sweden)
In a national population-based cohort of 7 million people, from July 2005 to December 2008, they performed an analysis for different cardiovascular outcomes in the entire population after excluding individuals with a prior diagnosis of cardiovascular disease (size of sample, n = 6,991,645). Proportional hazard ratios (HRs) revealed no significant association of coxib use with the risk of myocardial infarction, ischemic stroke, or heart failure. In contrast to these findings, coxib use was associated with an increased risk for a first episode of atrial fibrillation [HR 1.16; Confidence interval (CI) of 95%: 1.05-1.29]. A post hoc analysis for different coxibs revealed a significant association with incident atrial fibrillation for etoricoxib (HR 1.35; 95% CI 1.19–1.54), but not for celecoxib (HR 0.94; 95% CI 0. 79–1.11). [13]

DISCUSSION

This review suggests that the risk of these adverse effects is greater in patients with an earlier history of cardiovascular disease or at elevated risk of developing it. In these patients, the use of COX-2 inhibitors should be limited to those for whom there is no proper alternative, and then only at the lowest effective dose and for the shortest period needed.
Evidence shows that among the widely used NSAIDs, low-dose naproxen and ibuprofen are less likely to increase cardiovascular risk.

Data for etoricoxib were sparse, but in pairwise comparisons this drug had a significantly higher relative risk than either naproxen or ibuprofen. Indomethacin is an older drug that is also toxic to the gastrointestinal system, and evidence of cardiovascular risk casts doubt on its continued clinical use.
As the differences between the various NSAIDs are small, large comparative clinical trials are necessary to find which anti-inflammatory regimen minimizes cardiovascular effects.
Although the most frequent adverse effects are related to the selective inhibition of COX-2, the lack of selectivity for this isoenzyme does not drop the risk of cardiovascular events. Thus, all drugs from the broad spectrum of NSAIDs should only be prescribed after considering the risk/benefit ratio for each patient.
Therefore, physicians should always advise NSAID users to seek immediate medical attention if they experience symptoms such as chest pain and dyspnea.

REFERENCES

1. SOGAC. Los antiinflamatorios no esteroideos en Reumatología [Internet]. 2016. https://sogacot.org/los-antiinflamatorios-no-esteroideos-en-reumatologia/.
2. Bäck M, Yin L, Ingelsson E. Cyclooxygenase-2 inhibitors, and cardiovascular risk in a nationwide cohort study after the withdrawal of rofecoxib. Eur Heart J. 2012;33(15):1928-33. https://doi.org/10.1093/eurheartj/ehr421.
3. Orellana I. Inhibidores de Cox2 en gastroenterología. Medwave. 2003;3(01). http://doi.org/10.5867/medwave.2003.02.2334.
4. Domper Arnal MJ, Hijos-Mallada G, Lanas A. Gastrointestinal and cardiovascular adverse events associated with NSAIDs. Expert Opin Drug Saf. 2022;21(3):373-384. https://doi.org/10.1080/14740338.2021.1965988.
5. Abraham NS, El-Serag HB, Hartman C, Richardson P, Deswal A. Cyclooxygenase-2 selectivity of non-steroidal anti-inflammatory drugs and the risk of myocardial infarction and cerebrovascular accident. Aliment Pharmacol Ther. 2007;25(8):913-24. https://doi.org/10.1111/j.1365-2036.2007.03292.x.
6. Batlouni M. Anti-inflamatórios não esteroides: Efeitos cardiovasculares, cérebro-vasculares e renais. Arq Bras Cardiol. abril de 2010; 94:556-63. Sharma JN, Jawad NM. Adverse effects of COX-2 inhibitors. ScientificWorldJournal. 2005;5:629-45. https://doi.org/10.1100/tsw.2005.82.
7. E. Rahme, H. Nedjar, Risks and benefits of COX-2 inhibitors *vs* non-selective NSAIDs: does their cardiovascular risk exceed their gastrointestinal benefit? A retrospective cohort study. *Rheumatology*. 2007;46(3):435–438, https://doi.org/10.1093/rheumatology/kel428.
8. Lee T, Lu N, Felson DT, Choi HK, Dalal DS, Zhang Y, et al. Use of non-steroidal anti-inflammatory drugs correlates with the risk of venous thromboembolism in knee osteoarthritis patients: a UK population-based case-control study. Rheumatology (Oxford). 2016;55(6):1099-105. https://doi.org/10.1093/rheumatology/kew036.
9. Angiolillo DJ, Weisman SM. Clinical Pharmacology and Cardiovascular Safety of Naproxen. Am J Cardiovasc Drugs. 2017;17(2):97–107. https://doi.org/10.1007/s40256-016-0200-5.
10. Capone ML, Tacconelli S, Di Francesco L, Sacchetti A, Sciulli MG, Patrignani P. Pharmacodynamic of cyclooxygenase inhibitors in humans. Prostaglandins Other Lipid Mediat. 2007;82(1–4):851. https://doi.org/10.1016/j.prostaglandins.2006.05.019.
11. Sánchez Serrano JL, Tenias Burillo JM, Arias Arias Á, Muñoz Carreras MI, Valenzuela Gámez JC. Riesgo cardiovascular asociado al consumo de antiinflamatorios no esteroideos: estudio de cohortes retrospectivo en un área de salud, 2008-2012. Revista Española de Salud Pública. 2015;89(6):607-13. https://doi.org/10.4321/s1135-57272015000600008.
12. McGettigan P, Henry D (2011) Cardiovascular Risk with Non-Steroidal Anti-Inflammatory Drugs: Systematic Review of Population-Based Controlled Observational Studies. PLoS Med 8(9):e1001098. https://doi.org/10.1371/journal.pmed.1001098.
13. Bäck M, Yin L, Ingelsson E. Cyclooxygenase-2 inhibitors, and cardiovascular risk in a nationwide cohort study after the withdrawal of rofecoxib. Eur Heart J. 2012;33(15):1928-33. https://doi.org/10.1093/eurheartj/ehr421.

CONFLICTS OF INTEREST

None.

FINANCING

None.

AUTHORSHIP CONTRIBUTION

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