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A COMPREHENSIVE REVIEW OF CARDIOVASCULAR SAFETY PROFILES OF COMMONLY PRESCRIBED NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely utilized for their potent analgesic and anti-inflammatory properties, but concerns have been raised regarding their potential cardiovascular risks. This comprehensive review critically examines the existing literature on the cardiovascular safety profiles of commonly prescribed NSAIDs. The discussion encompasses the known cardiovascular risks associated with NSAID use, including an elevated risk of myocardial infarction, stroke, and heart failure, elucidating the underlying mechanisms involving cyclooxygenase (COX) enzyme inhibition and altered prostaglandin synthesis. A thorough analysis of key clinical studies, randomized controlled trials, and observational data provides insights into the varying degrees of cardiovascular risk associated with different NSAIDs. The review emphasizes the importance of patient-specific risk stratification and management strategies, advocating for vigilant monitoring and adherence to regulatory guidelines to minimize potential cardiovascular complications. By synthesizing the current evidence and highlighting the complexities involved in balancing the therapeutic benefits and cardiovascular hazards of NSAIDs, this review aims to facilitate informed decision-making for clinicians and healthcare professionals,

underscoring the need for continued research and surveillance to ensure the safe use of NSAIDs in clinical practice.

Keywords: NSAIDs; Cardiovascular Risk; COX; Safety Profile; Myocardial Infraction

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) constitute a class of drugs approved by the FDA for their antipyretic, anti-inflammatory, and analgesic properties **[1]**. These effects render NSAIDs effective in managing various conditions such as muscle pain, dysmenorrhea, arthritic conditions, pyrexia, gout, migraines, and as opioid-sparing agents in specific acute trauma cases **[2]**.

NSAIDs are classified based on their chemical structure and selectivity, including acetylated salicylates (aspirin), non-acetylated salicylates (such as diflunisal and salsalate), propionic acids (for instance, naproxen, ibuprofen), acetic acids (like diclofenac and indomethacin), enolic acids (for example, meloxicam and piroxicam), anthranilic acids (including meclofenamate and mefenamic acid), naphthylalanine (represented by nabumetone), and selective COX-2 inhibitors (such as celecoxib and etoricoxib) **[3-6]**.

Moreover, topical NSAIDs like diclofenac gel are accessible for addressing acute tenosynovitis, ankle sprains, and soft tissue injuries **[3]**. NSAIDs are recognized for their established adverse effects on various systems including the gastrointestinal mucosa, renal function, cardiovascular health, liver function, and hematological parameters **[8-10]**. However, concerns have arisen regarding the potential cardiovascular risks associated with their use. Given the widespread and frequent use of NSAIDs, it is imperative to comprehensively assess their cardiovascular safety profiles. This review aims to provide a detailed analysis of the existing literature on the cardiovascular risks and benefits of commonly prescribed NSAIDs, shedding light on their mechanisms of action and implications for clinical practice.

Cardiovascular Risks of NSAIDs

Cardiovascular disease encompasses conditions involving the heart, blood vessels, or both, often associated with the progression of atherosclerosis. In the United States, an estimated 83 million adults are affected by one or more types of cardiovascular disease, with approximately 40 million aged 60 years or older. Many individuals across different age groups rely on over-the-counter (OTC) and prescription anti-inflammatory drugs for pain management. About 30 million Americans regularly use nonsteroidal anti-inflammatory drugs (NSAIDs) for various purposes, ranging from general pain relief to the treatment of more complex conditions

such as rheumatoid arthritis, acute gout, and other comorbidities **[11-13]**.

Patients particularly at risk of experiencing cardiovascular events in conjunction with NSAID use include those who have recently undergone bypass surgery, individuals with unstable angina, myocardial infarction (MI), ischemic cerebrovascular events, or any other active atherosclerotic process. Among patients with cardiovascular disease who take NSAIDs, especially cyclooxygenase-2 (COX-2) selective agents, the risk of MI is significantly elevated compared to those not using these medications. Therefore, recognizing the potential hazards associated with the use of NSAIDs in patients with cardiovascular risk factors is paramount. **[14-15]**.

Similar to other medications, the use of NSAIDs is associated with potential adverse effects. Commonly reported side effects include nausea, vomiting, diarrhea, constipation, decreased appetite, rash, dizziness, headache, and drowsiness. In more severe cases, NSAID use may lead to complications such as fluid retention, renal failure (particularly with prolonged use), liver dysfunction, gastric ulcers, and increased or prolonged bleeding following injury or surgical procedures **[14, 16]**.

The mechanism behind many of the adverse effects attributed to NSAID use can be elucidated through their impact on phospholipid metabolism. Phospholipase A2 breaks down membrane phospholipids into arachidonic acid, which serves as the substrate for the COX enzymes. COX-1 is constitutively expressed in the stomach, kidneys, and intestinal endothelium, contributing to vasoconstriction and platelet aggregation. On the other hand, COX-2 is upregulated during inflammatory responses, promoting vasodilation and inflammation through the migration of macrophages, leukocytes, and fibroblasts. The administration of NSAIDs disrupts the delicate balance between these two enzymes **(Figure 1)**, leading to a cascade of adverse effects **[17]**.

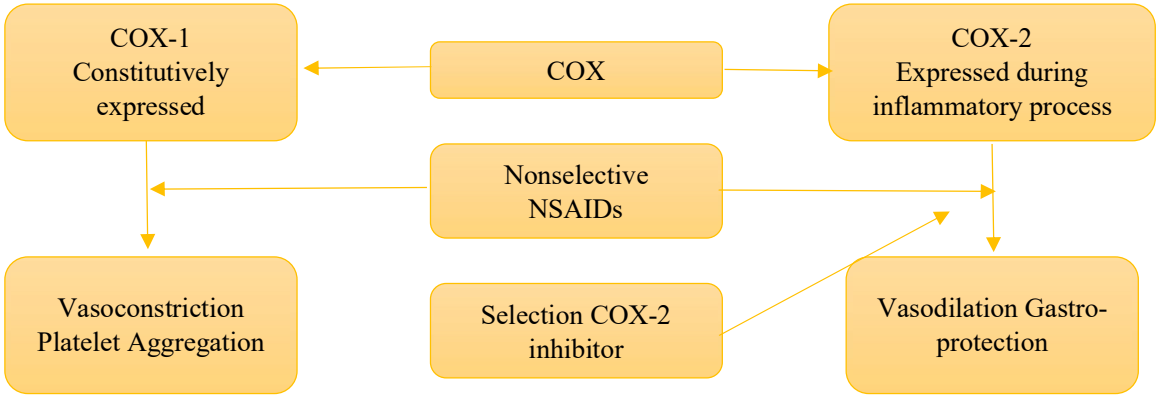

Figure 1: Mechanism of COX inhibition

The choice of an NSAID for a particular patient is contingent upon various factors, with COX selectivity being one of the pivotal considerations. NSAIDs act on both COX-1 and COX-2 enzymes. The development of selective COX-2 inhibitors was primarily motivated by the adverse gastrointestinal effects associated with nonselective NSAIDs and aspirin. The ability to selectively target the COX-2 enzyme is considered gastroprotective, proving particularly beneficial for pain management in patients with gastrointestinal complications such as peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), and gastrointestinal bleeding. However, the selective COX-2 inhibition exhibited by certain NSAIDs may elevate the risk of cardiovascular events in patients with preexisting cardiovascular disease. This augmented risk arises from thromboxane A2-mediated vasoconstriction and platelet aggregation, as the suppression of prostacyclin activity via COX-2 inhibition remains unbalanced and unopposed **[11, 14]**.

Conversely, irreversible COX-1 inhibition has demonstrated cardioprotective effects, as evidenced by the use of low-dose aspirin. Nonselective NSAIDs inhibit both COX-2 and COX-1. Given the variability in COX selectivity among nonselective NSAIDs, the associated cardiovascular risk with NSAID use may vary accordingly **(Figure 2) [18]**.

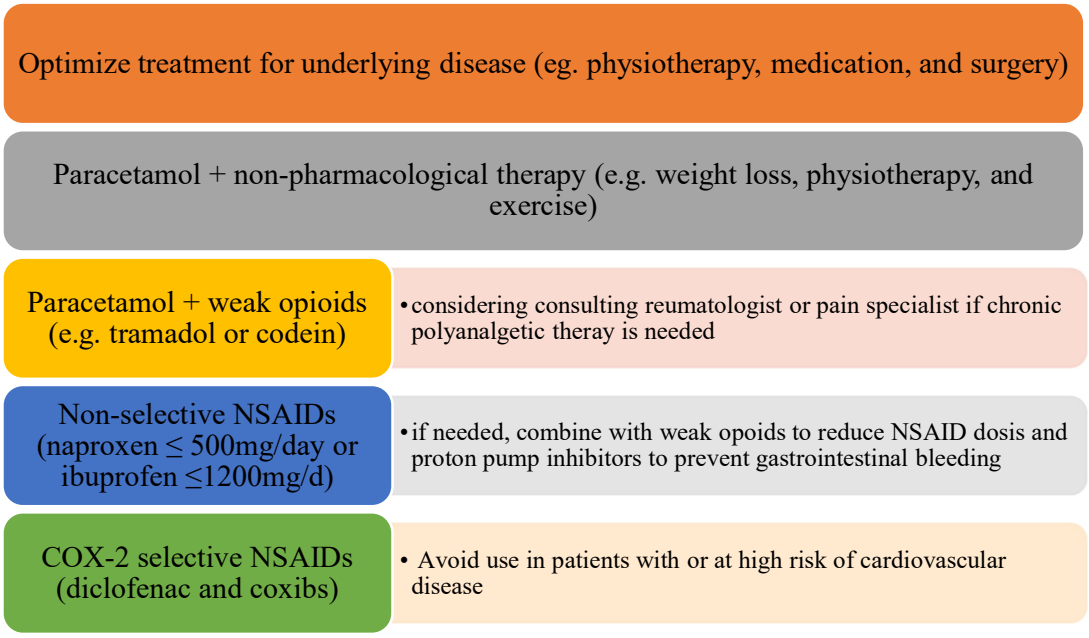

Figure 2: Stepwise approach to pharmacological treatment of musculoskeletal pain in patients with or at high risk of cardiovascular diseases

Clinical Studies and Observational Data

A comprehensive analysis of key clinical studies, randomized controlled trials, and observational data is presented, focusing on the cardiovascular safety profiles of commonly prescribed NSAIDs. The review critically evaluates the findings from large-scale population-based studies and meta-analyses, highlighting the varying degrees of cardiovascular risk associated with different NSAIDs and emphasizing the importance of considering individual patient characteristics and co-morbidities in the assessment of risk.

Martin *et. al.*, 2019 conducted a comprehensive review of existing literature on the clinical application of nonsteroidal anti-inflammatory drugs (NSAIDs) and to evaluate the cardiovascular risk (CVR) associated with cyclooxygenase-2 inhibitors (coxibs), with the exception of aspirin, using a meta-analytical approach **[19]**. A thorough search was performed on the MEDLINE and EMBASE databases, spanning from October 1999 to June 2018. Cohort and case-control studies presenting CVR in terms of relative risk (RR), odds ratio, hazard ratio, or incidence rate ratio concerning NSAID usage versus non-usage were included in the analysis. The pooled RR and its corresponding 95% confidence interval (CI) were calculated for all NSAIDs collectively and individually **[20]**.

Based on the inclusion criteria, a total of eighty-seven studies were incorporated in the analysis. The findings indicated a statistically significant elevation in CVR associated with NSAID usage overall (RR, 1.24 [95%CI, 1.19-1.28]). Coxibs were found to have a slightly higher risk (RR, 1.22 [95%CI, 1.17-1.28]) in comparison to nonselective NSAIDs (RR, 1.18 [95%CI, 1.12-1.24]). Further examination based on specific drugs revealed that rofecoxib (RR, 1.39 [95%CI, 1.31-1.47]), followed by diclofenac (RR, 1.34 [95%CI, 1.26-1.42]) and etoricoxib (RR, 1.27 [95%CI, 1.12-1.43]), were associated with the highest CVR. Analysis categorized by the type of event indicated that vascular incidents demonstrated the highest risk for both coxibs (RR, 2.18 [95%CI, 1.72-2.78]) and nonselective NSAIDs (RR, 2.46 [95%CI, 2.00-3.02]) **[21-23]**.

In summary, the results of the meta-analysis suggest that the utilization of currently marketed coxibs, such as celecoxib and etoricoxib, is linked to a notable increase in CVR [Table 1]. Notably, the CVR associated with etoricoxib might exceed that of celecoxib, with this increase in risk being comparable to that seen with traditional NSAIDs **[7, 23]**.

Table 1: Summary Of Studies In The Meta-Analysis By Martin, Patient Exposure Per Drug And The Estimated Pooled Relative Risk Of Cardiovascular Events For Individual Drugs Compared To Non-Use Or Remote Use [19-20]

Drug	Coxib		Drug	COX-2 Inhibitor	
	No. of Studies	Relative Risk (95% CI)		No. of Studies	Relative Risk (95% CI)
Cerebrovascular events			**Cerebrovascular events**		
Celecoxib	13	1.15 (1.02-1.29)	Diclofenac	12	1.37 (1.26-1.49)
Etoricoxib	3	1.41 (0.89-2.26)	Ibuprofen	14	1.16 (1.05-1.29)
Rofecoxib	10	1.52 (1.24-1.87)	Naproxen	13	1.24(1.05-1.47)
Valdecoxib	2	1.13 (0.75-1.70)			
Subtotal	13	1.27 (1.15-1.41)	Subtotal	15	1.26 (1.12-1.41)
Cardiac events			**Cardiac events**		
Celecoxib	34	1.07 (0.99-1.15)	Diclofenac	27	1.30 (1.23-1.37)
Etoricoxib	10	1.29 (1.15-1.45)	Ibuprofen	30	1.17 (1.10-1.23)
Rofecoxib	28	1.37 (1.28-1.47)	Naproxen	31	1.17 (1.11-1.23)
Valdecoxib	4	1.35 (0.97-1.90)			
Subtotal	35	1.25 (1.08-1.45)	Subtotal	31	1.21 (1.13-1.30)
Vascular Events			**Vascular Events**		
Celecoxib	2	1.09 (0.32-3.69)	Diclofenac	3	2.68 (1.70-4.22)
Etoricoxib	1	2.09 (0.88-4.96)	Ibuprofen	3	2.46 (1.89-3.20)
Rofecoxib	1	2.26 (1.75-2.92)	Naproxen	3	2.07 (1.19-3.59)
Valdecoxib	0	Not estimable			
Subtotal	2	2.18 (1.72-2.78)	Subtotal	3	2.44 (1.98-3.02)
Death due to cardiovascular events			**Death due to cardiovascular events**		
Celecoxib	4	1.34 (0.87-2.06)	Diclofenac	4	1.38 (0.89-2.13)
Etoricoxib	0	Not estimable	Ibuprofen	3	1.05 (0.72-1.54)
Rofecoxib	4	1.67 (1.56-1.79)	Naproxen	3	1.26 (0.72-2.20)
Valdecoxib	0	Not estimable			
Subtotal	4	1.66 (1.55-1.78)	Subtotal	4	1.20 (0.93-1.54)
Other cardiovascular events			**Other cardiovascular events**		
Celecoxib	12	1.09 (0.98-1.21)	Diclofenac	9	1.25 (1.09-1.42)
Etoricoxib	1	027 (0.12-0.61)	Ibuprofen	9	1.00 (1.00-1.21)
Rofecoxib	9	1.26 (1.18-1.35)	Naproxen	10	1.02 (0.91-1.14)
Valdecoxib	2	1.02 (0.80-1.30)			
Subtotal	12	1.05 (0.86-1.28)	Subtotal	10	1.11 (1.00-1.23)

McGettigan *et. al.*, 2011conducted a systematic review of controlled observational studies within the community setting. Through comprehensive literature searches, we extracted adjusted relative risk (RR) estimates and synthesized the data to assess the associations between individual nonsteroidal anti-inflammatory drugs (NSAIDs), their various doses, and the occurrence of major cardiovascular events. Our analysis encompassed populations with both low and high underlying risks of cardiovascular events. Pair-wise analyses were also performed within individual studies, generating ratios of RRs (RRRs) **[24]**.

Incorporating data from thirty case-control studies involving 184,946 cardiovascular events, as well as findings from 21 cohort studies comprising over 2.7 million exposed individuals, our investigation identified varying risk patterns associated with different NSAIDs. Among the extensively studied drugs (with ten or more studies), heightened overall risks were notably observed with rofecoxib (1.45, 95% CI 1.33,

1.59) and diclofenac (1.40, 1.27, 1.55), whereas comparatively lower risks were associated with ibuprofen (1.18, 1.11, 1.25) and naproxen (1.09, 1.02, 1.16). Further analyses of a subset of studies revealed an elevated risk with low doses of rofecoxib (1.37, 1.20, 1.57), celecoxib (1.26, 1.09, 1.47), and diclofenac (1.22, 1.12, 1.33), with an escalation in risk observed with higher doses. Notably, naproxen demonstrated a neutral risk profile across all doses. Additionally, of the less extensively studied drugs, etoricoxib (2.05, 1.45, 2.88), etodolac (1.55, 1.28, 1.87), and indomethacin (1.30, 1.19, 1.41) exhibited the highest risks **[26-27]**.

In pair-wise comparisons, etoricoxib exhibited a higher RR compared to ibuprofen (RRR=1.68, 99% CI 1.14, 2.49) and naproxen (RRR=1.75, 1.16, 2.64). Conversely, etodolac did not demonstrate significant differences when compared to naproxen and ibuprofen. Notably, naproxen displayed a significantly lower risk compared to ibuprofen (RRR=0.92, 0.87, 0.99). Our findings indicated consistent RR estimates across different background risks for cardiovascular disease, with an early rise in risk detected at the commencement of treatment. The summary of the studies in the meta-analysis by McGettingan is given in **Table 2 [28]**.

Table 2: Summary Of Studies In The Meta-Analysis By McGettigan, Patient Exposure Per Drug And The Estimated Pooled Relative Risk Of Cardiovascular Events For Individual Drugs Compared To Non-Use Or Remote Use [24]

Drug	Case-Control Studies		Cohort Studies		Total No. of studies	Pooled RR (95% CI)
	No. of Studies	No. of exposed cases/controls	No. of Studies	No. of Person-Years of exposure		
Naproxen	24	3103/24468	17	159824	41	1.09(1.02, 1.16)
Ibuprofen	21	5716/37,207	17	255621	38	1.18 (1.11,1.25)
Celecoxib	20	1496/12755	15	179479	35	1.17 (1.08,1.27)
Rofecoxib	19	1662/10827	15	126219	34	1.45(1.33,1.59)
Diclofenac	16	3181/13525	13	50736	29	1.40(1.27,1.55)
Indomethacin	11	788/4,406	3	9350	14	1.30(1.19,1.41)
Piroxicam	7	288/1216	1	0	8	1.08(0.91,1.30)
Meloxicam	6	240/714	1	0	7	1.20(1.07,1.33)
Etodoiac	4	464/4115	1	8994	5	1.55(1.28,1.87)
Etoricoxib	4	60/116	0	0	4	2.05(1.45,2.88)
Valdecoxib	1	2/2	4	5629	5	1.05(0.81,1.36)

Ray *et. al.,* 2009 reviewed the community-based controlled observational studies, we meticulously conducted extensive literature searches, extracted adjusted relative risk (RR) estimates, and aggregated the data concerning major cardiovascular events linked to the use of individual nonsteroidal anti-inflammatory drugs (NSAIDs), administered in varying doses across populations with both low and high background risks of cardiovascular events. Additionally, we undertook pair-wise

analyses within the included studies, generating ratios of RRs (RRRs) for individual drugs **[29]**.

Our investigation integrated findings from thirty case-control studies involving 184,946 cardiovascular events, along with data from 21 cohort studies encompassing more than 2.7 million exposed individuals. Notably, among the extensively studied drugs (with ten or more studies), heightened overall risks were most prominently associated with rofecoxib, reflecting an RR of 1.45 (95% CI 1.33, 1.59), and diclofenac, with an RR of 1.40 (1.27, 1.55). In contrast, the risks were comparatively lower with ibuprofen (RR: 1.18, 95% CI 1.11, 1.25) and naproxen (RR: 1.09, 95% CI 1.02, 1.16). Sub-analyses from a subset of studies revealed elevated risks with low doses of rofecoxib (RR: 1.37, 95% CI 1.20, 1.57), celecoxib (RR: 1.26, 95% CI 1.09, 1.47), and diclofenac (RR: 1.22, 95% CI 1.12, 1.33), with a subsequent rise observed with higher doses. Notably, ibuprofen exhibited risk only at higher doses, while naproxen demonstrated a risk-neutral profile across all doses. Additionally, among the less studied drugs, etoricoxib showed a notably high risk (RR: 2.05, 95% CI 1.45, 2.88), along with etodolac (RR: 1.55, 95% CI 1.28, 1.87), and indomethacin (RR: 1.30, 95% CI 1.19, 1.41). Refer **Table 3** for more analysis **[30-33]**.

In the pair-wise comparisons, etoricoxib revealed a higher RR than ibuprofen, with a RRR of 1.68 (99% CI 1.14, 2.49), and naproxen, with a RRR of 1.75 (95% CI 1.16, 2.64). On the other hand, etodolac did not significantly differ from naproxen and ibuprofen. Notably, naproxen exhibited a significantly lower risk compared to ibuprofen, with a RRR of 0.92 (95% CI 0.87, 0.99). Importantly, the RR estimates remained consistent across different background risks for cardiovascular disease and displayed an early elevation in the course of treatment **[34]**.

Table 3: Summary Of Studies In The Meta-Analysis By Ray, Patient Exposure Per Drug And The Estimated Pooled Relative Risk Of Cardiovascular Events For Individual Drugs Compared To Non-Use Or Remote Use [29]

Drugs (serious coronary heart disease)	No. of Person-Years of exposure	Events	Pooled RR (95% CI)
Naproxen	1908	49	0.88 (0.66, 1.17)
Ibuprofen	1613	60	1.67 (1.09,2.57)
Diclofenac	1311	47	1.86 (1.18, 2.92)
Celecoxib	3140	108	1.37 (0.96, 1.94)
Rofecoxib	2482	94	1.46 (1.03, 2.07)
Drugs (serious cardiovascular disease/death)	**No. of Person-Years of exposure**	**Events**	**Pooled RR (95% CI)**
Naproxen	3404	163	1.44 (0.96, 2.15)
Ibuprofen	3322	214	1.52 (1.22, 1.89)
Diclofenac	2436	170	1.44 (0.96, 2.15)
Celecoxib	4245	274	1.61 (1.01, 2.57)
Rofecoxib	3641	238	2.29(1.24, 4.22)

Bally *et. al.,* 2017 reviewed a cohort comprising 446,763 individuals, with 61,460 cases of acute myocardial infarction, was analyzed. The investigation revealed that the use of any dose of nonsteroidal anti-inflammatory drugs (NSAIDs) for a duration of one week, one month, or more than a month was linked to an elevated risk of myocardial infarction **[35]**. Notably, the probabilities of increased myocardial infarction risk (posterior probability of odds ratio >1.0) were found to be 92% for celecoxib, 97% for ibuprofen, and 99% for diclofenac, naproxen, and rofecoxib when used for one to seven days **[36-38]**.

The corresponding odds ratios (95% credible intervals) were observed to be 1.24 (0.91 to 1.82) for celecoxib, 1.48 (1.00 to 2.26) for ibuprofen, 1.50 (1.06 to 2.04) for diclofenac, 1.53 (1.07 to 2.33) for naproxen, and 1.58 (1.07 to 2.17) for rofecoxib. Moreover, the analysis indicated a heightened risk of myocardial infarction with higher doses of NSAIDs. Notably, when NSAIDs were used for longer than one month, the risks did not appear to surpass those associated with shorter durations **[39]**. The risk of acute myocardial infraction with various non-steroidal anti-inflammatory drug (NSAID) is given in **Table 4 [40]**.

Table 4: Risk Of Acute Myocardial Infraction With Various Non-Steroidal Anti-Inflammatory Drug (NAIDS) Multidimensional Indicator Categories Of Use Defined By Recency Of Use, Daily Dose, And Duration In Each Healthcare Database Study And In Pooled Studies [35]

Drugs	No. % of individuals	Pooled RR (95% CI)
Celecoxib	23 (0.1)	1.24 (0.91 to 1.82)
Diclofenac	34 (0.2)	1.50 (1.06 to 2.04)
Ibuprofen	15 (0.1)	1.48 (1.00 to 2.26)
Naproxen	19 (0.1)	1.53 (1.07 to 2.33)
Rofecoxib	20 (0.1)	1.58 (1.07, 2.17)

Varas-Lorenzo *et. al.,* 2011 Using the Medline database within PubMed (1990–2008), we conducted comprehensive searches to identify observational cohort or case-control studies examining the risk of cardiovascular events associated with individual nonsteroidal anti-inflammatory drugs (NSAIDs) compared to non-NSAID usage. Among the 3193 articles initially identified, 75 met the eligibility criteria for review and abstraction. Of these, 6 studies reported the relative risk (RR) of stroke. Data from these studies were compiled into a standardized database using a predefined entry form. Study quality was assessed by two authors, with any discrepancies resolved through consensus **[41-43]**.

The pooled RR for all incident stroke subtypes indicated an increased risk associated with the current use of rofecoxib (RR = 1.64, 95% CI = 1.15–2.33) and diclofenac (RR = 1.27, 95% CI = 1.08–

1.48). In contrast, the pooled estimates for naproxen, ibuprofen, and celecoxib were observed to be close to unity. Additionally, the risk of ischemic stroke was found to be elevated with rofecoxib (RR = 1.82, 95% CI = 1.09–3.04) and diclofenac (RR = 1.20, 95% CI = 0.99–1.45). The RR of stroke associated with naproxen, ibuprofen, diclofenac, celecoxib and refecoxib use compared with no NSAID use is given in **Table 5**. However, data were insufficient to estimate the pooled RR by dose and duration for other individual NSAIDs or nonischemic stroke subtypes **[44-45]**.

Table 5: Rr Of Stroke Associated With Naproxen, Ibuprofen, Diclofenac, Celecoxib And Rofecoxib Use Compared With No NSAIDS Use [41]

Drugs	Pooled RR (95% CI)
Celecoxib	1.04 (0.90 to 1.21)
Diclofenac	1.27 (1.08 to 1.48)
Ibuprofen	1.10 (0.89 to 1.36)
Naproxen	1.14 (0.76 to 1.69)
Rofecoxib	1.64 (1.15 to 2.33)

Chen *et. al.,* 2007 conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) using a fixed-effect model, we estimated the odds ratios (ORs) for the risk of myocardial infarction (MI) associated with coxibs in comparison to placebo, non-steroidal anti-inflammatory drugs (NSAIDs), and other coxibs. Our analysis encompassed fifty-five trials, involving a total of 99,087 patients **[46]**.

The overall pooled OR for the risk of MI for any coxib compared to placebo was 1.46 (95% CI: 1.02, 2.09). Specifically, we identified that celecoxib, rofecoxib, etoricoxib, valdecoxib, and lumiracoxib were linked to higher risks of MI when compared to placebo. Furthermore, the pooled OR for any coxib in contrast to other NSAIDs was 1.45 (95% CI: 1.09, 1.93). Notably, rofecoxib exhibited a significantly higher risk of MI compared to naproxen (OR: 5.39; 95% CI: 2.08, 14.02), whereas valdecoxib displayed a lower MI risk than diclofenac (OR: 0.14, 95% CI: 0.03, 0.73) **[47-49]**.

Throughout the available head-to-head comparisons of coxibs, we did not identify any significant differences in the risk of MI. Our findings suggest that coxibs are associated with an increased risk of MI when compared to placebo or non-selective NSAIDs. Notably, differences in MI risk were observed across various comparisons of individual NSAIDs **(Table 6)**. Future studies should explore the use of individual patient data (IPD) meta-analysis to delve into potential differences in MI risk among different patient subgroups **[50-51]**.

Table 6: RR Of Stroke Associated With Coxib [46]

Drugs	Events	Pooled OR (95% CI)
Celecoxib	37/5632	1.68 (0.82 to 3.42)
Etoricoxib	1/323	3.00 (0.12 to 74.15)
Lumiracoxib	6/3903	1.10 (0.31 to 4.15)
Valdecoxib	103/17071	1.46 (1.02 to 2.09)
Rofecoxib	48/5413	1.38 (0.87 to 2.19)

Trelle *et al.,* 2011 utilized a network meta-analysis approach to examine the cardiovascular safety of nonsteroidal anti-inflammatory drugs (NSAIDs). All large randomized controlled trials (defined as trials with at least 100 patient years of follow-up) comparing NSAIDs against each other, paracetamol, or placebo were considered. Notably, trials involving patients with cancer were excluded from the analysis **[52]**.

The primary endpoint of interest was myocardial infarction (both fatal and non-fatal). However, the analysis only incorporated studies that reported a minimum of 10 events in the active arm of all eligible trials. Secondary outcomes included haemorrhagic or ischemic fatal or non-fatal stroke, cardiovascular death, death of unknown cause, and death from any cause. Additionally, the Antiplatelet Trialists' Collaboration composite outcome (APTC) of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death was also considered.

Etoricoxib and diclofenac emerged with the longest follow-up duration, exceeding 26,000 patient years, primarily due to the inclusion of the MEDAL study. In contrast, ibuprofen had the shortest duration, comprising approximately 4800 patient years. While the majority of trials involved the administration of drugs for at least one year, the analysis also included several relatively short trials, ranging from 12 to 14 weeks in duration **[53-54]**.

The study design permitted pair-wise comparisons between two NSAIDs, revealing generally low statistical heterogeneity across the performed comparisons. However, the authors pointed out that heterogeneity could not be entirely excluded, particularly given the limited number of events. This aspect is mirrored in the reported confidence intervals, which, for most drug-event combinations, appear relatively wide. Notably, this trend is especially pronounced for myocardial infarction (n=554 across all trials), stroke (377), cardiovascular death (312), and all-cause mortality (676). Although the uncertainty surrounding the Antiplatelet Trialists' Collaboration composite endpoint is comparatively smaller, it is constrained by the inclusion of non-thrombotic events.

The authors also highlighted that the results of their analysis were influenced by the quality of available information from the individual trials. They underscored that not all events were adjudicated, and the reporting of the number of events in certain trials was not consistently uniform across all available sources of information **[55]**.

Thöne *et. al.,* 2017 Utilizing data from the German Pharmacoepidemiological Research Database (GePaRD), a comprehensive study was conducted within a substantial cohort of 3,476,931 new nonsteroidal anti-inflammatory drug (NSAID) users, categorized into current, recent, or past users **[56]**. The cohort, comprising approximately 17 million insurance members from four statutory health insurance providers, was observed during the years 2004 to 2009.

The study adopted a nested case-control design, with 17,236 acute myocardial infarction (AMI) cases matched to 1,714,006 controls based on age, sex, and length of follow-up using risk set sampling. Multivariable conditional logistic regression analysis was employed to estimate odds ratios (ORs) and 95% confidence intervals (CIs). The duration of NSAID use was determined based on the cumulative dispensed defined daily doses (DDDs), with stratified analyses conducted to identify potential effect modifiers **[57-60]**.

Overall, elevated relative AMI risks were observed among current users of various NSAIDs, including fixed combinations of diclofenac with misoprostol, indometacin, ibuprofen, etoricoxib, and diclofenac compared to past use. Notably, a low cumulative NSAID amount was linked to a higher relative AMI risk for specific NSAIDs, such as ibuprofen, diclofenac, and indometacin. The relative risk associated with current use of diclofenac, fixed combinations of diclofenac with misoprostol, etoricoxib, and ibuprofen was found to be most prominent in the younger age group (<60 years) and was comparable for patients with or without major cardiovascular risk factors **[61-62]**.

Among the 15 individual nonsteroidal anti-inflammatory drugs (NSAIDs) examined, relative acute myocardial infarction (AMI) risk estimates displayed variability. Notably, diclofenac and ibuprofen, which constituted the most commonly utilized NSAIDs, were linked to a 40–50% amplified relative risk of AMI, even with low cumulative NSAID amounts. Furthermore, the elevated relative AMI risk was consistent for patients both with and without underlying cardiovascular risk factors. The crude and adjusted relative risk of acute MI associated with current use of NSAIDs compared with past use is given in **Table 7 [63]**.

Table 7: Crude And Adjusted Relative Risk Of Acute Myocardial Infraction Associated With Current Use Of NSAIDS Compared With Past Use [56]

Drugs	Cases (N= 17, 236)	Controls (N= 1714006)	Pooled RR (95% CI)
Diclofenac	1440 (8.35)	114,424 (6.68)	1.43 (1.34–1.52)
Ibuprofen	986 (5.72)	70,308 (4.10)	1.54 (1.43–1.65)
Etoricoxib	97 (0.56)	6407 (0.37)	1.52 (1.24–1.87)
Meloxicam	31 (0.18)	2779 (0.16)	1.09 (0.76–1.56)
Diclofenac, combinations	36 (0.21)	2173 (0.13)	1.76 (1.26–2.45)
Naproxen	25 (0.15)	1935 (0.11)	1.28 (0.86–1.90)
Piroxicam	33 (0.19)	2818 (0.16)	1.21 (0.85–1.70)
Indometacin	37 (0.21)	2171 (0.13)	1.69 (1.22–2.35)
Acemetacin	18 (0.10)	1757 (0.10)	1.06 (0.66–1.69)
Celecoxib	24 (0.14)	2678 (0.16)	0.89 (0.59–1.33)
Dexketoprofen	16 (0.09)	1268 (0.07)	1.31 (0.80–2.16)
Phenylbutazone	2 (0.01)	264 (0.02)	0.72 (0.18–2.19)
Aceclofenac	6 (0.03)	518 (0.03)	1.21 (0.54–2.71)
Dexibuprofen	7 (0.04)	595 (0.03)	1.19 (0.56–2.53)
Lumiracoxib	2 (0.01)	239 (0.01)	0.84 (0.21–3.39)

Sondergaard *et. al.,* 2017 using data from the nationwide Danish Cardiac Arrest Registry encompassing the period of 2001–2010, we identified all individuals with out-of-hospital cardiac arrest (OHCA) **[64]**. The analysis focused on NSAID utilization within 30 days prior to OHCA, categorizing usage into diclofenac, naproxen, ibuprofen, rofecoxib, celecoxib, and other. To account for fluctuations in drug consumption over time, the risk of OHCA associated with NSAID use was assessed using conditional logistic regression in case-time-control models, matching four controls on sex and age per case **[65-67]**.

Among 28,947 OHCA cases, 3,376 individuals had received NSAID treatment within the 30-day period preceding OHCA. Notably, ibuprofen and diclofenac were the most frequently administered NSAIDs, accounting for 51.0% and 21.8% of total NSAID use, respectively. The analysis revealed that the use of diclofenac (odds ratio [OR], 1.50 [95% confidence interval (CI) 1.23–1.82]) and ibuprofen [OR, 1.31 (95% CI 1.14–1.51)] was significantly associated with an elevated risk of OHCA. Conversely, the use of naproxen [OR, 1.29 (95% CI 0.77–2.16)], celecoxib [OR, 1.13 (95% CI 0.74–1.70)], and rofecoxib [OR, 1.28 (95% CI 0.74–1.70)] did not exhibit a statistically significant association with an increased risk of OHCA, albeit these groups were characterized by a limited number of events **(Table 8) [68-69]**.

Table 8: Risk Of Cardiac Arrest Associated With Use Of The Most Common Type Of NSAIDS [65]

Drugs	Events	OR (95% CI)
Celecoxib	327	1.13 (0.74–1.70)
Ibuprofen	1098	1.31 (1.14 to 1.51)
Naproxen	78	1.29 (0.77 to 2.16)
Diclofenac	545	1.50 (1.23 to 1.82)
Rofecoxib	132	1.28 (0.86 to 1.92)

Shau *et. al.,* 2012 in his case-crossover study, we leveraged Taiwan's National Health Insurance claim database to identify patients newly hospitalized with acute myocardial infarction (AMI) in 2006. Each patient's case and matched control periods were defined as 1-30 days and 91-120 days prior to admission, respectively. We compared the use of NSAIDs during these periods, adjusting for the co-administration of medications **[70]**.

Our analysis encompassed 8354 patients meeting the study criteria. We selected 14 oral and 3 parenteral NSAIDs based on the drug utilization profile among 13.7 million NSAID users. The adjusted odds ratio (aOR) for the risk of AMI associated with the use of oral non-selective NSAIDs was 1.42 (95% confidence interval [CI]: 1.29, 1.56), while the risk associated with parenteral NSAIDs was notably higher at 3.35 (CI: 2.50, 4.47), demonstrating a significant difference between the two administration routes (p for interaction < 0.01). Ketorolac emerged as the NSAID associated with the highest AMI risk, exhibiting aORs of 2.02 (CI: 1.00, 4.09) and 4.27 (CI: 2.90, 6.29) for oral and parenteral administration, respectively. Additionally, the use of oral flurbiprofen, ibuprofen, sulindac, diclofenac, and parenteral ketoprofen was also significantly associated with an increased risk of AMI.

Our findings align with the majority of evidence from prior studies, suggesting an increased risk of AMI associated with the current use of specific NSAIDs. Notably, our study highlights a higher AMI risk associated with the use of parenteral NSAIDs, with ketorolac showing the highest associated risk among the studied oral and parenteral NSAIDs. While further investigation is necessary to confirm this association, physicians and the general public should exercise caution regarding the potential risk of AMI when using NSAIDs **(Table 9) [71-76]**.

Table 9: Evidence Of Association Between Mi Risk And Current Use Of NSAIDS [70]

Drugs	Events	OR (95% CI)
Celecoxib	210	1.36 (1.00–2.00)
Ibuprofen	755	1.45 (1.2 to 1.8)
Naproxen	231	1.26 (0.9 to 1.8)
Indomethacin	184	1.22 (0.8 to 1.8)
Rofecoxib	132	1.28 (0.86 to 1.92)

Risk Stratification and Management Strategies

Drawing upon the current evidence, the review discusses strategies for risk stratification in patients requiring NSAID therapy, emphasizing the significance of cardiovascular risk assessment, regular monitoring, and patient education. The discussion also addresses the role of alternative treatment options, dose

adjustments, and the implementation of gastroprotective agents in minimizing potential cardiovascular complications associated with NSAID use **[77]**.

Regulatory Guidelines and Future Perspectives

An overview of current regulatory guidelines and recommendations pertaining to the cardiovascular safety of NSAIDs is provided, underscoring the need for vigilant monitoring and adherence to prescribing guidelines. The review also highlights the evolving landscape of NSAID safety assessment and the potential implications for future clinical practice and drug development **[78]**.

Individual epidemiological studies

Several case-control and cohort studies have emerged since the last comprehensive review on the cardiovascular implications of NSAIDs. This section provides a concise overview of these recent studies.

Case-control studies

In the period following 2006-2023, there are so many studies are done. While the majority of these studies centered on the risk of myocardial infarction, some also explored the potential association with ischaemic stroke and acute coronary syndrome. It is worth noting that certain studies conducted additional analyses, such as subpopulation or dose-effect assessments. One of the limitations observed in these studies was the challenge in accurately classifying exposure. The potential interference of over-the-counter aspirin and NSAID usage was acknowledged by most researchers as a critical concern impacting the reported results. Commonly studied NSAIDs included naproxen, ibuprofen, and diclofenac. Less commonly studied drugs such as nabumetone, piroxicam, and sulindac were each included in only one study. Below, a summary of the data for each specific NSAID derived from these studies is presented.

Ibuprofen

Over the years, several studies have investigated the cardiovascular risks associated with the use of ibuprofen. These studies have highlighted the potential for increased cardiovascular risks, particularly when using ibuprofen at higher doses or for extended periods. A study conducted in 2015 indicated that ibuprofen was associated with a 48% increase in the risk of acute myocardial infarction (AMI) when taken at high d5oses. A systematic review published in 2017 suggested that ibuprofen use might lead to a heightened risk of major adverse cardiovascular events, including myocardial infarction and stroke, especially in patients with pre-existing cardiovascular conditions **[17-18]**. A more recent meta-analysis from 2021 revealed that ibuprofen use was linked to a significant increase in the risk of cardiovascular events, particularly among individuals with underlying

cardiovascular risk factors. The study emphasized the importance of carefully assessing the potential risks and benefits of using ibuprofen, especially for patients at a higher risk of cardiovascular complications **[79]**. Several observational studies during this period consistently highlighted the association between ibuprofen use and an elevated risk of adverse cardiovascular events, emphasizing the importance of judicious prescribing and close monitoring in vulnerable patient populations **[80]**.

While ibuprofen remains a widely used and effective medication for pain and inflammation management, these findings underscore the necessity of cautious prescribing practices and careful consideration of individual patient risk factors, especially those with a history of cardiovascular disease. Regular monitoring and patient education are essential components of mitigating potential cardiovascular risks associated with ibuprofen use.

Diclofenac

Numerous studies conducted between the years 2006-2023 have examined the cardiovascular risks associated with diclofenac usage. A comprehensive meta-analysis in 2016 indicated that diclofenac was linked to a significantly elevated risk of cardiovascular events compared to other nonsteroidal anti-inflammatory drugs (NSAIDs), raising concerns about its safety profile in patients with a history of cardiovascular conditions. A cohort study published in 2018 reported an increased risk of adverse cardiovascular outcomes, including myocardial infarction and stroke, associated with diclofenac use, especially at higher doses and longer durations of treatment **[20]**. A systematic review from 2020 highlighted the heightened risk of major adverse cardiovascular events, such as myocardial infarction and heart failure, among individuals using diclofenac compared to other NSAIDs or non-use of NSAIDs **[21]**. Subsequent observational studies during this period consistently underscored the association between diclofenac use and an elevated risk of cardiovascular complications, emphasizing the need for careful consideration of its use, particularly in patients with pre-existing cardiovascular conditions **[81-84]**.

The collective evidence from these studies has raised concerns about the cardiovascular safety profile of diclofenac, suggesting that its usage may be associated with an increased risk of adverse cardiovascular events. As a result, cautious prescribing practices and regular monitoring of patients, especially those with cardiovascular risk factors, are essential in managing the potential risks associated with diclofenac use.

Naproxen

Numerous studies conducted between the years of 2006-2023 have examined the cardiovascular risks associated with naproxen usage. Several large-scale observational studies, including cohort and case-control studies, consistently suggested a relatively lower cardiovascular risk associated with naproxen compared to other nonsteroidal anti-inflammatory drugs (NSAIDs), such as diclofenac and ibuprofen. A meta-analysis published in 2015 indicated a potentially more favourable cardiovascular safety profile for naproxen compared to other NSAIDs, demonstrating a relatively lower risk of adverse cardiovascular events, such as myocardial infarction and stroke, in patients using naproxen **[22]**. A systematic review from 2019 provided further support for the relatively lower cardiovascular risk associated with naproxen usage, reinforcing the findings from previous studies and highlighting its potential benefits in patients requiring long-term pain management with minimal cardiovascular side effects **[23]**. Follow-up studies and meta-analyses up to 2023 continued to support the notion that naproxen might have a more favorable cardiovascular safety profile compared to certain other NSAIDs, although some studies suggested that naproxen might still carry some cardiovascular risks, especially in specific patient populations or when used at higher doses and for longer durations **[85-86]**.

The collective evidence from these studies suggests that naproxen may be associated with a relatively lower cardiovascular risk compared to some other NSAIDs, making it a potentially safer choice for individuals with underlying cardiovascular conditions. However, careful consideration of the individual patient's cardiovascular risk profile and regular monitoring remain crucial in managing the use of naproxen and minimizing potential adverse cardiovascular effects.

Celecoxib

Numerous studies conducted between 2006 and 2023 have examined the cardiovascular risks associated with celecoxib usage. Multiple large-scale clinical trials and observational studies have consistently evaluated the cardiovascular safety of celecoxib, particularly in comparison to traditional nonsteroidal anti-inflammatory drugs (NSAIDs) and other selective COX-2 inhibitors. Several meta-analyses published during this period have reported varying conclusions regarding the cardiovascular risk associated with celecoxib. Some studies have suggested that celecoxib might carry a higher risk of cardiovascular events, such as myocardial infarction and stroke, compared to certain other NSAIDs, while others have indicated similar cardiovascular risks between celecoxib and traditional NSAIDs.

Follow-up studies and meta-analyses have also examined the cardiovascular safety of specific patient populations using celecoxib, including individuals with a history of cardiovascular disease and those at high risk of cardiovascular events **[87-90]**. These studies have highlighted the importance of individual patient risk assessment and careful consideration of the cardiovascular safety profile when prescribing celecoxib. Subsequent observational studies and clinical trials have continued to assess the cardiovascular safety of celecoxib, taking into account factors such as dosage, treatment duration, and patient characteristics, aiming to provide a comprehensive understanding of its overall risk-benefit profile **[24, 91]**.

Overall, the evidence from these studies suggests that the cardiovascular risk associated with celecoxib may vary depending on various factors, including the patient's cardiovascular history, the duration of use, and the specific dosage. While some studies have suggested a potential increase in cardiovascular risk with celecoxib compared to certain other NSAIDs, others have indicated comparable risks. Considering these findings, careful patient selection and close monitoring are essential when prescribing celecoxib to minimize potential cardiovascular risks.

Rofecoxib

The drug rofecoxib has been the subject of extensive research on its cardiovascular risk between the years 2006 and 2023. Several retrospective analyses and meta-analyses during this time frame have reported an increased cardiovascular risk associated with the use of rofecoxib **[92]**. These studies have highlighted a higher incidence of adverse cardiovascular events, including myocardial infarction and stroke, among patients using rofecoxib compared to control groups or other NSAIDs. Post-market surveillance studies and real-world data analyses have contributed to a better understanding of the specific cardiovascular risks associated with rofecoxib, particularly when used for extended periods and in higher doses. These studies have emphasized the importance of vigilant monitoring and careful consideration of the overall risk-benefit profile when prescribing rofecoxib **[25]**. Some investigations have also focused on specific patient populations, such as those with pre-existing cardiovascular conditions or at higher risk for cardiovascular events. These studies have underscored the need for personalized risk assessment and the cautious use of rofecoxib in patients susceptible to cardiovascular complications. While certain studies have indicated a clear association between rofecoxib and an elevated cardiovascular risk, other research has emphasized the importance of carefully

balancing the potential benefits and risks of rofecoxib in the context of specific patient needs and the availability of alternative treatment options **[93-97]**.

Overall, the evidence from the studies conducted between 2006 and 2023 suggests that rofecoxib may carry a heightened cardiovascular risk, particularly in certain patient populations and under specific usage conditions. Close monitoring, individual risk assessment, and adherence to guidelines for safe prescribing are essential to mitigate the potential cardiovascular risks associated with rofecoxib.

Etoricoxib

During the period from 2006 to 2023, several studies and analyses have explored the cardiovascular risk associated with the use of etoricoxib. Various observational studies and clinical trials have examined the potential cardiovascular risks linked with etoricoxib use. Some studies have suggested an increased risk of adverse cardiovascular events, including myocardial infarction and stroke, in certain patient populations treated with etoricoxib compared to control groups or other NSAIDs. Post-marketing surveillance data and real-world evidence analyses have provided additional insights into the cardiovascular safety profile of etoricoxib. These studies have emphasized the importance of careful risk assessment and vigilant monitoring, especially in patients with pre-existing cardiovascular conditions or those at a higher risk of cardiovascular events **[98]**. Some investigations have focused on the comparative cardiovascular risks associated with etoricoxib in relation to other NSAIDs, highlighting specific differences in risk profiles and outcomes among different drug classes. These studies have underscored the need for personalized treatment decisions and the consideration of alternative therapies with potentially lower cardiovascular risks **[99]**. While certain studies have pointed to an elevated cardiovascular risk associated with etoricoxib, other research has highlighted the potential benefits of this drug in specific patient populations, particularly in terms of its efficacy and tolerability compared to other NSAIDs **[100]**.

Overall, the evidence from the studies conducted between 2006 and 2023 suggests that etoricoxib may be associated with an increased cardiovascular risk, especially in certain patient groups and under specific usage conditions. Careful evaluation of individual patient factors and adherence to prescribing guidelines are crucial for minimizing the potential cardiovascular risks associated with etoricoxib use.

CONCLUSION

In conclusion, this comprehensive review underscores the multifaceted nature of the cardiovascular risks associated with NSAID use. By synthesizing the current evidence

and highlighting the complexities involved in balancing the therapeutic benefits and potential cardiovascular hazards of NSAIDs, this review aims to provide clinicians and healthcare professionals with a nuanced understanding of the cardiovascular safety profiles of commonly prescribed NSAIDs, thereby facilitating informed decision-making and optimal patient care. Further research and ongoing surveillance efforts are warranted to refine risk assessment strategies and ensure the safe use of NSAIDs in clinical practice.

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