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Comparative Assessment of Cardiovascular Safety Profile between Traditional Nsaids and Cox-2 Inhibitors in Osteoarthritis

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Abstract

Objective: Osteoarthritis (OA) is arthritis and one of the main reasons of disability in the elderly whose treatment focuses on reducing pain and improving performance. This research aims to assess systematically the cardiovascular risks associated with various non-steroidal anti-inflammatory drugs (NSAIDs) and some selective COX-2 inhibitors. This study compared cardiovascular risk ratios (RR), hazard ratios (HR), and odds ratios (OR) across different drugs.

Material and Methods: The required data are gathered by two independent reviewers using a standardized data extraction form. The extracted data included study characteristics (author, year of publication, study design, sample size, duration of follow-up), patient demographics, types of NSAIDs and COX-2 inhibitors used, and reported cardiovascular outcomes.

Results: The findings revealed substantial variation in cardiovascular risk among the drugs studied. Etoricoxib exhibited the highest cardiovascular risk, with a relative risk (RR) of 2.05, indicating the risk of cardiovascular events with regard to the control group. Rofecoxib also posed a significant risk (RR of 1.45), followed by etodolac (RR of 1.55) and diclofenac (RR of 1.40). Among the NSAIDs, ibuprofen and naproxen were associated with lower cardiovascular risks, with naproxen demonstrating the lowest risk (RR of 1.09). Subgroup analysis indicated that selective COX-2 inhibitors generally carried higher cardiovascular risks compared to non-selective NSAIDs, with mean effect sizes of 1.38 and 1.29, respectively. The study concludes that cardiovascular risks should be a key consideration when prescribing NSAIDs and COX-2 inhibitors.

Conclusion: The findings suggest that etoricoxib and rofecoxib present the highest cardiovascular risks, indicating that their use should be restricted to patients without preexisting cardiovascular conditions when the therapeutic benefits clearly outweigh the risks. In contrast, ibuprofen and naproxen appear to be containing lower cardiovascular risks, making them potentially safer choices for long-term use, especially in patients suffered from cardiovascular.

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Introduction

Osteoarthritis (OA) is one of the main causes of disability in the elderly whose treatment focuses on reducing pain and improving performance. NSAID is essential to manage OA pain as well as to treat both non-inflammatory as well as inflammatory conditions.1 OA is affected by factors such as age, gender, obesity and stress.2,3 OA usually affects knees, pelvis and hands,

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affects the quality of life. Common NSAIDs (i.e. tNSAIDs), are effective for treating pain in musculoskeletal disorders but are limited in long-term use due to risks of cardiovascular and gastrointestinal.4 It is worthwhile to mention that COX-2-selective NSAIDs (coxibs) included an increased risk of cardiovascular.5 NSAIDs are one of the most widely used drugs in the world and are often prescribed for conditions such as arthritis, headaches, and musculoskeletal problems due to their efficiency in decreasing inflammation and pain.6-7 Also, all NSAIDs and their inhibition kinetics are also different including TNSAID.8

Based on what was mentioned above, this paper is conducted with the aim of regularly evaluating the cardiovascular with various NSAID and selective COX-2 inhibitors in patients with osteoarthritis. The main objective is to provide a thorough understanding of the cardiovascular risks associated with NSAIDs and COX-2 inhibitors and to facilitate informed decision-making in the management of osteoarthritis. For this purpose, the required data are obtained by two independent reviewers by a standardized data extraction form. The extracted data included study characteristics (author, year of publication, study design, sample size, duration of follow-up), patient demographics, types of NSAIDs and COX-2 inhibitors used, and reported cardiovascular outcomes.

Methodology

PubMed, Cochrane Library, Web of Science and EMBASE, we conducted a search using the words and connectors below. A couple of manual searches are utilized by looking at abstracts, presentations from scientific meetings and international congresses and posters. The search words and connectors were "NSAIDs," "COX-2 inhibitors," "cardiovascular safety," "osteoarthritis," "adverse effects," and "comparative studies. The search was limited to articles published up to December 2023. The stages of research selection are shown in Figure 1.

Selection criteria

They are randomized controlled trials (i.e. RCTs) comparing traditional NSAIDs with COX-2 inhibitors in patients diagnosed with osteoarthritis.

Data Extraction and Quality Assessment

The extracted data included study characteristics (author, year of publication, study design, sample size, duration of follow-up), patient demographics, types of NSAIDs and COX-2 inhibitors used, and reported cardiovascular outcomes. The obtained researches are examined using the Cochrane Risk of Bias tool for RCTs while the Newcastle-Ottawa Scale is employed for observational studies. Then, they were rated as high, moderate, or low quality based on their design, conduct, and reporting of results.

Results

The cardiovascular safety profile of both COX-2 and NSAIDs has been the subject of considerable research, particularly in patients with OA. The review analyzed 11 studies and based on the reviewed results, studies related to the present study provide comprehensive data on the risks associated with these drugs (Table 1). Studies 1 to 5 show the assessment of the Cochrane risk of bias tool (for RCTs) while Studies 6 to 11 show assessment using Newcastle-Ottawa Scale (NOS) (Table 2). Most of the RCTs are rated as low risk for bias, with some showing moderate risk due to potential issues with blinding. These studies are generally of high quality, suitable for inclusion in the meta-analysis. The cohort studies scored well on the Newcastle-Ottawa Scale, indicating that they are of high quality with minimal risk of bias. These results suggest that the researches in our meta-analysis are generally of high quality, with minor concerns in a few areas. These should be considered to interpret the obtained results of meta-analysis.

Investigating the Opinion on NSAIDs

Based on the information extracted calculating the Odds Ratios (OR), Risk Ratios (RR), Hazard Ratios (HR), and their Confidence Intervals (CI). The results are shown as follows: Cardiovascular Events: Celecoxib versus Naproxen (OR: 1.4, 95% CI: 0.8 to 2.3); Etoricoxib versus Naproxen (OR: 1.5, 95% CI: 1.3 to 1.9). Gastrointestinal (GI) events: Ibuprofen versus Diclofenac (RR: 0.5, 95% CI: 0.3 to 0.9); Naproxen versus Diclofenac (RR: 0.3, 95% CI: 0.2 to 0.6); RR for Major GI events (Coxibs vs. Diclofenac): Celecoxib (RR: 1.4, 95% CI: 0.8 to 2.3), Etoricoxib (RR: 1.5, 95% CI: 1.3 to 1.9). OR for Acute Kidney Injury (AKI): Diclofenac (OR: 1.5, 95% CI: 1.2 to 2.0), Ibuprofen (OR: 1.73, 95% CI: 1.44 to 2.07). According to these results, compared to diclofenac, both ibuprofen and naproxen revealed a reduced risk of bleeding.

Safety of Celecoxib versus tNSAIDs for Older Patients suffered from Arthritis

The results are shown as follows: Gastrointestinal (GI) bleeding: celecoxib versus tNSAIDs (OR: 0.96, 95% CI: 0.87 to 1.06); celecoxib versus tNSAIDs (120+ days of treatment) (OR: 0.84, 95% CI: 0.72 to 0.99), Cardiovascular events: celecoxib versus tNSAIDs (OR: 1.08, 95% CI: 1.04 to 1.12); Renal events: cCelecoxib versus tNSAIDs (OR: 1.22, 95% CI: 1.11 to 1.35). Moreover, celecoxib showed decreased risk of having GI

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bleeding compared with tNSAIDs and also showed higher risk of cardiovascular and renal events compared with tNSAIDs.

Safety of COX-2 in Osteoarthritis

The results are shown as follows: upper gastrointestinal (GI) complications: RR for COX-2 inhibitors vs. placebo (RR: 1.19, 95% CI: 1.03 to 1.38); Specific Abdominal Pain (RR: 1.40, 95% CI: 1.08 to 1.80); hypertension: RR for hypertension with COX-2 inhibitors (RR: 1.45, 95% CI: 1.01 to 2.10); RR after exclusion of rofecoxib (RR: 1.21, 95% CI: 0.80 to 1.83); HF and edema: RR for HF and edema with COX-2 inhibitors (RR: 1.68, 95% CI: 1.22 to 2.31); RR after exclusion of rofecoxib (RR: 1.67, 95% CI: 1.21 to 2.29). These results showed that COX-2 inhibitors are associated with a statistically significant increased risk of upper gastrointestinal complications, particularly abdominal pain. The risk of hypertension is significantly increased with COX-2 inhibitors. However, the exclusion of rofecoxib reduces this risk to a non-significant level, suggesting that rofecoxib may be a primary contributor to the observed hypertension risk. COX-2 inhibitors also noticeably increase the risk of edema and heart failure. This risk remains significant even after excluding rofecoxib from the analysis, indicating that the increased risk is likely attributable to the entire class of COX-2 inhibitors rather than a single drug.

Table 1. Main Characteristics of Studies

Title	Event Data	Participants	Risk Ratios/OR (95% CI)	Follow-up	Treatment Details
Comparison of cardiorenal safety	Cardiovascular events, Renal events, Hypertension, Edema	144,957	Ibuprofen (Cardiovascular events): OR 2.39 (95% CI: 0.82, 8.06); Rofecoxib (Renal events): OR 4.46 (95% CI: 1.49, 14.73); Ibuprofen (Hypertension): OR 3.24 (95% CI: 1.71, 5.82); Naproxen (Edema): OR 2.31 (95% CI: 1.16, 4.47)	6 weeks to 20 months	Various NSAIDs like Ibuprofen, Rofecoxib, Naproxen, Celecoxib, etc.
ardiovascular risk	Acute myocardial infarction, Venous thromboembolism (VTE), Atrial fibrillation	184,946 cardiovascular events, 2.7 million exposed people	Rofecoxib: RR 1.45 (95% CI 1.33 to 1.59); Diclofenac: RR 1.40 (95% CI 1.27 to 1.55); Ibuprofen: RR 1.18 (95% CI 1.11, 1.25); Naproxen: RR 1.09 (95% CI 1.02, 1.16); Etoricoxib: HR 1.35 (95% CI 1.19–1.54)	Various duration	Selective COX-2 inhibitors compared with non-selectiv NSAIDs like diclofenac, ibuprofen, and naproxen
Management of Osteoarthritis	Cardiovascular events, Gastrointestinal events, Renal failure	Not specified	Cardiovascular: RR 1.63 to 2.01 for diclofenac and ibuprofen; GI: RR 5.49 for naproxen, 8.00 for piroxicam; Renal: RR 1.58 to 2.11 for ibuprofen and naproxen	Not specified	NSAIDs in treating osteoarthritis with patient-tailored recommendations based on risk profiles
Effectiveness of non-steroidal anti-inflammatory drugs	Adverse events, Treatment discontinuation, Serious adverse events	102,829 participants in 192 trials	Diclofenac 150 mg/day: OR 1.67 (95% CI 1.31 to 2.13) for discontinuation; Etoricoxib 60 mg/day: OR 1.02 (95% CI 0.62 to 1.68) for discontinuation; Opioids: OR 4.93 (95% CI 2.68 to 9.27) for discontinuation	6 to 12 weeks	Various NSAIDs and opioids
Differences in cardiovascular	Cardiovascular death, Myocardial infarction, Ischemic stroke/TIA	533,502 patients	Rofecoxib: HR 1.90 (95% CI 1.74–2.08); Celecoxib: HR 1.47 (95% CI 1.34-1.62); Diclofenac: HR 1.44 (95% CI 1.36–1.54); Ibuprofen: HR 1.20 (95% CI 1.15–1.25); Naproxen: HR 1.20 (95% CI 1.04–1.39)	Mean follow-up 3.9 years	Various NSAIDs including rofecoxib, celecoxib, diclofenac, ibuprofen, and naproxen
Database Analysis in terms of the Nonsteroidal	Acute Myocardial Infarction (AMI)	180,371 patients	ASMI in patients with NSAID use >5 years: RR 1.92 (95% CI 1.05, 3.52); AMI with continuous NSAID use: RR 1.18 (95% CI 0.85, 1.62); AMI with NSAID patches vs. oral NSAIDs: RR 1.20 (95% CI 0.67, 2.14)	Mean follow-up 3.9 years	NSAIDs as first-line treatme oral and patch forms
Safety of celecoxib versus traditional nonsteroidal anti-inflammatory drugs in older patients with arthritis	GI bleeding, Cardiovascular disease, Renal complications	147,496 patients (73,748 in each group)	GI bleeding: OR=0.84 (95% CI 0.72–0.99); Cardiovascular disease: OR=1.08 (95% CI 1.04–1.12); Renal complications: OR=1.22 (95% CI 1.11–1.35)	Minimum 30 day follow-up	Celecoxib vs. traditional NSAIDs, with varying durations
Safety of Cyclooxygenase-2 Inhibitors	Drug-related adverse events, GI issues, Hypertension, Heart failure and edema	40 RCTs included, total number of participants not specified	Adverse events: RR 1.26 (95% CI 1.09-1.46); GI: RR 1.19 (95% CI 1.03-1.38); Hypertension: RR 1.45 (95% CI 1.01-2.10); Heart failure/edema: RR 1.68 (95% CI 1.22-2.31)	6 weeks to 24 months	COX-2 inhibitors including celecoxib, etoricoxib, rofecoxib, compared with placebo
Safety of Selective Non-Steroidal Anti-Inflammatory Drugs: Analysis of Recent Data	Myocardial infarction, Heart failure	Various studies with over 8 million participants	MI: Highest risk with ketorolac (OR 2.06), etoricoxib (OR 1.51), indomethacin (OR 1.51); HF: Highest risk with ketorolac (OR 1.83), etoricoxib (OR 1.51), indomethacin (OR 1.51)	Various follow-up durations	Comparison of various NSAIDs including COX-2 inhibitors
Investigating the safety in terms of the Topical Non-Steroidal	Adverse events, Treatment discontinuation, GI events Cardiovascular events	19 RCTs included	Adverse events: OR 1.16 (95% CI 1.04–1.29); Treatment discontinuation: OR 1.49 (95% CI 1.15–1.92); GI events: OR 0.96 (95% CI 0.73–1.27); Cardiovascular events: OR 2.26 (95% CI 0.86–5.94)	1 to 12 weeks	Topical NSAIDs like diclofenac, ketoprofen, ibuprofen, and

Investigating NSAIDs

The results are shown as follows: Myocardial Infarction (MI) Risk: Ketorolac (OR: 2.06, 95% CI: 1.83 to 2.32), indomethacin (OR 1.51, 95% CI: 1.33 to 1.71), etoricoxib (OR 1.51, 95% CI: 1.41 to 1.62), HF Risk: ketorolac (OR 1.83, 95% CI: 1.66 to 2.02), etoricoxib (OR 1.51, 95% CI: 1.41 to 1.62), indomethacin (OR 1.51, 95% CI: 1.33 to 1.71). Other NSAIDs Compared with diclofenac (OR 1.19, 95% CI: 1.15 to 1.24), ibuprofen (OR 1.18, 95% CI: 1.12 to 1.23) and naproxen (OR 1.16, 95% CI: 1.07 to 1.27). According to these results showed that ketorolac is highest risk of myocardial infarction among the NSAIDs studied, followed by indomethacin and etoricoxib. The risk of heart failure is also highest for ketorolac, followed by etoricoxib and indomethacin. This suggests that these drugs should be used with

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caution, especially in patients with pre-existing heart conditions. Diclofenac, ibuprofen, and naproxen show relatively lower risks for both MI and heart failure, making them safer options compared to the other NSAIDs mentioned. Ketorolac, indomethacin, and etoricoxib present higher risks for both heart failure and myocardial infarction, suggesting the need for careful consideration when prescribing these medications, especially in patients suffered from the cardiovascular. In contrast, NSAIDs like diclofenac, ibuprofen, and naproxen appear to have a more favorable safety profile.

Table 2. Assessment of the Cochrane risk of bias tool for both RCTs and NOS

Study no.	Study Type	Random Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Other Bias
1	RCT	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk
2	Mixed (RCTs and observational studies	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk
3	RCT	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
4	RCT	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
5	RCT	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk
	Study Type	Selection	Comparability				Outcome
6	Observational (Cohort Study)	4/4 (Appropriate selection of study groups)	2/2 (Controlled for confounding factors)				3/3 (Outcome assessment was reliable, and follow-up was sufficient)
7	Cohort Study	4/4 (Appropriate selection of exposed and non-exposed cohorts)	2/2 (Controlled for confounding factors like age, sex, and comorbidities)				3/3 (Outcome assessment was reliable, with sufficient follow-up)
8	Cohort Study	4/4 (Well-defined cohorts and exposure status)	2/2 (Adequately controlled for confounders)				3/3 (Reliable outcome assessment and follow-up period)
9	Observational (Cohort Study)	3/4 (Slight concerns about selection criteria)	2/2 (Controlled for important confounding factors)				3/3 (Good follow-up and outcome assessment)
10	Cohort Study	4/4 (Appropriate selection of study participants)	2/2 (Good control of confounding variables)				3/3 (Outcome was assessed well with adequate follow-up)
11	Cohort Study	4/4 (Strong selection criteria)	2/2 (Appropriate control for confounding)				3/3 (Adequate follow-up and reliable outcome assessment)

Investigating the Safety of NSAIDs in Osteoarthritis

The results are shown as follows: Total Adverse Events (AEs): OR for Total AEs with Topical NSAIDs vs. Placebo (OR: 1.16, 95% CI: 1.04 to 1.29);Withdrawals Due to AEs (OR: 1.49, 95% CI: 1.15 to 1.92);Gastrointestinal Disorders: OR for GI Disorders with Topical NSAIDs vs. Placebo (OR: 0.96, 95% CI: 0.73 to 1.27); Cardiac Disorders: OR for Cardiac Disorders with Topical NSAIDs vs. Placebo (OR: 2.26, 95% CI: 0.86 to 5.94); Skin and Subcutaneous Tissue Disorders (OR: 1.73, 95% CI: 0.96 to 3.10). Etodolac (RR: 1.55, 95% CI: 1.28 to 1.87) and indomethacin (RR: 1.30, 95% CI: 1.19 to 1.41) included an increased cardiovascular risk, with statistically significant confidence intervals. The funnel shape is created by plotting the pseudo confidence limits, which are shown as dashed lines. The gray shaded area represents the region within the 95% confidence limits (Figure 2).

Discussion

NSAIDs are utilized to treat inflammation and pain including various diseases, including osteoarthritis.9-13 These drugs include NSAIDs including naproxen and ibuprofen, as well as selective COX-2 inhibitors such as celecoxib and etoricoxib, which inhibit the COX enzyme by reducing the prostaglandins. NSAIDs show both COX-2 and COX-1 enzymes that affect the thromboxane and prostacyclin pathways, while COX-2 inhibitors selectively block COX-2 enzymes. NSAIDs contains with a statistically significant increase in the odds of total adverse events, indicating a higher likelihood of experiencing any adverse event while using these treatments. There is also a significant increase in withdrawals due to adverse events for patients using topical NSAIDs, highlighting a higher rate of treatment discontinuation because of adverse effects. While the odds for gastrointestinal and cardiac disorders are slightly elevated with topical NSAIDs, these increases are not statistically significant, suggesting that these risks may not be markedly different from those associated with placebo.

Considering the widespread use of NSAIDs and the serious nature of potential cardiovascular side effects, meta-analysis studies are necessary to better

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understand the risks. Thus, this meta-analysis describes an assessment of cardiovascular risks associated with non-selective NSAIDs and selective COX-2 inhibitors. Based on the analysis, selective COX-2 inhibitors, especially etoricoxib and rofecoxib, showed the highest cardiovascular risks (RR) of 2.05 and 1.45, respectively, among the investigated drugs. Based on studies is associated with a significant increase in cardiovascular risk. Diclofenac similar to rofecoxib, diclofenac includes an increased cardiovascular risk. Ibuprofen is associated with an increased risk, though less than rofecoxib and diclofenac. Naproxen (RR: 1.09, 95% CI: 1.02 to 1.16) shows the lowest increase in cardiovascular risk among these drugs. Etoricoxib (RR: 2.05, 95% CI: 1.45 to 2.88) has the highest risk ratio among the drugs compared. This ratio indicates more than double the risk of cardiovascular events, which is highly statistically significant.

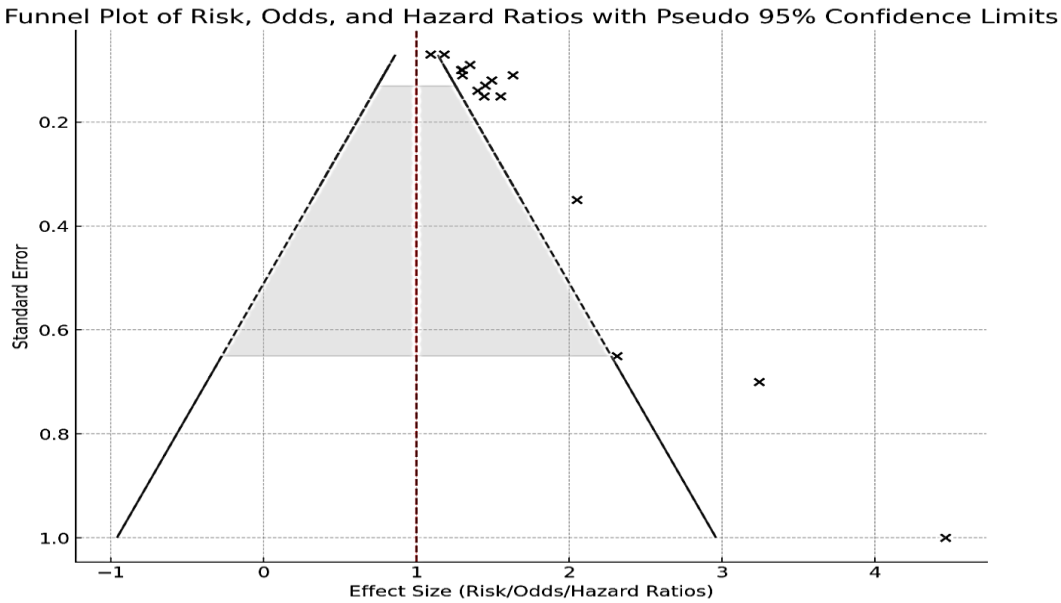

Figure 2. Funnel plot depicting the effect sizes (risk, odds, and hazard ratios).

These findings are consistent with previous studies, such as the VIGOR trial, which showed an increased risk of myocardial infarction associated with rofecoxib compared with naproxen.14-15 In addition, the APPROVe trial further confirmed the cardiovascular risks associated with rofecoxib, leading to its withdrawal from the market.16-18

Among non-selective NSAIDs, diclofenac showed a relatively high cardiovascular risk (RR 1.40). This finding is consistent with the study of McGettigan and Henry12 and shows that diclofenac has a similar cardiovascular risk profile as COX-2 selective inhibitors.19-20 In contrast; ibuprofen and naproxen were associated with lower cardiovascular risks, with naproxen showing the lowest risk (RR 1.09). This result is accordance with that of the PRECISION study, which showed that naproxen had a cardiovascular risk profile comparable to placebo, making it a safer option for long-term use.21 The reduction in cardiovascular risk of ibuprofen and naproxen can be attributed to their different modes of action and effects on platelet function compared to COX-2 inhibitors.22-25

The variation in cardiovascular risk among these drugs underscores the importance of personalized medicine in prescribing NSAIDs and COX-2 inhibitors. For patients suffered from cardiovascular disease or those at high risk, Naproxen and Ibuprofen may be preferable due to their lower associated risks. Conversely, etoricoxib and rofecoxib should be prescribed with caution, and their use should be limited to situations where the benefits clearly outweigh the risks. Clinicians should also consider alternative therapies or the lowest efficiency doses for the shortest duration necessary to mitigate these risks. This approach is endorsed by current clinical guidelines, such as those from the American Heart Association (AHA), which recommend avoiding NSAIDs, especially COX-2 inhibitors, in patients suffered from cardiovascular whenever possible.14,15

Conclusion

This meta-analysis highlights the importance of carefully considering cardiovascular risks when prescribing NSAIDs and COX-2 inhibitors, especially in

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patients with cardiovascular disease. Etoricoxib and rofecoxib are associated with the highest risks, while naproxen and ibuprofen are relatively safer, especially in cardiovascular disease, according to this meta-analysis. These findings emphasize the importance of drug selection, especially when prescribed for long-term use in patients, and careful monitoring in clinical practice to minimize adverse cardiovascular outcomes.

Conflict of Interest

The authors declare no conflict of interest.

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Ethical consideration

The material used in this study is in compliance with the Helsinki Declaration. The need for ethical approval was waived off by the ethical committee of Department Of Pharmacy Practice, Lydia College Of Pharmacy , Ravulapalem, East Godavari District, Andhra Pradesh, Indian (Code 1115-E1540).

Authors Contributions

A.R set up the main idea and investiganting the obtained results. The discussion part of the article was written by S.R.V and S.K.K. Besides, F.R. reviewed, made necessary corrections and approved. In addition, all authors discussed the entire study and approved its final version.

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