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SYSTEMATIC REVIEW

Current Evidence on Celecoxib Safety in the Management of Chronic Musculoskeletal Conditions: An Umbrella Review

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Abstract

Objectives Our objective was to systematically synthesize and evaluate the existing evidence from meta-syntheses (systematic reviews and meta-analyses) reporting on the safety of celecoxib in adults with chronic musculoskeletal disorders.

Methods We conducted a comprehensive literature search in November 2024 across MEDLINE, Cochrane Central, and Scopus databases, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines for umbrella reviews. Only systematic reviews and meta-analyses involving celecoxib safety in osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis were included. We assessed the risk of bias using the AMSTAR-2 tool and graded the certainty of evidence using GRADE.

Results Of 2294 retrieved records, 16 systematic reviews based on randomized controlled trials met the inclusion criteria (14 of 16 were rated as critically low quality). Celecoxib was consistently associated with a lower risk of gastroduodenal ulcers than were non-selective non-steroidal anti-inflammatory drugs (NSAIDs), and some studies also reported fewer gastrointestinal complaints and serious events with celecoxib than with non-selective NSAIDs. Cardiovascular safety outcomes were generally similar to those with non-selective NSAIDs, although one meta-analysis showed a lower risk of cardiovascular mortality with celecoxib. Compared with placebo or non-selective NSAIDs, celecoxib did not increase the risk of renal dysfunction or elevated creatinine and may be associated with fewer renal adverse events. Evidence on all-cause mortality was limited and inconsistent, but one study suggested a lower risk than with non-selective NSAIDs.

Conclusions Celecoxib appears to offer better gastrointestinal safety than non-selective NSAIDs. Although data on cardiovascular, renal, and mortality outcomes suggest possible advantages, the evidence remains limited and of low certainty. Moreover, some real-world evidence raises concerns in specific high-risk populations. Future research should integrate data from both randomized trials and observational studies to better inform long-term safety assessments and guide individualized treatment decisions.

1 Introduction

Chronic musculoskeletal conditions such as osteoarthritis (OA), rheumatoid arthritis (RA), and ankylosing spondylitis (AS) significantly affect the quality of life of millions of

Key points

This umbrella review synthesized evidence from 16 systematic reviews of randomized controlled trials evaluating the safety of celecoxib in chronic musculoskeletal conditions.

Celecoxib demonstrates superior gastrointestinal safety than non-selective non-steroidal anti-inflammatory drugs, with a lower risk of gastroduodenal ulcers and related adverse events.

Although data on cardiovascular, renal, and mortality outcomes suggest possible advantages, the evidence remains limited and of low certainty.

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people worldwide [1]. These conditions are characterized by persistent pain, inflammation, and progressive joint damage, leading to significant disability and economic burden [2]. Effective management of these conditions, including pharmacological and non-pharmacological interventions [3–6], is critical to alleviate symptoms, improve functional outcomes, and enhance patients' overall quality of life.

Non-steroidal anti-inflammatory drugs (NSAIDs) are a cornerstone in the management of chronic musculoskeletal conditions because of their analgesic and anti-inflammatory properties [7]. Celecoxib, a selective cyclooxygenase (COX)-2 inhibitor, is one such NSAID that is widely used in the treatment of OA, RA, and AS. Compared with traditional non-selective NSAIDs, celecoxib is thought to have a more favorable safety profile, particularly in terms of gastrointestinal side effects [8]. However, the safety of celecoxib, particularly its cardiovascular, gastrointestinal, and renal safety, continues to be the subject of extensive debate and research [9]. Previous studies and reviews have produced mixed results, leading to uncertainty and controversy in the medical community. Given the significant morbidity and mortality associated with these adverse events, a comprehensive understanding of the safety of celecoxib in the management of chronic musculoskeletal conditions is imperative.

Despite its long-standing availability, celecoxib's safety profile has continued to generate debate and has prompted multiple updates to product labeling over time. These changes were largely informed by evolving evidence from both observational studies and major randomized controlled trials (RCTs). This highlights the importance of regularly reassessing the totality of available evidence to guide clinical use. This umbrella review aims to contribute to this ongoing appraisal by systematically identifying all meta-synthesis works (i.e., systematic literature reviews and meta-analyses) reporting safety data on the use of celecoxib for OA, RA, and AS.

2 Methods

We followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [10] and the Joanna Briggs Institute manual, specific to umbrella reviews [11], throughout the whole process of this systematic review. The completed PRISMA checklist is available in Appendix A in the electronic supplementary material (ESM).

A protocol was developed before the umbrella review was conducted and was published in Open Science Framework, a platform for sharing scientific research (record ID https://osf.io/jn52b/). All materials and resources associated with this work are accessible through this open-access repository. No deviations from the protocol were made.

2.1 Literature Search

MEDLINE (via Ovid platform), Cochrane Central Systematic Reviews (via Ovid platform), and Scopus were searched in November 2024 to identify any meta-synthesis work (i.e., systematic reviews, meta-analyses, network meta-analyses) reporting safety data associated with the use of celecoxib for the treatment of OA, RA, and AS. A combination of medical subject headings and keywords was used in the search strategy (the complete search strategies for the three databases are available in Appendix B in the ESM). We also conducted a manual search within the bibliographies of relevant papers and contacted experts in the field to complete the bibliographic search. We consulted Epistemonikos (https://www.epistemonikos.org/) to ensure that the search strategies had not missed any relevant references. The search was limited to studies published in English [12, 13]. No limits were applied to publication dates.

The search results from the electronic sources and hand searching were imported into Covidence software for data management. Covidence is a web-based collaboration software platform that streamlines the production of systematic and other literature reviews (https://support.covidence.org/help/how-can-i-cite-covidence).

2.2 Study Selection

Two independent reviewers (OB, CBe, and CBr) screened all identified articles for eligibility, first based on their titles and abstracts and then based on their full texts. Any conflicts were resolved by discussion and consensus. The following inclusion criteria guided the study selection: (1) systematic reviews with or without meta-analysis; (2) included data from adult humans of any gender and any age with OA, RA, and/or AS; (3) analyzed data from randomized and non-randomized designs (prospective, retrospective cohort); (4) used celecoxib as an intervention at any dose and any length of treatment; (5) reported cardiovascular safety, gastrointestinal safety, renal safety, and all-cause mortality associated with the use of celecoxib; and (6) were published in a peer-reviewed journal.

Systematic reviews including RCTs with patients with other diseases or healthy participants were included only if separate analyses were performed for patients with OA, RA, or AS.

2.3 Data Extraction

One independent reviewer (CBr) extracted the study characteristics according to a standardized data extraction form pre-tested on a sample of two studies. A second reviewer (OB or CBe) checked the data extraction. The following

data were extracted: information related to the study (author, year of publication, journal, DOI), population characteristics (including mean age, gender ratio, health condition), number of studies included in the meta-synthesis, safety outcome, fundings, and conflicts of interest.

Any disagreements were resolved through consensus between reviewers. Authors of individual papers were contacted if information was missing.

2.4 Quality Appraisal

Two independent reviewers used the AMSTAR-2 tool to assess the methodological quality and risk of bias of the included systematic reviews (and meta-analyses). Any conflicts between reviewers were resolved by discussion and consensus. The AMSTAR-2 tool consists of a 16-item checklist, with seven criteria deemed crucial to the overall validity of a review. The systematic reviews/meta-analyses were categorized as very low quality, low quality, moderate quality, or high quality.

2.5 Strategy for Data Synthesis

Data synthesis involved a narrative synthesis approach. Additionally, we applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines to assess and integrate the strength of evidence for each outcome. As this research synthesis was an umbrella review, we used an adapted version of GRADE [14].

3 Results

3.1 Study Selection and Characteristics

A total of 2294 records were retrieved from the search of the three databases: 775 from MEDLINE, 40 from Cochrane Central Systematic Reviews, and 1479 from Scopus. After duplicates were removed, 1800 articles remained, of which 1719 were then excluded based on the screening of titles and abstracts. Finally, 16 articles that met our inclusion criteria were included in the umbrella review (see the flowchart in Fig. 1 and the Open Science Framework deposit for the list of studies excluded from the systematic review based on full-text screening and the reasons for exclusion). The characteristics of the studies included in the umbrella review are presented in Table 1. Studies were published between 2001 [15] and 2021 [16]. Of the 16 studies, 13 (81.25 %) were in patients with OA, 11 (68.75 %) were in patients with RA, and four (25%) were in patients with AS. All the systematic reviews included in this umbrella review were based on RCTs. Meta-analyses were performed in all the systematic reviews covered by the work except in the study by Garner et al. [17] in which meta-analyses had been planned but not conducted because of a lack of data. Two studies (12.5%) were funded by industry, eight (50.0%) were funded by national research institutes or universities, one (6.25%) reported no funding, and the remaining four (25.0%) did not report any funding information.

Using AMSTAR-2, two studies [18, 19] were rated as high quality, and all the other studies were rated as critically low quality. The results of the quality assessment for all studies are reported in Table 1.

The efficacy and safety of celecoxib was most often compared with placebo and/or traditional NSAIDs such as naproxen, diclofenac, or ibuprofen. Of the 16 studies, 13 (81.25%) compared the safety of celecoxib against placebo, 13 (81.25%) compared non-selective NSAIDs, and two (12.5%) compared non-selective NSAIDs plus proton pump inhibitors [20, 21].

3.2 Cardiovascular Safety

Five meta-analyses [16, 19, 21–23] assessed the impact of celecoxib on cardiovascular safety in patients with OA, RA, or AS. Only one of these was of good quality [19]. The meta-analysis by Cheng et al. [16] reported that cardiovascular mortality was not significantly different between patients taking celecoxib and those receiving placebo but was lower in patients receiving celecoxib than in those receiving non-selective NSAIDs. No significant effect on the risk of myocardial infarctions and strokes was found when celecoxib was compared with placebo [16, 19]. Similarly, no change in the risk of myocardial infarctions and strokes was detected when celecoxib was compared with non-selective NSAIDs [16, 22]. Finally, two meta-analyses assessed the impact of celecoxib on cardiovascular events, which were not further defined. The meta-analysis by Wang et al. [21] reported that celecoxib did not affect cardiovascular events when compared with non-selective NSAIDs plus proton pump inhibitors. Moreover, Zeng et al. [24] reported no significant effect on cardiovascular events when celecoxib was compared with placebo in their meta-analysis (Table 2).

3.3 Gastrointestinal Safety

The impact of celecoxib on gastrointestinal safety in patients with OA, RA, or AS was assessed in 12 meta-analyses [15, 18, 20–22, 24–30], only one of which was of good quality [18]. Three meta-analyses showed that the incidence of gastroduodenal ulcers was lower with celecoxib than with non-selective NSAIDs [15, 18, 25]. One of these meta-analyses [18], rated as a high-quality study, reported a pooled risk ratio based on five studies (and 1568 patients) of 0.22 (95% confidence interval [CI]

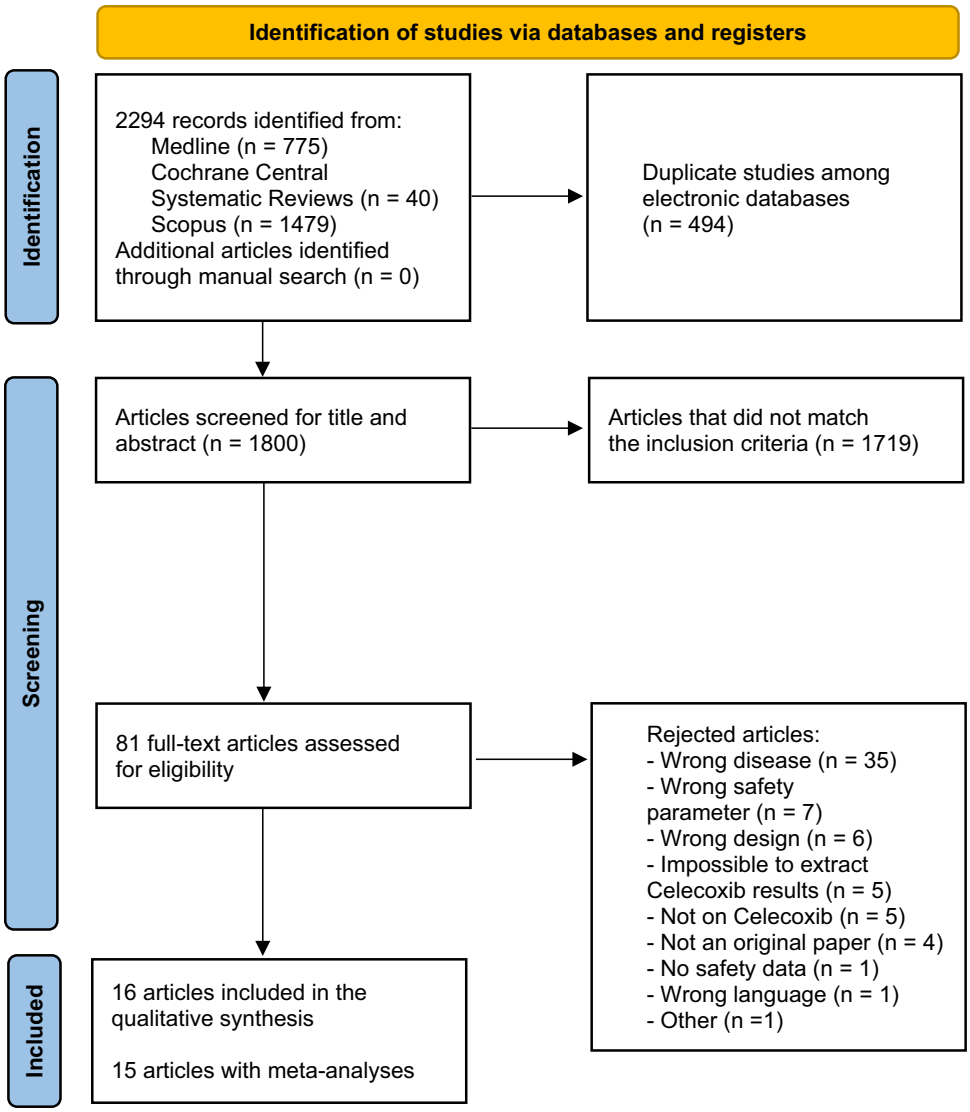

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart.

0.15–0.32; $I^2 = 0\%$). However, the meta-analysis by Ashcroft et al. [15] showed that the rate of gastroduodenal ulcers was significantly higher with celecoxib than with placebo. Results regarding the other gastrointestinal safety outcomes were mixed. In two meta-analyses [25, 29], the risk of gastrointestinal complaints such as abdominal pain was significantly higher with celecoxib than with placebo, whereas three other meta-analyses [22, 26, 28] reported that celecoxib caused fewer abdominal and gastrointestinal complaints (including abdominal pain, diarrhea, dyspepsia, and nausea) than non-selective NSAIDs such as naproxen or diclofenac [22, 25, 27]. Finally, two other meta-analyses reported no effect of celecoxib on these gastrointestinal complaints when compared with non-selective NSAIDs [21, 26]. Rostom et al. [25] reported fewer cases of gastrointestinal bleeding, perforation, and obstruction with celecoxib than with NSAIDs, but this finding was not supported by Deeks et al. [30] or Jarupongprapa et al. [20]. Finally, the odds of developing gastrointestinal events were higher with celecoxib than with placebo in the meta-analysis by Zeng et al. [24]. Unfortunately, these gastrointestinal events were not defined in detail (Table 3).

3.4 Renal Safety

Only two meta-analyses [22, 23] assessed the impact of celecoxib on renal safety in patients with OA, RA, or AS, and both were rated as low quality. Zhang et al. [23] reported that the risk of renal events (including renal

Table 1 Characteristics of the systematic reviews (SRs) of randomized controlled trials (RCTs) included in the umbrella review

Study	Studies (n)	Inclusion/exclusion criteria of SR	Participants (n)	Disease	Celecoxib dose range	Main outcomes	Funding	AMSTAR-2 rating
Ashcroft et al. [15], 2001	5	Inclusion: RCT including pts with RA or OA who had scheduled endoscopies	4632	OA, RA	50–400 mg BID	Rate of gastroduodenal ulcers	NR	Critically low quality
Cheng et al. [16], 2021	21	Inclusion: RCT including pts with RA or OA Exclusion: RCT including pts with other rheumatic diseases such as systemic lupus erythematosus or Sjogren's syndromes	NR	OA, RA	100 mg OD–400 mg BID	Cardiovascular mortality, MI, stroke, AF, angina, arrhythmias, HF, drug-related CV events, all-cause mortality	Supported by the Natural Science Foundation project	Critically low quality
Deeks et al. [30], 2002	9	Inclusion: RCT, double blinded, compared celecoxib at a licensed therapeutic dose for ≥12 wks in pts with active RA or OA	15,187	OA, RA	100–400 mg BID	Ulcers detected by endoscopy; bleeds, perforations, and obstructions	Supported by Pfizer and Searle	Critically low quality
Fan et al. [26], 2020	9	Inclusion: RCT, double blinded, enrolling pts fulfilling the modified 1984 AS New York Criteria Exclusion: RCT in pts with concomitant treatment with prednisone >10 mg/d or biologics	3647	AS	200–400 mg OD	GI events, defined as any abdominal complaints, including nausea, vomiting, dyspepsia, heartburn, diarrhea, constipation, and abdominal pain	Supported by the National Science Foundation of China and the Natural Science Foundation of Guangdong Province	Critically low quality
Fidahic et al. [18], 2017	8	Inclusion: RCT including a minimum of 50 pts and treatment of >4 wks, involving pts of any age and either sex with clinical confirmation of RA. Exclusion: RCT with pts with JA	3988	RA	200–400 mg OD	CV events (MI, stroke analyzed together); incidence of gastroduodenal ulcer ≥3 mm	Supported by the University of Split School of Medicine (Croatia)	High quality

Table 1 (continued)

Study	Studies (n)	Inclusion/exclusion criteria of SR	Participants (n)	Disease	Celecoxib dose range	Main outcomes	Funding	AMSTAR-2 rating
Garner et al. [17], 2002	5	Inclusion: RCT including a minimum of 50 pts and treatment of >4 wks, involving pts of any age and either sex with clinical confirmation of RA	4465	OA, RA	40–400 mg BID	Incidence of ulcers and erosions detected by endoscopy	Supported by NICE (UK) and the Institute for Population Health (University of Ottawa, Canada)	Critically low quality
Jarupongprapa et al. [20], 2013	9	Inclusion: RCT including pts aged ≥18 y; no disease criteria (only subgroup analyses with OA and RA were considered in this review)	7616	OA, RA	200–400 mg OD	Major GI complications including hemorrhage, perforation, and obstruction; minor GI symptoms, including nausea, vomiting, dyspepsia, abdominal pain, or diarrhea; GI bleeding; endoscopically detected GI ulcers; all-cause mortality	NR	Critically low quality
Mallen et al. [27], 2011	21	Inclusion: RCT including pts with OA, RA, or AS with a planned treatment duration ≥2 wks	23,545	OA, RA, AS	200–400 mg OD	Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea	Supported by Pfizer	Critically low quality
Moore et al. [22], 2005	31	Inclusion: RCT ≥2 wks in OA or RA Exclusion: open-label extension studies	39,605	OA, RA	50–800 mg OD	MI, cardiac failure, hypertension, nausea, vomiting, abdominal pain, dyspepsia, diarrhea, clinical ulcers and bleeds, raised creatine	Supported by Pfizer and the Pain Research funds of the Oxford Pain Relief Trust	Critically low quality

Table 1 (continued)

Study	Studies (n)	Inclusion/exclusion criteria of SR	Participants (n)	Disease	Celecoxib dose range	Main outcomes	Funding	AMSTAR-2 rating
Puljak et al. [19], 2017	36	Inclusion: RCT including at least 50 participants and treatment of >4 wks, involving pts of any age and either sex with clinical or radiologically confirmed OA Exclusion: RCT including only participants with inflammatory arthritis, such as RA	17,206	OA	100–400 mg OD	CV events (MI, stroke analyzed together); intestinal events (perforations, ulcers, bleeds)	Supported by the University of Split School of Medicine (Croatia)	High quality
Rostom et al. [25], 2007	69 (total) 13 (celecoxib)	Inclusion: RCT included pts aged ≥18 y, treatment exposure ≥4 wks	31,106 (celecoxib)	OA, RA	25–400 mg BID	Gastroduodenal ulcers, ulcer complications (perforation, obstruction, bleeding), adverse GI symptoms (dyspepsia, nausea, abdominal pain, or diarrhea)	NR	Critically low quality
Wang et al. [21], 2011	6	Inclusion: RCT including pts aged ≥18 y with OA or RA with exposure to treatment ≥12 wks. Pts with a history of ulcer and ulcer bleeding should be healed and confirmed on endoscopy or be without a history of it. Pts had to test negative for *Helicobacter pylori* at the screening visit or have confirmed eradication of the infection. Low-dose aspirin use was acceptable	6219	OA, RA	Unclear	CV events (unspecified), upper GI AEs (gastroduodenal ulcers or duodenal ulcers confirmed by endoscopy), dyspepsia events (abdominal discomfort, dyspepsia, belching, nausea, loss of appetite, vomiting, abdominal pain, and diarrhea), all-cause mortality	NR	Critically low quality

Table 1 (continued)

Study	Studies (n)	Inclusion/exclusion criteria of SR	Participants (n)	Disease	Celecoxib dose range	Main outcomes	Funding	AMSTAR-2 rating
Wang et al. [28], 2016	26	Inclusion: RCT including adult pts with active AS Exclusion: RCTs with concomitant use of other anti-inflammatory drugs (i.e., corticosteroids, aspirins, immunosuppressants, or biologics)	3410	AS	200–400 mg OD	GI AEs, defined as nausea, vomiting, diarrhea, or abdominal pain; GI bleeding	Supported by the Intramural Research Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health	Critically low quality
Xu et al. [29], 2016	15	Inclusion: blinded or nonblinded RCT including pts with OA	7868	OA	200 mg OD	Abdominal pain, diarrhea, dyspepsia, nausea	Authors had no funding	Critically low quality
Zeng et al. [24], 2015	54	Inclusion: RCT including pts with knee OA	16,427	OA	200 mg OD	CV AEs (unspecified), GI AEs (unspecified)	Supported by the Hunan Provincial Innovation Foundation for Postgraduate and the National Natural Science Foundation of China	Critically low quality
Zhang et al. [23], 2006	114	Inclusion: double-blind RCT Exclusion: RCT including pts with abnormal baseline renal function or combining simultaneous intervention of >1 COX-2 inhibitor	116,094	OA, RA, AS	NR	Composite renal events, including peripheral edema, hypertension, and renal dysfunction	Supported by the National Institute of Diabetes, Digestive, and Kidney Diseases and the National Cancer Institute, National Institutes of Health	Critically low quality

AE adverse event, *AF* atrial fibrillation, *AS* ankylosing spondylitis, *BID* twice daily, *COX-2* cyclooxygenase-2, *CV* cardiovascular, *GI* gastrointestinal, *HF* heart failure, *JA* juvenile arthritis, *MI* myocardial infarction, *NICE* National Institute for Health and Care Excellence, *NR* not reported, *OA* osteoarthritis, *OD* once daily, *pts* patients, *RA* rheumatoid arthritis, *wks* weeks, *y* year(s).

Table 2 Main results for cardiovascular (CV) safety

Study	Studies (n)	Intervention	Comparator	Participants (n)	Effect size, CI, heterogeneity (if reported)	p-Value	Main results
CV mortality							
Cheng et al. [16], 2021	2	Celecoxib 100 mg OD–400 mg BID	Placebo	Celecoxib: 891 Placebo: 659	RR 3.02 (95% CI 0.36–25.27); I^2 = 0%	P = 0.31	Celecoxib had no significant impact on CV mortality
	5	100 mg OD–400 mg BID	Non-selective NSAIDs	Celecoxib: 20,157 NSAIDs: 28,044	RR 0.75 (95% CI 0.57–0.99); I^2 = 0%	**P = 0.04**	Celecoxib significantly reduced CV mortality vs non-selective NSAIDs
MI							
Cheng et al. [16], 2021	4	Celecoxib 100 mg OD–400 mg BID	Placebo	Celecoxib: 1650 Placebo: 731	RR 1.87 (95% CI 0.39–8.90); I^2 0%	P = 0.43	Celecoxib had no significant impact on MI rates
	6	Celecoxib 100 mg OD–400 mg BID	Non-selective NSAIDs	Celecoxib: 20,264 NSAIDs: 28,151	RR 1.08 (95% CI 0.88–1.33); I^2 0%	P = 0.46	Celecoxib did not affect MI rates vs non-selective NSAIDs
Moore et al. [22], 2005	16	Celecoxib 200–400 mg	Non-selective NSAIDs (maximum daily dose)	Total: 21,818	RR 1.9 (95% CI 0.87–4.1)	NS	Celecoxib did not affect MI rates vs non-selective NSAIDs
Strokes							
Cheng et al. [16], 2021	2	Celecoxib 100 mg OD–400 mg BID	Placebo	Celecoxib: 685 Placebo: 664	RR 0.96 (95% CI 0.13–6.92); I^2 = 0%	P = 0.97	Celecoxib had no significant impact on stroke rates
	5	Celecoxib 100 mg OD–400 mg BID	Non-selective NSAIDs	Celecoxib: 20,157 NSAIDs: 28,044	RR 0.94 (95% CI 0.71–1.24); I^2 = 10%	P = 0.64	Celecoxib did not affect stroke rates vs non-selective NSAIDs
MI and strokes analyzed together							
Puljak et al. [19], 2017	5	Celecoxib 100 mg OD–400 mg OD	Placebo	Celecoxib: 1785 Placebo: 1162	Peto OR 3.40 (95% CI 0.73–15.88); I^2 = 0%	P = 0.12	Celecoxib had no significant impact on the odds of MI and strokes
CV events (unspecified)							
Zeng et al. [24], 2015	NR	Celecoxib 200 mg OD	Placebo	NR	OR 1.12 (95% CI 0.66–1.90); I^2 = 0%	NS	Celecoxib had no significant impact on CV events
Wang et al. [21], 2011	4	COX-2 inhibitors, including celecoxib	NSAIDs + PPIs	NR	RR 1.67 (95% CI 0.78–3.59); I^2 = 0%	NS	Celecoxib did not affect CV events vs non-selective NSAIDs plus PPIs

BID twice daily, *CI* confidence interval, *COX-2* cyclooxygenase-2, *MI* myocardial infarction, *NR* not reported, *NS* not significant, *NSAIDs* non-steroidal anti-inflammatory drugs, *OD* once daily, *OR* odds ratio, *PPI* proton pump inhibitor, *RR* risk ratio.

Table 3 Main results for gastrointestinal (GI) events

Study	Studies (n)	Intervention	Comparator	Participants (n)	Effect size, CI, heterogeneity (if reported)	p-Value	Main results
Gastroduodenal ulcers							
Ashcroft et al. [15], 2001	2	Celecoxib 200 mg BID	Placebo	Celecoxib: 468 Placebo: 473	Rate ratio 2.35 (95% CI 1.02–5.38)	**P < 0.05**	Celecoxib significantly increased the rate of gastroduodenal ulcers
	3	Celecoxib 200 mg BID	Naproxen 500 mg BID	Celecoxib: 738 Placebo: 718	Rate ratio 0.24 (95% CI 0.17–0.33)	**P < 0.05**	Celecoxib significantly decreased the rate of gastroduodenal ulcers vs naproxen (non-selective NSAID)
Fidahic et al. [18], 2017	5	Celecoxib 200–400 mg OD	Non-selective NSAIDs	Celecoxib: 870 NSAIDs: 698	RR 0.22 (95% CI 0.15–0.32); $I^2 = 0\%$	**P < 0.01**	Celecoxib significantly decreased the risk of gastroduodenal ulcers vs non-selective NSAIDs
Rostom et al. [25], 2007	5	Celecoxib 25–400 mg BID	Non-selective NSAIDs	Total: 2439	RR 0.21 (95% CI 0.16–0.28)	**P < 0.05**	Celecoxib significantly decreased the risk of gastroduodenal ulcers vs non-selective NSAIDs
Abdominal and GI complaints, including abdominal pain, diarrhea, dyspepsia, and nausea							
Fan et al. [26], 2020	NR	Celecoxib 200–400 mg OD	Placebo	NR	OR 1.71 (95% CI 0.81–3.70)	NS	Celecoxib had no significant impact on the odds of GI complaints
	NR	Naproxen	Celecoxib 200–400 mg OD	NR	OR 1.39 (95% CI 0.56–3.12)	NS	Celecoxib did not affect GI complaints vs naproxen (non-selective NSAID)
	NR	Diclofenac	Celecoxib 200–400 mg OD	NR	OR 1.68 (95% CI 0.86–3.13)	NS	Celecoxib did not affect GI complaints vs diclofenac (non-selective NSAID)
Mallen et al. [27], 2011	NR	Naproxen	Celecoxib 200–400 mg OD	Celecoxib: 5872 Naproxen: 1104	RR 1.67 (95% CI 1.52–1.84)	**P < 0.05**	Celecoxib significantly decreased the risk of GI complaints vs naproxen (non-selective NSAID)
	NR	Diclofenac	Celecoxib 200–400 mg OD	Celecoxib: 5872 Diclofenac: 2334	RR 1.20 (95% CI 1.10–1.31)	**P < 0.05**	Celecoxib significantly decreased the risk of GI complaints vs diclofenac (non-selective NSAID)

Table 3 (continued)

Study	Studies (n)	Intervention	Comparator	Participants (n)	Effect size, CI, heterogeneity (if reported)	p-Value	Main results
Moore et al. [22], 2005	19	Celecoxib 200–400 mg OD	Placebo	Total: 9919	RR 1.0 (95% CI 0.82–1.20)	NS	Celecoxib had no significant impact on the risk of GI complaints
	19	Celecoxib 200–400 mg OD	Non-selective NSAIDs (maximum daily dose)	Total: 22,615	RR 0.62 (95% CI 0.56–0.68)	**P < 0.05**	Celecoxib significantly decreased the risk of GI complaints vs non-selective NSAIDs
Rostom et al. [25], 2007	20	COX-2 inhibitors, including celecoxib	Placebo	Total: >10,000	RR 1.26 (95% CI 1.13–1.42)	**P < 0.05**	Celecoxib significantly increased the risk of GI complaints
	28	COX-2 inhibitors, including celecoxib	NSAIDs	Total: ~60,000	RR 0.78 (95% CI 0.74–0.82)	**P < 0.05**	Celecoxib significantly decreased the risk of GI complaints vs non-selective NSAIDs
Wang et al. [21], 2011	5	COX-2 inhibitors, including celecoxib	NSAIDs + PPIs	COX-2: 3134 NSAIDs+: 3146	RR 1.10 (95% CI 0.88–1.39); $I^2 = 58\%$	P = 0.40	Celecoxib did not affect GI complaints vs non-selective NSAIDs plus PPIs
Wang et al. [28], 2016	NR	Celecoxib 200–400 mg OD	Placebo	NR	RR 0.07 (95 % CrI −1.3–1.3) (results presented in the form of log (HR) with 95% CrI)	NS	Celecoxib had no significant impact on the risk of GI complaints
Xu et al. [29], 2016	Abdominal pain						
	6	Celecoxib 200 mg OD	Placebo	Celecoxib: 1604 Placebo: 1381	RR 2.24 (95% CI 1.40–3.58); $I^2 = 0\%$	**p < 0.05**	Celecoxib significantly increased the risk of abdominal pain
	Diarrhea						
	11	Celecoxib 200 mg OD	Placebo	Celecoxib: 3104 Placebo: 2625	RR 0.99 (95% CI 0.76–1.30); $I^2 = 0\%$	NS	Celecoxib had no significant impact on the risk of diarrhea
	Dyspepsia						
	9	Celecoxib 200 mg OD	Placebo	Celecoxib: 2509 Placebo: 2043	RR 1.13 (95% CI 0.87–1.46); $I^2 = 0\%$	NS	Celecoxib had no significant impact on the risk of dyspepsia
	Nausea						
	6	Celecoxib 200 mg OD	Placebo	Celecoxib: 1542 Placebo: 1551	RR 1.17 (95% CI 0.80–1.69); $I^2 = 0\%$	NS	Celecoxib had no significant impact on the risk of nausea

Table 3 (continued)

Study	Studies (n)	Intervention	Comparator	Participants (n)	Effect size, CI, heterogeneity (if reported)	p-Value	Main results
Bleeds, perforations, and obstructions							
Deeks et al. [30], 2002	2 (trial stratified into 2)	Celecoxib 100–400 mg BID	Non-selective NSAIDs	NR	RR 0.55 (95% CI 0.26–1.14); heterogeneity: NS	NS	Celecoxib did not affect bleeds, perforations, and obstructions vs non-selective NSAIDs
Jarupongprapa et al. [20], 2013	4	COX-2 inhibitors, including celecoxib	NSAIDs + PPIs	COX-2: 2924 NSAIDs+: 2923	RR 0.83 (95 % CI 0.36–1.89); $I^2 = 0\%$	P = 0.66	Celecoxib did not affect bleeds, perforations, and obstructions vs non-selective NSAIDs plus PPIs
Rostom et al. [25], 2007	4	Celecoxib 25–400 mg BID	Non-selective NSAIDs	NR	RR 0.23 (95% CI 0.07–0.76)	**P < 0.05**	Celecoxib significantly decreased the risk of bleeds, perforations, and obstructions vs non-selective NSAIDs
GI adverse events (unspecified)							
Zeng et al. [24], 2015	NR	Celecoxib 200 mg OD	Placebo	NR	OR 1.17 (95% CI 1.02–1.34); $I^2 = 0\%$	**P < 0.05**	Celecoxib significantly increased the odds of GI events

BID twice daily, *CI* confidence interval, *CrI* credible interval, *HR* hazard ratio, *NR* not reported, *NS* not significant, *NSAIDs* non-steroidal anti-inflammatory drugs, *OD* once daily, *OR* odds ratio, *PPI* proton pump inhibitor, *RR* risk ratio.

Table 4 Main results for renal events

Study	Studies (n)	Intervention	Comparator	Participants (n)	Effect size, CI, heterogeneity (if reported)	p-Value	Main results
Composite renal events (including renal dysfunction, peripheral edema, and hypertension)							
Zhang et al. [23], 2006	25	Celecoxib (dose range NR)	Placebo	NR	RR 0.79 (95% CI 0.66–0.94)	**P < 0.05**	Celecoxib significantly decreased the risk of renal events, including renal dysfunction, peripheral edema, and hypertension
Raised creatinine (>1.3 × upper limit of normal)							
Moore et al. [22], 2005	5	Celecoxib 50–800 mg OD	Placebo	Total: 2776	RR 1.65 (95% CI 0.69–4.0)	NS	Celecoxib had no significant impact on raised creatinine
	9	Celecoxib 200–400 mg OD	Non-selective NSAIDs (maximum daily dose)	Total: 15,319	RR 0.78 (95% CI 0.46–1.3)	NS	Celecoxib did not affect raised creatinine vs non-selective NSAIDs

CI confidence interval, *NR* not reported, *NS* not significant, *NSAIDs* non-steroidal anti-inflammatory drugs, *QD* once daily, *RR* relative risk.

dysfunction, peripheral edema, and hypertension) was lower with celecoxib than with placebo. Moore et al. [22] showed that celecoxib did not significantly affect raised creatinine (defined as >1.3 × upper limit of normal) when compared with patients treated with a placebo or with non-selective NSAIDs (Table 4).

3.5 All-Cause Mortality

Two meta-analyses [16, 21] assessed the impact of celecoxib on all-cause mortality in patients with OA, RA, or AS, and both were rated as low quality. The meta-analysis by Cheng et al. [16] found no change in the risk of all-cause mortality when celecoxib was compared with placebo. The same meta-analysis also showed that celecoxib diminished the risk of all-cause mortality when compared with non-selective NSAIDs. Nevertheless, these findings did not appear to be supported by Wang et al. [21]. In the four studies on all-cause mortality included in their systematic review, six deaths were reported among patients treated with COX-2 inhibitors and six deaths among those treated with NSAIDs plus proton pump inhibitors. Unfortunately, the total number of subjects in each group was not reported. Moreover, no statistical analysis was conducted, and the references of the four articles based on all-cause mortality were not indicated [21] (Table 5).

3.6 Summary of Results and GRADE Assessment

The main results of our umbrella review are summarized in Fig. 2. Three meta-analyses [15, 18, 25] consistently reported that the incidence of gastroduodenal ulcers was lower with celecoxib than with non-selective NSAIDs. The most methodologically robust meta-analysis [18] was based on primary studies with very consistent results that were rated as moderate to high quality. Nevertheless, only one high-quality primary study was included in Fidahic et al. [18]. The quality of the other primary studies was rated as moderate by this research team, and a high risk of bias was detected in most of the included studies. Therefore, although the meta-analysis by Fidahic et al. [18] itself was high quality, we downgraded the certainty of evidence to moderate because of the risk of bias in the primary studies included in this meta-analysis (see Appendix C in the ESM). We conclude that the evidence that celecoxib causes fewer gastroduodenal ulcers than non-selective NSAIDs is of only moderate quality. Regarding all the other outcomes, we found no high-quality meta-analyses based on primary studies of high- or moderate-quality evidence. In addition, most of these outcomes were affected by imprecision and/or inconsistency, leading to a downgrade in the certainty of evidence (see Appendix C in the ESM). Accordingly, we rated the certainty of evidence as low for all the other outcomes [14].

Table 5 Main results for all-cause mortality

Study	Studies (N)	Intervention	Comparator	Participants (n)	Effect size, confidence interval, heterogeneity (if reported)	p-Value	Main results
Cheng et al. [16], 2021	4	Celecoxib 100 mg OD–400 mg BID	Placebo	Celecoxib: 1222 Placebo: 886	RR 0.92 (95% CI 0.26–3.27); $I^2 = 0\%$	NS	Celecoxib had no significant impact on all-cause mortality
	5	Celecoxib 100 mg OD–400 mg BID	Non-selective NSAIDs	Celecoxib: 20,157 NSAIDs: 28,044	RR 0.81 (95% CI 0.66–0.98); $I^2 = 21\%$	**P = 0.03**	Celecoxib significantly reduced the risk of all-cause mortality vs non-selective NSAIDs
Wang et al. [21], 2011	4	COX-2 inhibitors, including celecoxib	NSAIDs + PPIs	NR	Six deaths reported in the group taking COX-2 inhibitors and six reported in the group taking NSAIDs plus PPIs (no statistical analysis)	NR	COX-2 inhibitors (including celecoxib) did not seem to affect all-cause mortality vs non-selective NSAIDs plus PPIs

BID twice daily, *CI* confidence interval, *COX-2* cyclooxygenase-2, *NR* not reported, *NS* not significant, *NSAIDs* non-steroidal anti-inflammatory drugs, *OD* once daily, *PPI* proton pump inhibitor, *RR* risk ratio.

4 Discussion

A total of 16 systematic reviews, all based on RCTs, were included in this umbrella review after a comprehensive search and selection process. Most studies focused on patients with OA or RA and assessed both the efficacy and the safety of celecoxib, primarily compared with placebo or traditional NSAIDs. Although cardiovascular safety outcomes were generally neutral, one high-quality meta-analysis reported a reduced risk of cardiovascular mortality with celecoxib compared with non-selective NSAIDs. Regarding gastrointestinal safety, celecoxib was consistently associated with a lower risk of gastroduodenal ulcers than were non-selective NSAIDs, although findings were more heterogeneous for other gastrointestinal outcomes. Notably, although based on a limited number of low-quality meta-analyses, celecoxib appeared to be associated with a lower risk of renal adverse events and reduced all-cause mortality than non-selective NSAIDs, suggesting a potentially more favorable overall safety profile that warrants further investigation. Overall, despite the predominance of critically low-quality reviews, some consistent trends suggest a favorable gastrointestinal profile for celecoxib and potentially reduced all-cause or cardiovascular mortality compared with traditional NSAIDs.

Our findings are largely consistent with the existing body of literature concerning the safety profile of celecoxib [31, 32]. The observed reduction in the incidence of gastroduodenal ulcers compared with traditional non-selective NSAIDs aligns with previous individual studies and some clinical guidelines, which have recognized the more favorable gastrointestinal safety profile of celecoxib [33–35]. Several pharmacological studies have attributed this effect to the selective inhibition of COX-2 by celecoxib, thereby sparing COX-1-mediated gastroprotective prostaglandin synthesis [36]. In contrast, the evidence regarding cardiovascular safety remains less definitive. Earlier concerns were raised after the withdrawal of rofecoxib, another selective COX-2 inhibitor, because of an increased cardiovascular risk [37]. Subsequent investigations have sought to determine whether celecoxib carries a similar risk profile [38]. Notably, the PRECISION trial, a large, pragmatic RCT, demonstrated non-inferiority of celecoxib compared with naproxen and ibuprofen with respect to cardiovascular outcomes in patients with OA or RA at moderate cardiovascular risk [39]. In addition to cardiovascular safety, PRECISION provided valuable insights into other organ-specific outcomes. A prespecified secondary analysis focusing on major NSAID toxicity, including cardiovascular, gastrointestinal, and renal events and all-cause mortality, showed that celecoxib was associated with a significantly lower incidence of composite major toxicity than both ibuprofen and naproxen [40]. Specifically,

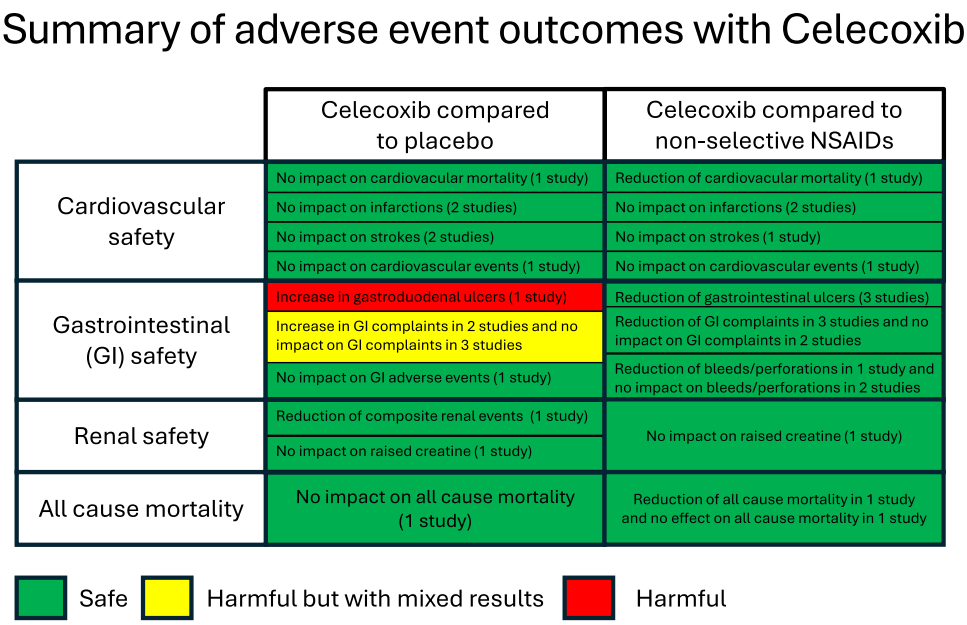

Fig. 2 Summary of adverse event outcomes with celecoxib identified from systematic reviews and meta-analyses. *GI* gastrointestinal, *NSAIDs* non-steroidal anti-inflammatory drugs.

the numbers needed to harm were 82 for ibuprofen and 135 for naproxen compared with celecoxib, highlighting a more favorable overall safety profile of celecoxib. In terms of gastrointestinal safety, a dedicated sub-analysis of PRECISION confirmed a significantly lower incidence of clinically significant gastrointestinal events and iron deficiency anemia with celecoxib [41]. Celecoxib also maintained its advantage when used in combination with low-dose acetylsalicylic acid (aspirin) or corticosteroids, suggesting a robust gastrointestinal safety profile across different risk profiles. In addition, the PRECISION ABPM sub-study, which evaluated the impact of these NSAIDs on ambulatory blood pressure, showed a significantly lower increase in 24-h systolic blood pressure with celecoxib than with ibuprofen [42]. The incidence of new-onset hypertension was also significantly lower with celecoxib, which may contribute to its superior cardiovascular tolerability. Finally, renal outcomes, a growing concern with chronic NSAID use, were also evaluated in a recent secondary analysis of the PRECISION trial [43]. Celecoxib was associated with a lower incidence of renal events, including acute kidney injury and hospitalization for heart failure or hypertension, than were ibuprofen and naproxen. These findings were consistent in both intention-to-treat and on-treatment analyses, reinforcing the favorable cardiorenal safety profile of celecoxib. Taken together, the data from the PRECISION program suggest that celecoxib is not only as safe as non-selective NSAIDs but may be safer, particularly when gastrointestinal, blood pressure, and renal outcomes are considered in addition to cardiovascular risk. Furthermore, the distinct methodology of the PRECISION trial compared with most other RCTs included in our review is important to emphasize. As a large-scale, long-term RCT with a mean treatment duration of approximately 20 months, PRECISION incorporated independently adjudicated outcomes and was conducted independently of industry influence. This distinguishes PRECISION from other trials, which often involve shorter treatment durations and less rigorous, more heterogeneous endpoint evaluation processes. When interpreting comparative safety findings between celecoxib and non-selective NSAIDs, this distinction in trial quality should be acknowledged.

It must be noted that many of the systematic reviews included in our umbrella review excluded observational studies, which could have provided interesting complementary information, particularly regarding long-term and rare adverse events. For example, the population-based observational study by McGettigan and Henry [44] provided robust comparative data on the cardiovascular risks associated with different NSAIDs in real-world settings. Their findings showed that, although celecoxib was associated with a modest increase in cardiovascular risk (RR 1.17 [95% CI 1.08–1.27]), this risk remained lower than that observed with diclofenac or rofecoxib, and was comparable to that of ibuprofen, particularly at typical doses. Such studies offer valuable insights that complement randomized evidence, particularly with regard to populations not commonly included in clinical trials. In fact, large-scale observational studies and real-world evidence have generally supported that celecoxib, when used at recommended doses, does not increase the cardiovascular risk compared with traditional NSAIDs [38]. Consequently, the reliance on RCT-derived data only, as observed in most of the included reviews, may limit the generalizability of findings to patients seen in routine clinical practice. Taken together, the current literature suggests that, although celecoxib offers distinct gastrointestinal safety advantages over non-selective NSAIDs, emerging

evidence—albeit limited and of low quality—also indicates a potentially more favorable renal and all-cause mortality profile. Cardiovascular safety appears generally comparable to that of non-selective NSAIDs, but further high-quality studies are needed. These findings highlight the importance of considering both the available evidence and individual patient risk factors when selecting anti-inflammatory treatment.

Recent studies have further emphasized the importance of patient context when evaluating the safety of celecoxib. Antonioli et al. [45] reported an increased risk of postoperative heart failure among patients with type 2 diabetes mellitus undergoing total knee arthroplasty when celecoxib was used perioperatively, compared with meloxicam. Although the study was observational in nature, these findings suggest that celecoxib may not be the optimal choice in certain high-risk settings. Similarly, Kim et al. [46] found no significant cardiovascular or gastrointestinal safety advantage for celecoxib over non-selective NSAIDs in patients with AS, a younger group at lower risk, potentially indicating that safety benefits are more apparent in older, comorbid populations. Taken together, these results emphasize that NSAID safety profiles are highly dependent on context, and there remain patient groups for whom the use of NSAIDs or COX-2 inhibitors is either inappropriate or poorly characterized in the literature.

This umbrella review has several important strengths. It followed a registered protocol and adhered to established methodological standards (PRISMA 2020, Joanna Briggs Institute guidelines), ensuring transparency and rigor. A comprehensive search strategy across multiple databases and additional manual searches minimized the risk of missing relevant studies. The methodological quality of the reviews included was critically appraised using the AMSTAR-2 tool, providing important information for interpretation of the level of evidence. Finally, the focus on clinically meaningful outcomes based on RCT data enhances the internal validity of the findings, despite recognized limitations in generalizability.

Several limitations should be acknowledged. Most of the included systematic reviews did not provide detailed information on participant demographics or comorbidities, limiting our ability to draw conclusions for subpopulations such as older adults or those with prior cardiovascular or renal conditions. Earlier RCTs typically included relatively homogeneous and healthier adult populations, often excluding patients at higher risk for adverse events. However, the PRECISION trial included individuals with established cardiovascular disease or elevated cardiovascular risk, improving the generalizability to more complex real-world populations. This distinction highlights the need for more granular safety data across age groups and comorbidity profiles, particularly in older adults who represent a large proportion of those treated for chronic musculoskeletal conditions. Another important limitation is that most included systematic reviews were of critically low methodological quality, reducing confidence in the overall findings. Substantial heterogeneity across studies regarding populations, interventions, and outcome definitions complicates interpretation. The exclusive reliance on randomized trial data, often limited by short follow-up periods, may underestimate long-term or rare adverse events. The limited inclusion of observational studies further restricts the assessment of real-world safety. In addition, potential publication bias, particularly from industry-sponsored trials, cannot be entirely ruled out. Also, an important potential limitation of this review is the use of the AMSTAR-2 checklist to assess the methodological rigor of the included reviews. Although AMSTAR-2 is a widely accepted tool for assessing risk of bias, it does not really provide an overall "quality score" and instead focuses on the presence or absence of critical and non-critical methodological areas. As a result, reviews may be rated as "critically low" because of the absence of items that are not necessarily central to the reliability of their findings (e.g., lack of protocol registration or funding source reporting). This severe downgrading may limit the overall value of some reviews, especially if core methodological components such as study selection, data extraction, and risk-of-bias assessment have been adequately addressed. Therefore, AMSTAR-2 ratings should be interpreted as indicators of potential bias rather than as absolute judgments of quality. Finally, another important limitation of this umbrella review is the deliberate restriction of the target population to patients with OA, RA, or AS. As a result, the findings should be interpreted strictly within the context of these specific conditions and cannot be generalized to other musculoskeletal disorders. Several potentially relevant systematic reviews were excluded because they included mixed populations (e.g., patients with OA or RA alongside those with low back pain or other non-inflammatory conditions) without reporting separate outcomes for the populations of interest. In such cases, our inability to extract stratified data limited their inclusion and may have led to the omission of useful evidence related to OA, RA, or AS.

The results of this umbrella review suggest that celecoxib may be a preferable therapeutic option for patients at increased gastrointestinal risk who require long-term NSAID therapy, as it has a lower incidence of gastroduodenal ulcers than traditional non-selective NSAIDs. Nevertheless, clinical decision-making should be individualized and take into account each patient's comorbidities, risk factors, and treatment goals, particularly in high-risk populations. Future research should prioritize the integration of high-quality randomized and observational data to better assess the long-term safety of celecoxib, especially with regard to rare cardiovascular and renal events. Systematic reviews

using methods capable of synthesizing evidence from different study designs are warranted to provide a more comprehensive and applicable assessment of the benefit–risk profile of celecoxib in routine clinical practice.

5 Conclusions

In summary, celecoxib appears to offer a favorable gastrointestinal safety profile compared with traditional NSAIDs, with a potential reduction in the risk of gastroduodenal ulcers. Cardiovascular and renal safety outcomes were generally neutral, although limited evidence, mostly from low-quality meta-analyses, suggests that celecoxib may be associated with reduced risks of cardiovascular mortality, renal adverse events, and all-cause mortality compared with non-selective NSAIDs. However, some real-world studies have reported safety concerns in specific high-risk populations, and the predominance of critically low-quality systematic reviews further limits the strength of conclusions. Caution is therefore advised, especially in patients with advanced cardiovascular, renal, or metabolic comorbidities. Individualized risk–benefit assessment remains essential when considering celecoxib for the management of chronic musculoskeletal conditions.

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Consent (participation and publication) Not applicable.

Author contributions OB, CBe, and J-YR initiated the research question. OB, CBe, and J-YR were the main investigators. CB and OB drafted the protocol. CBe ran the search strategies and identified potential references to be included in the project. OB, CBe, and CBr screened and selected relevant references. CBr extracted the data, and OB and CBe double checked the data extraction. OB, CBe, and CBr performed the risk-of-bias assessment. The results were interpreted by all authors. OB and CBe wrote the first draft of the manuscript. All authors reviewed and approved the final manuscript.

Data availability All materials related to this work are freely available on the Open Science Framework deposit (https://osf.io/jn52b/).

Code availability Not applicable.

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