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Complete List of Authors:	Li, Mengtao ; Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Department of Rheumatology and Clinical Immunology Yu, Chen ; Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Department of Rheumatology and Clinical Immunology Zeng, Xiaofeng; Peking Union Medical College Hospital (West), Peking Union Medical College & Chinese Academy of Medical Sciences, Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Rheumatology
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Comparative efficacy of non-steroidal anti-inflammatory drugs in patients with acute gout: a systematic review and meta-analysis

Running title: NSAIDs for acute gout

Mengtao Li, PhD[1], Chen Yu, PhD[1], Xiaofeng Zeng, PhD[1*]

[1]Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

***Address correspondence and reprint requests to**

Xiaofeng Zeng, PhD

Address: Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China

E-mail: zengxfpumc@163.com

Tel: +8613501069845

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Abstract

Objective: To assess the comparative efficacy of traditional non-steroidal anti-inflammatory drugs and selective cycloxygenase-2 inhibitor (COXIB) for patients with acute gout.

Design: Systematic review and meta-analysis.

Data sources: Medline, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang Data.

Methods: We performed meta-analysis of randomized controlled trials (RCTs) of traditional non-selective NSAIDs versus COXIBs and RCTs that compared the efficacy of various COXIBs in patients with acute gout. The main outcome measures were mean change in pain visual analog scale (VAS) score and 5-point Likert scale score for days 2–8.

Results: Twenty trials (n=2233) involving five drugs were evaluated. In the pain Likert scale, etoricoxib was comparable to indomethacin (SMD: -0.09, 95%CI: -0.27, 0.08) but better than diclofenac 50 mg tid (SMD: -0.53, 95% CI: -0.98, -0.09). Regarding pain VAS score, etoricoxib and diclofenac 75 mg bid (SMD: -1.63, 95% CI: -4.60, 1.34) and diclofenac 75 mg qd (SMD: -0.12, 95% CI: -0.58, 0.33), celecoxib and diclofenac 100 mg qd (SMD: -2.41, 95% CI: -5.91, 1.09) were comparable, respectively. Etoricoxib and indomethacin were similar in patients' global assessment of response (SMD: -0.10, 95% CI: -0.27, 0.07) and swollen joint count (SMD: -0.25, 95% CI: -0.74, 0.24). However, etoricoxib showed better investigator's global assessment of response than indomethacin (SMD: -0.29, 95% CI: -0.46, -0.11). Etoricoxib showed favorable pain VAS scale than celecoxib (SMD: -2.36, 95% CI: -3.36, -1.37) and meloxicam (SMD: -7.25, 95% CI: -8.63, -5.86), and favorable pain Likert scale than meloxicam (SMD: -0.56, 95%CI: -1.10, -0.02).

Conclusion: Etoricoxib is probably the best option to consider when a COXIB is indicated.

Keywords: acute gout, NSAIDs, selective cycloxygenase-2 inhibitors, efficacy

Strengths and limitations of this study

- The study evaluates available randomized controlled trials comparing the efficacy of traditional non-steroidal anti-inflammatory drugs and selective cycloxygenase-2 inhibitor for patients with acute gout.
- Stringent and sensitive search strategy of the internet databases is used to minimize potential publication bias.
- Most included studies published in Chinese although we do not set specific language restriction in search strategy.
- The main limitations of included trails are relatively few number, small sample size and generally low quality.

Introduction

Gout is a chronic disease characterized by the deposition of monosodium urate crystals in various tissues as a result of elevated serum urate concentration [1]. According to the Global Burden of Disease (GBD) 2010 study, the estimated global prevalence of gout is 0.08% and there is an increasing trend in the burden of gout [2]. Worldwide, the reported prevalence of gout ranges from 0.1% to approximately 10%, and the incidence rates range from 0.3 to 6 cases per 1,000 person-years [3]. The prevalence and incidence of gout is highly variable across various regions of the world. In general, there is a higher prevalence of gout in developed countries than in developing countries [3]. There is no national epidemiological data on the prevalence of gout in China; however, based on data from different local regions at different time points in China, the prevalence of gout is currently 1% to 3% and is steadily increasing every year [4].

Acute gout most frequently begins with the involvement of a single joint in the lower limbs (85–90% of cases) – usually, the first metatarsophalangeal joint [1]. The management of acute gout includes rapid treatment of acute flares and effective long-term therapy [5-9]. The main therapeutic options for an acute flare are colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids [5]. The deposition of monosodium urate microcrystals in the articular and periarticular tissues elicits acute or chronic inflammatory responses that are known as gouty arthritis [1, 10, 11].There is evidence that monosodium urate microcrystals induce the production of cyclooxygenase-2 (COX-2) in human monocytes [12]. NSAIDs include traditional NSAIDs and selective COX-2 inhibitors (COXIBs) – the former inhibits both COX-1 and -2 enzymes whereas the latter specifically antagonizes COX-2. The efficacy of COXIBs is comparable to that of traditional NSAIDs; however, COXIBs have fewer adverse effects, particularly gastrointestinal adverse effects [13].

In the past decade, NSAIDs as a first-line option for the management of acute gout have been emphasized, in accordance with the 2006 and 2016 European League Against Rheumatism (EULAR) recommendations [5, 8] and American College of Rheumatology guidelines [6, 7]. A meta-analysis found no significant difference between traditional NSAIDs and COXIBs with regard to the pain score, inflammation score, change in patient's global assessment from baseline, and the health-related quality of life (HRQoL) [13]. Another meta-analysis indicated that the efficacy of etoricoxib in acute gout is similar to that of indomethacin and diclofenac; however, etoricoxib showed better performance than indomethacin in terms of the investigator's global assessment of response to therapy and better analgesic efficacy in comparison to diclofenac [14]. Two meta-analyses have assessed whether COXIBs are more effective for acute gout than traditional NSAIDs [13, 14]. However, a comparison between celecoxib and diclofenac [15] was not included.

Given the increasing use of COXIBs and the relatively large number of recent trials, an evaluation of the comparative efficacy of various COXIBs is a key imperative – both from the clinical and policy perspectives. After the withdrawal of rofecoxib, lumiracoxib, and valdecoxib, three COXIBs are currently used in clinical practice (etoricoxib, celecoxib, and meloxicam). Meloxicam, an agent synthesized as a traditional NSAID, has a selective inhibitory effect against COX-2 [16]. Four studies revealed etoricoxib had better efficacy than meloxicam[17-20] , and another four studies revealed etoricoxib had better efficacy than celecoxib [21-24]. Moreover, many studies published in Chinese were not included in previous meta-analyses. Therefore, we conducted a meta-analysis to provide an updated picture of the comparative clinical efficacy of traditional non-selective NSAIDs and COXIBs, as well as that of the three COXIBs in patients with acute gout.

Materials and methods

Literature strategy

Biomedical databases, including Medline, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang Data, were searched for randomized controlled trials (RCTs; published as of April 2018) that investigated the comparative efficacy of traditional non-selective NSAIDs and COXIBs or that of the three COXIBs in patients with acute gout. The key words used were: "selective cyclooxygenase-2 inhibitors", "COXIBs", "etoricoxib", "celecoxib", "meloxicam", "acute gout", and "randomized controlled trials". The reference lists of the studies, recent reviews, and meta-analyses we retrieved were manually screened to identify additional studies. Two authors independently conducted the literature search; disagreements, if any, were resolved by consensus.

Selection criteria

We included RCTs into the meta-analysis if they met the following criteria. *Study population*: Adult patients (age≥18 years) with a diagnosis of acute gout defined by the American Rheumatology Association diagnostic criteria [25]. *Study design*: RCTs. *Intervention*: Trials that compared COXIBs with traditional non-selective NSAIDs or compared the various COXIBs. *Comparison*: Comparator treatments included one traditional non-selective NSAID or COXIBs. *Primary outcomes*: Pain assessed using a visual analog scale (VAS) score and 5-point Likert scale for days 2–8. *Secondary outcomes* were: i) response rate (defined as the proportion of patients who achieved improvement in clinical symptoms) for days 2–8; ii) onset of efficacy (hours); iii) post-treatment serum C-reactive protein level; iv) patient's global assessment of

response; v) investigator's global assessment of response; and vi) inflammatory swelling. The exclusion criteria were: (i) trials that included a mix of people with acute gout and other musculoskeletal pain, unless the results for the acute gout population could be separately analyzed; (ii) trials that investigated obsolete NSAIDs (e.g. rofecoxib, lumiracoxib, valdecoxib); and (iii) trials that compared between traditional non-selective NSAIDs.

Data collection

The titles and abstracts of articles retrieved on database searches were independently screened by two authors to determine the eligibility of the articles according to predetermined selection criteria. The full texts of papers were obtained if more information was required to assess the eligibility for inclusion. Disagreements, if any, were resolved by consensus after review of the full-text article and with the involvement of a third author, if necessary.

Data pertaining to the following variables were independently extracted by two authors by using a standardized data collection form: study design, patient characteristics, treatment details, duration of follow-up, and relevant outcome measures. We extracted the raw data (mean and standard deviation for continuous variables, and frequency of events or participants for dichotomous outcomes). Any differences in data extraction were resolved by referring to the original articles or by consulting a third reviewer author, if required.

Risk of bias assessment

Two authors assessed the risk of bias of the included studies using the methods recommended by the Cochrane Collaboration for the following items [26]. We scored each study on six domains: sequence generation, allocation concealment, blinding, incomplete outcome

data, selective reporting, and other sources of bias. The risk of bias was graded as high, low, or unclear risk of bias.

Furthermore, the quality of evidence across pooled studies (risk of bias, inconsistency, indirectness, imprecision, and publication bias) was assessed by two researchers as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and using the online version of GRADEpro GDT software (www.gradepro.org, McMaster University, 2016) [27, 28]. Tables of summary of findings were created for every rated outcome in compliance to the Cochrane rules. Disagreements were resolved, first, by discussion and, then, by consulting a third senior author for arbitration.

Statistical analysis

Traditional meta-analyses were conducted for studies that directly compared COXIBs and traditional non-selective NSAIDs and those that compared between etoricoxib, celecoxib, and meloxicam. Odds ratios (OR) and standardized mean difference (SMD) with corresponding 95% confidence intervals (CIs) were used for dichotomous and continuous outcomes, respectively. Heterogeneity was examined by using the Cochran's Q-statistic; *P*-value <0.01 was considered significant. In addition, the I^2 test was used to quantify heterogeneity (range, 0–100%). $P < 0.01$ for Q-test or $I^2 > 50\%$ indicated the existence of heterogeneity among the studies [29]. In case of significant heterogeneity, the random effects model was used; in addition, a subgroup analysis was conducted to identify the source of heterogeneity. Publication bias was assessed by using funnel plots. The Review Manager 5 (RevMan 2014) was used for the meta-analysis.

Patient and Public Involvement

There was no patient and public involvement as this was a database research study.

Results

Characteristics of included studies

Of the 476 articles retrieved on database search, 456 were excluded after a review of titles and abstracts or full-text articles (n=62) owing to duplication or irrelevant efficacy outcomes or measures. Finally, 20 RCTs involving five drugs and six treatment arms (etoricoxib 120 mg qd, indomethacin 50 mg tid, diclofenac 75 mg bid, diclofenac 100 mg qd, celecoxib 200 mg bid, and meloxicam 15 mg qd), with a combined study population of 2233 patients, were included in the meta-analysis[15, 17-24, 30-40]. Three studies were published in English [34, 37, 40] and 17 in Chinese [15, 17-24, 30-33, 35-38]. The sample size of the included studies ranged from 12 to 140; one of the RCTs (5%) had less than 50 participants (Table 1).

Quality of included studies

Most of the included studies were rated as being of low quality. All studies [15, 17-24, 30-33, 35-38] published in Chinese had an unclear risk of allocation concealment, blinding of participants and personnel, blinding of outcome assessment, or selective reporting. Three studies showed no risk of bias [34, 37, 40] and one study [19] showed a high risk of random sequence generation (Figure S1, S2). The funnel plot of data from all comparisons included in the meta-analysis was symmetrical (Figures S3, S4, and S5).

The quality of evidence was rated as moderate in most comparisons. According to GRADE, the quality of evidence for comparison between traditional NSAIDs and COXIBs was rated as high for pain on the 5-point Likert scale but moderate for pain on the VAS score (Table S1).

However, the quality of evidence for comparison between the three COXIBs was rated as moderate for the pain component of both the 5-point Likert scale and the VAS score (Table S2).

Comparative efficacy of traditional non-selective NSAIDs and COXIBs

The COXIBs exhibited similar efficacy than the traditional NSAIDs in terms of the 5-point Likert scale (SMD: −0.15, 95% CI: −0.31, 0.01) with mild heterogeneity ($\chi^2 = 3.71$, degrees of freedom [df] = 3, *P*-value=0.29, $I^2 = 19.0\%$; Figure 1B). Subgroup analysis indicated comparable efficacy of etoricoxib 120 mg qd and indomethacin 50 mg tid (SMD: −0.09, 95% CI: −0.27, 0.08) with mild heterogeneity ($\chi^2 = 0.47$, df = 2, p =0.79, $I^2 = 0\%$). One study showed better efficacy of etoricoxib 120 mg qd versus diclofenac 50 mg tid (SMD: −0.53, 95% CI: −0.98, −0.09; Figure 1A).

In general, COXIBs exhibited better efficacy than traditional NSAIDs in terms of the pain VAS score (SMD: −1.64, 95% CI: −3.24, −0.03), but with significant heterogeneity ($\chi^2 = 244.29$, df = 4, *P*<0.001, $I^2 = 98.0\%$). However, subgroup analysis revealed that etoricoxib 120 mg qd showed similar efficacy as diclofenac 75 mg bid (SMD: −1.63, 95% CI: −4.60, 1.34) with significant heterogeneity ($\chi^2 = 115.35$, df = 1, *P*<0.001, $I^2 = 99.0\%$); moreover, diclofenac 75 mg qd (SMD: −0.12, 95% CI: −0.58, 0.33) and celecoxib 200 mg bid showed comparable effect to that of diclofenac 100 mg qd (SMD: −2.41, 95% CI: −5.91, 1.09) with significant heterogeneity ($\chi^2 = 47.05$, df = 1, *P*<0.001, $I^2 = 98.0\%$) in regard to the pain VAS score (Figure 1B).

A significantly greater proportion of patients who received etoricoxib 120 mg qd (OR: 6.71, 95% CI: 2.88, 15.64) showed clinical improvement, compared to those who received diclofenac 75 mg bid. In this regard, there was mild heterogeneity among the studies we included ($\chi^2 = 0.33$, df = 2, *P*-value=0.85, $I^2 = 0\%$; Figure 2A). However, the effect of etoricoxib 120 mg qd on C-

reactive protein was comparable to that of diclofenac 75 mg qd (SMD: −0.38, 95% CI: −0.77, 0.02) or diclofenac 75 mg bid (SMD: −1.15, 95% CI: −3.09, 0.79); there was significant heterogeneity among the four studies we included in this regard ($\chi^2 = 68.03$, df = 3, P <0.001, I^2 = 96%; Figure 2B).

With regard to the global assessment of response in patients, the efficacy of etoricoxib 120 mg qd was comparable to that of indomethacin 50 mg tid (SMD: −0.10, 95% CI: −0.27, 0.07) with mild heterogeneity ($\chi^2 = 1.75$, df = 2, P =0.42, I^2 = 0%; Figure 2C). However, etoricoxib 120 mg qd showed better efficacy than indomethacin 50 mg tid in terms of the investigator's global assessment of response (SMD: −0.29, 95% CI: −0.46, −0.11) with mild heterogeneity (χ^2 = 2.11, df = 2, P =0.35, I^2 = 5%; Figure 2D). The effect of etoricoxib 120 mg qd on joint swelling was comparable to that of indomethacin 50 mg tid (SMD: −0.25, 95% CI: −0.74, 0.24); in this regard, there was marked heterogeneity among the studies included in the meta-analysis ($\chi^2 = 4.80$, df = 1, P-value=0.03, I^2 = 79%; Figure 2E). Etoricoxib 120 mg qd had a shorter time to onset of therapeutic effect than diclofenac 75 mg qd (SMD: −0.94, 95% CI: −1.33, −0.55) [39].

Comparative efficacy of COXIBs

In terms of the effect on the pain VAS score, etoricoxib was generally better than the other two COXIBs (SMD: −3.24, 95% CI: −4.61, −1.86); there was marked heterogeneity among the included studies in this respect ($\chi^2 = 85.18$, df = 4, P<0.001, I^2 = 95%). Subgroup analysis revealed better efficacy of etoricoxib 120 mg qd compared to celecoxib 200 mg tid (SMD: −2.36, 95% CI: −3.36, −1.37) and meloxicam 15 mg qd (SMD: −7.25, 95% CI: −8.63, −5.86; Figure 3A). Besides this, a greater proportion of patients who received etoricoxib 120 mg qd

(89.47%) had improvement in clinical symptoms compared to those who received celecoxib 200 mg bid (71.05%) [24].With regard to the pain Likert scale score, etoricoxib 120 mg qd was better than meloxicam 15 mg qd (SMD: −0.56, 95% CI: −1.10, −0.02); there was marked heterogeneity among the included studies in this regard (χ^2 = 10.16, df = 2, *P*-value=0.006, I^2 = 80%; Figure 3B). Moreover, the onset time for etoricoxib 120 mg qd was significantly shorter than that for meloxicam 15 mg qd (SMD: −1.57, 95%CI: −2.07, −1.08) [20].

Discussion

In this meta-analysis, we evaluated the clinical outcomes of patients with acute gout treated with various NSAIDs. The results showed comparable performance of COXIBs and traditional NSAIDs with regard to the effect on the pain Likert score and pain VAS scores; however, COXIBs showed better efficacy than traditional NSAIDS with regard to several secondary outcomes, including the response rate and the investigator's global assessment of response. Therefore, we were unable to conclude that COXIBs clearly perform better than traditional NSAIDS. However, we found that etoricoxib 120 mg qd offers a clear advantage over celecoxib 200 mg tid and meloxicam 15 mg qd in terms of both pain Likert scale score and pain VAS scores.

We exclusively assessed evidence from available studies that compared the efficacy of currently used non-selective NSAIDs and COXIBs in patients with acute gout. Our meta-analysis incorporated all of the clinical outcomes of the available studies; however, most outcomes showed no difference, and several outcomes revealed that COXIBs performed better. Therefore, there was no conclusive evidence of the comparative efficacy between non-selective NSAIDs and COXIBs. However, our study revealed etoricoxib has superior clinical performance

in the management of patients with acute gout than either celecoxib or meloxicam. With regard to Likert scores, COXIBs showed better efficacy than non-selective NSAIDs; however, a subgroup analysis revealed no significant difference between the two groups of drugs. The inconsistency in the results between the pooled and subgroup analyses may be attributable to significant heterogeneity between subgroups, and we draw our conclusions on the basis of the results of subgroup analyses.

Several trials comparing traditional NSAIDS with oral corticosteroid, another recommended first-line options for acute flares, were excluded since these trials did not meet the inclusion criteria of the present study. Naproxen, as a traditional NSAIDs, was used worldwide, but it was not included in the meta-analysis due to the absence of trial comparing naproxen with COXIBs. However, several studies, comparing naproxen with other traditional NSAIDs and steroid, have proven the efficacy of naproxen in the management of acute gout. A double-blind, randomized trial on patients with crystal-proven gout found that naproxen was as effective as prednisolone for acute flares [41]. Similarly, a double-blind, parallel-group study revealed similar efficacy of etodolac compared with naproxen in alleviating symptoms of acute gouty arthritis [42]. Furthermore, naproxen and phenylbutazone had comparable efficacy in the management of acute gout, with few and relatively mild adverse events [43].

The issue of safety was not assessed because there is adequate evidence of the safety of short-term use of NSAIDs for acute gout. Several studies have revealed that COXIBs are preferable to traditional non-selective NSAIDs in terms of safety in patients with acute gout [13, 14] or other pain conditions [44]. Moreover, analysis of VIGOR and two capsule endoscopy studies showed significantly less distal gastrointestinal blood loss with COXIBs than with non-selective NSAIDs [45]. The rates of upper gastrointestinal adverse clinical events were lower

with etoricoxib than with diclofenac [46]. When compared with traditional NSAIDs at standard dosages, celecoxib – at dosages greater than those indicated clinically – was associated with a lower incidence of symptomatic ulcers, ulcer-related complications, as well as other clinically important toxic effects [47]. Gout and renal disorders are common comorbidities affecting elderly adults, leading to frequently administration of concomitant analgesics, especially NSAIDs. Several studies showed that COXIBs, such as celecoxib, has a better or similar renal safety profile than ibuprofen or other traditional NSAIDs [48, 49]. It may be hypothesized that COXIBs may decrease renal adverse effects relative to nonselective NSAIDs, as the kidney and vasculature express both COX-1 and -2. However, COXIBs, similar to traditional NSAIDs, must be used cautiously in patients with predisposing renal diseases [50].

The currently prevalent belief is that both traditional NSAIDs and COXIBs are associated with an increased cardiovascular risk, with the probable exception of naproxen [51]. However, the landmark PRECISION study seemingly refutes this widely held idea [52, 53]. Also, there is no clear-cut conclusion of whether COXIBs pose a higher cardiovascular risk when comparing traditional NSAIDs. The MEDAL study revealed similar rates of thrombotic cardiovascular events between long-term etoricoxib and diclofenac treatment in patients with arthritis [46]. In addition to efficacy, care must be exercised to consider gastrointestinal, cardiovascular, and renal conditions when choosing between NSAIDs and COXIBs.

Our study has clinical implications. The prevalence of gout has increased in both developed and developing countries, presumably due to lifestyle changes [54]. Of all the 291 conditions studied in the GBD 2010 study, gout ranked 138th in terms of disability, and 173rd in terms of overall burden [2]. NSAIDs have gradually been established as the first-line therapeutic option for acute gout [5, 7, 8]; therefore, a comparison of the efficacy of NSAIDs is of much clinical

relevance. Finally, we concluded that COXIBs are comparable to traditional NSAIDs with regard to pain relief, but are preferable to traditional NSAIDs in terms of clinical symptoms and investigator's global assessment of response. Etoricoxib may be the best option when COXIBs are indicated.

Our study has considerable strengths. We designed the meta-analysis according to the PRISMA guidelines and took meticulous care to minimize errors and ensure the validity of findings from all relevant studies. Our meta-analysis thoroughly addresses two key questions – that is, the comparative efficacy of traditional NSAIDs and COXIB and the comparative efficacy of the three COXIBs in terms of various clinical outcomes. Our findings may facilitate the selection of drugs for acute gout in clinical settings.

Nevertheless, there are several limitations of our study. First, a relatively strict searching strategy was used in the present study to achieve our goal, which resulted that only several RCT studies were included. That is, the RCT studies about the effect of NSAIDs on acute gout are limited in recent years. Moreover, most of them were published in Chinese. The relatively small number of studies and the small sample size in the studies include in the meta-analysis are the major limitations of our study. Besides, most of the included studies published in Chinese were of low quality. Moreover, confounding factors such as the underlying disease and the use of other drugs could have affected the analysis. However, our review emphasizes the potential importance of COXIBs for acute gout. Given the clinical importance and acute nature of a gout flare, more trials focusing on clinically relevant outcomes are essential, especially in those patients who really need care.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Authors' contributions

MTL, CY, and XFZ were responsible for the conception and design of the study. MTL and CY did the analysis and interpreted the analysis. MTL and CY wrote the first draft of the manuscript. All authors critically revised the manuscript and have approved the final version.

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Conflict of Interest

The authors declare that they have no conflict of interests.

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Table 1. Main characteristics of the studies included in this meta-analysis

Author	Year	Language	Treatment arms	N	Male	Age	Follow-up (d)
Schumacher H (39)	2002	English	Etoricoxib 120 mg qd	75	73	48.5 (13.29)	8
			Indomethacin 50 mg tid	75	69	49.5 (13.71)	
Rubin B (33)	2004	English	Etoricoxib 120 mg qd	103	98	51.1 (13)	8
			Indomethacin 50 mg tid	86	79	52.2 (12)	
Ye Q (32)	2010	Chinese	Etoricoxib 120 mg qd	40	33	45.12 (12.48)	7
			Diclofenac 75 mg qd	35	32	38.20 (15.51)	
Zhang J (19)	2012	Chinese	Etoricoxib 120 mg qd	48	48	63.4 (12)	8
			Meloxicam 15 mg qd	36	36	64.1 (11)	
Gao Q (37)	2013	Chinese	Etoricoxib 120 mg qd	140	89	41.78 (12.57)	7
			Diclofenac 75 mg bid	140	92	42.48 (13.23)	
Hong J (20)	2013	Chinese	Etoricoxib 120 mg qd	50	38	42.1 (9.8)	7
			Celecoxib 200 mg tid	50	40	41.5 (7.8)	
Li T (36)	2013	English	Etoricoxib 120 mg qd	89	85	52 (15)	5
			Indomethacin 75 mg bid	89	81	53 (14)	
Guo D (17)	2014	Chinese	Etoricoxib 120 mg qd	60	96	44.3 (15.6)	8
			Meloxicam 15 mg qd	60			
Guo M (38)	2014	Chinese	Etoricoxib 120 mg qd	57	56	40.52 (11.27)	5
			Diclofenac 75 mg qd	56	54	43.03 (13.02)	
Lu J (31)	2014	Chinese	Etoricoxib 120 mg qd	95	89	48.9 (2.3)	7
			Diclofenac 50 mg tid	51	49	46.7 (3.4)	
Kuang L (34)	2015	Chinese	Etoricoxib 120 mg qd	40	29	42.8 (10.3)	7

			Diclofenac 50 mg tid	40	31	43.7 (11.2)	
Liu C (18)	2015	Chinese	Etoricoxib 120 mg qd	32	21	45 (3.74)	7
			Meloxicam 15 mg qd	32	13	44 (3.53)	
Xia H (21)	2015	Chinese	Etoricoxib 120 mg qd	40	27	50.17 (25.13)	7
			Celecoxib 200 mg tid	40	25	50.09 (25.34)	
Zhu H (30)	2015	Chinese	Etoricoxib 120 mg qd	50	48	46.3 (6.9)	7
			Diclofenac 50 mg tid	50	49	46.5 (6.1)	
Cui M (14)	2016	Chinese	Diclofenac 100 mg qd	12	11	41.5 (3.8)	5
			Celecoxib 200 mg qd	12	10	43.2 (4.2)	
Li S (29)	2016	Chinese	Etoricoxib 120 mg qd	47	22	41.8 (11.3)	5
			Diclofenac 75 mg qd	47	21	40.5 (10.1)	
Ming H (23)	2016	Chinese	Etoricoxib 120 mg qd	38	22	52.64 (12.28)	7
			Celecoxib 200 mg bid	38	23	52.79 (12.35)	
Pan Q (35)	2016	Chinese	Etoricoxib 120 mg qd	68	126	43.2 (13.6)	7
			Diclofenac 50 mg tid	68			
Zhou S (22)	2016	Chinese	Etoricoxib 120 mg qd	28	16	53.37 (11.32)	7
			Celecoxib 200 mg tid	28	14	52.13 (10.13)	
Li Y (18)	2017	Chinese	Etoricoxib 120 mg qd	44	68	44.67 (14.99)	8
			Meloxicam 15 mg qd	44			

N = number, age presented as mean (standard deviation).

Figure legends

Figure 1. Schematic illustration of literature search and study selection

Figure 2. Forest plots of primary outcomes: COXIBs versus traditional NSAIDs.

Pain Likert scale for days 2–8) (A); pain VAS score for days 2–8 (B).

VAS, visual analog scale

Figure 3. Forest plots of secondary outcomes: COXIBs versus traditional NSAIDs

Response rate for days 2–8 (A); C-reactive protein (B); patient's global assessment (C); investigator's global assessment (D); and inflammatory swelling (E)

Figure 4. Forest plots of primary outcomes: comparative efficacy of various COXIBs

Pain Likert scale score for days 2–8 (A); Pain VAS score for days 2–8 (B).

VAS, visual analog scale

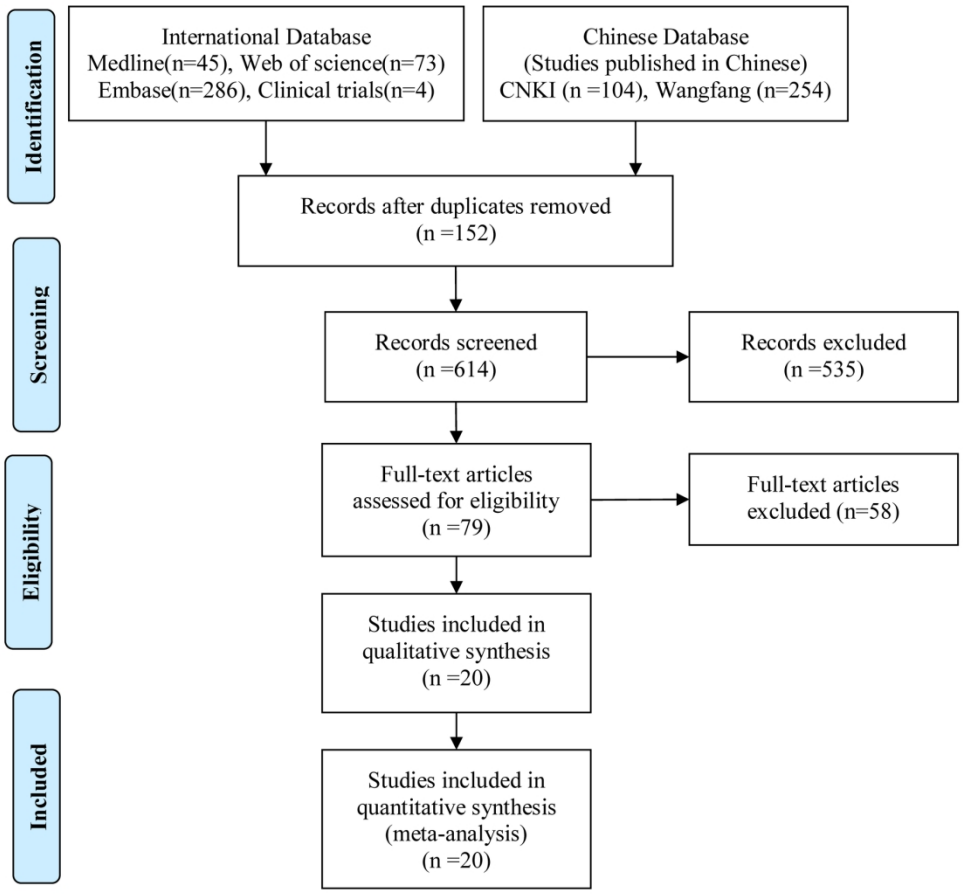

Figure 1. Schematic illustration of literature search and study selection

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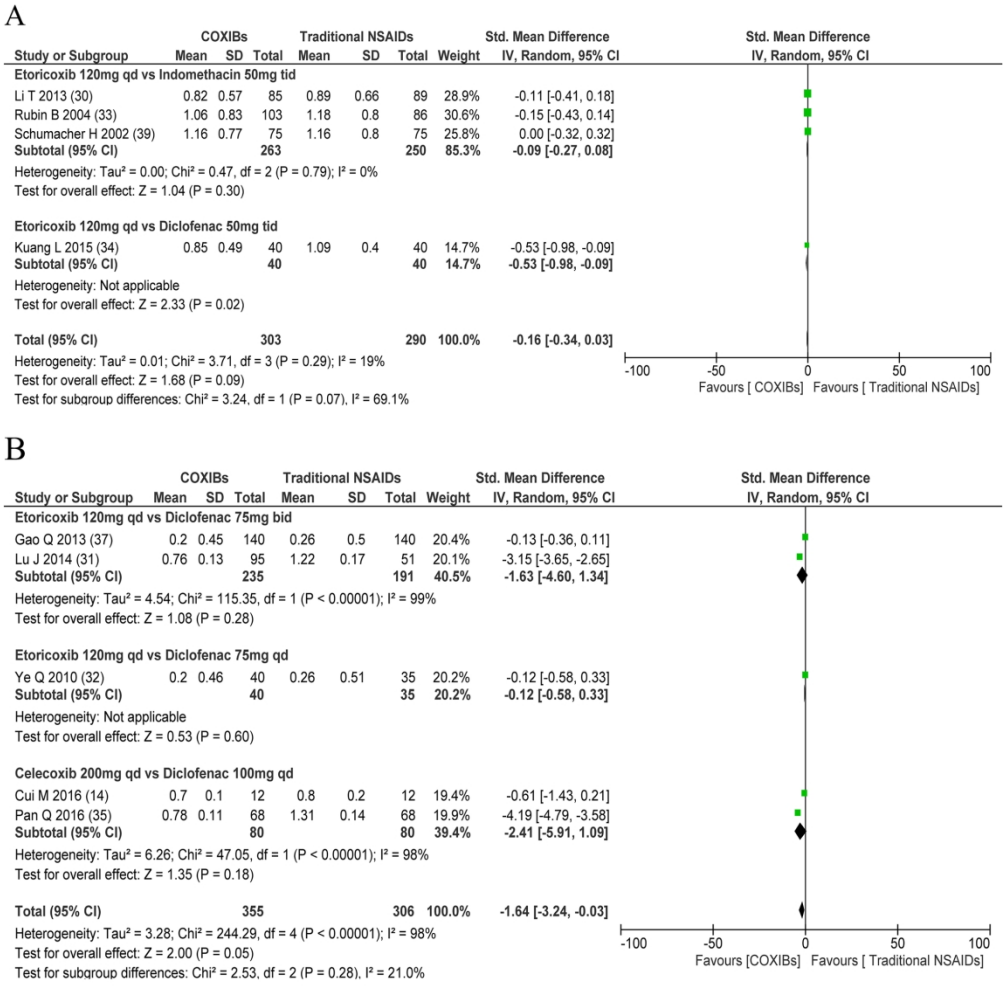

Figure 2. Forest plots of primary outcomes: COXIBs versus traditional NSAIDs. Pain Likert scale for days 2–8) (A); pain VAS score for days 2–8 (B). VAS, visual analog scale

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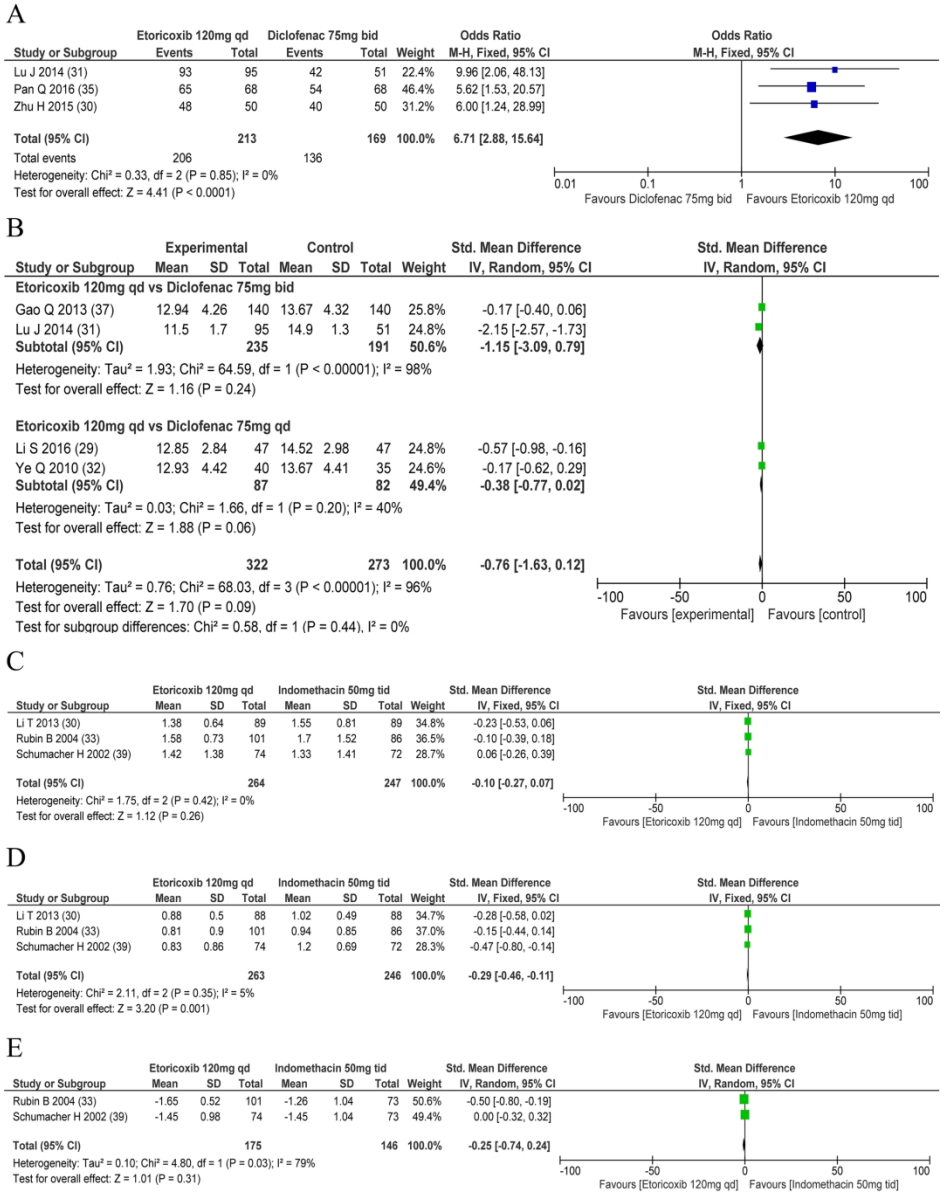

Figure 3. Forest plots of secondary outcomes: COXIBs versus traditional NSAIDs Response rate for days 2–8 (A); C-reactive protein (B); patient's global assessment (C); investigator's global assessment (D); and inflammatory swelling (E)

190x243mm (300 x 300 DPI)

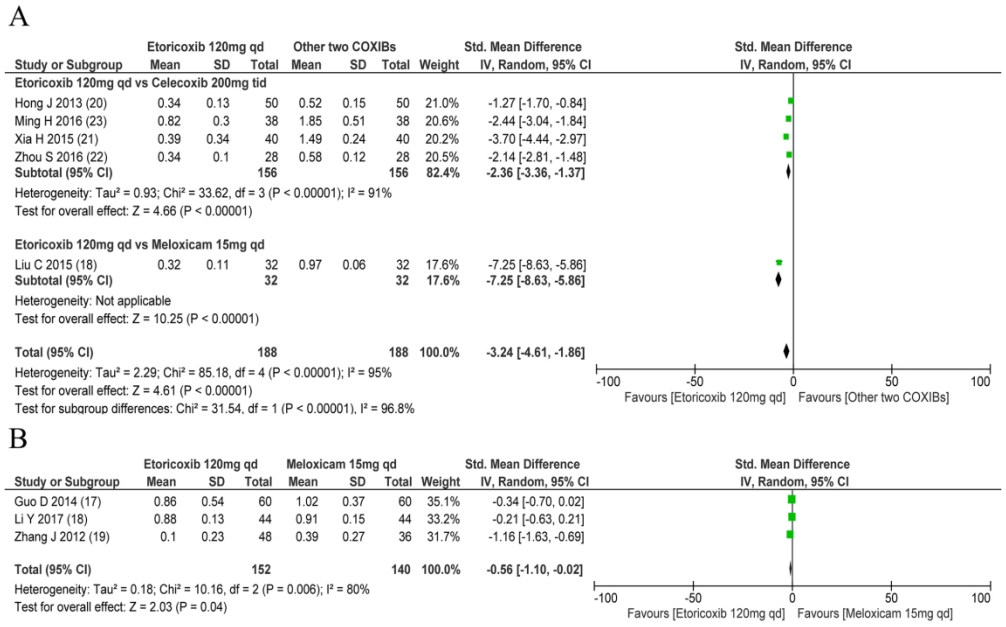

Figure 4. Forest plots of primary outcomes: comparative efficacy of various COXIBs Pain Likert scale score for days 2–8 (A); Pain VAS score for days 2–8 (B). VAS, visual analog scale

190x120mm (300 x 300 DPI)

Supplementary Material for: "Comparative efficacy of non-steroidal anti-inflammatory drugs in patients with acute gout: a systematic review and meta-analysis"

Journal: BMJ Open

Authors: Mengtao Li, PhD, Chen Yu, PhD, Xiaofeng Zeng, PhD

Corresponding author: Prof Xiaofeng Zeng, Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Table of content

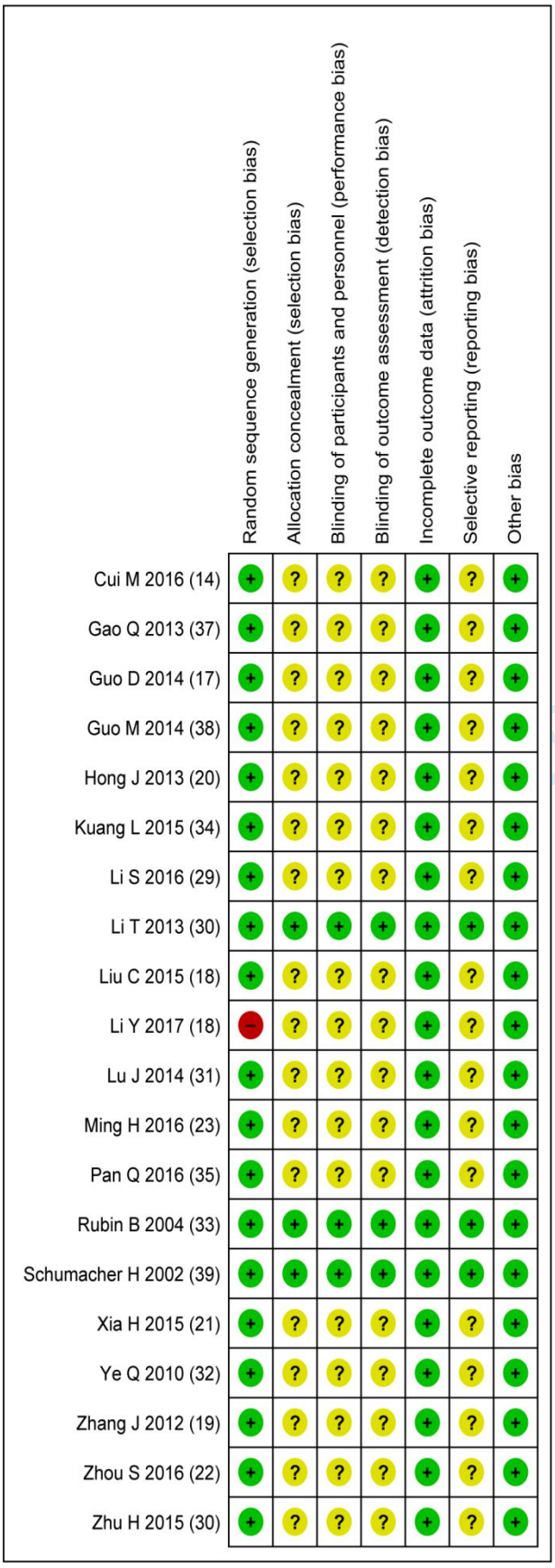

Figure S1. Risk of bias summary

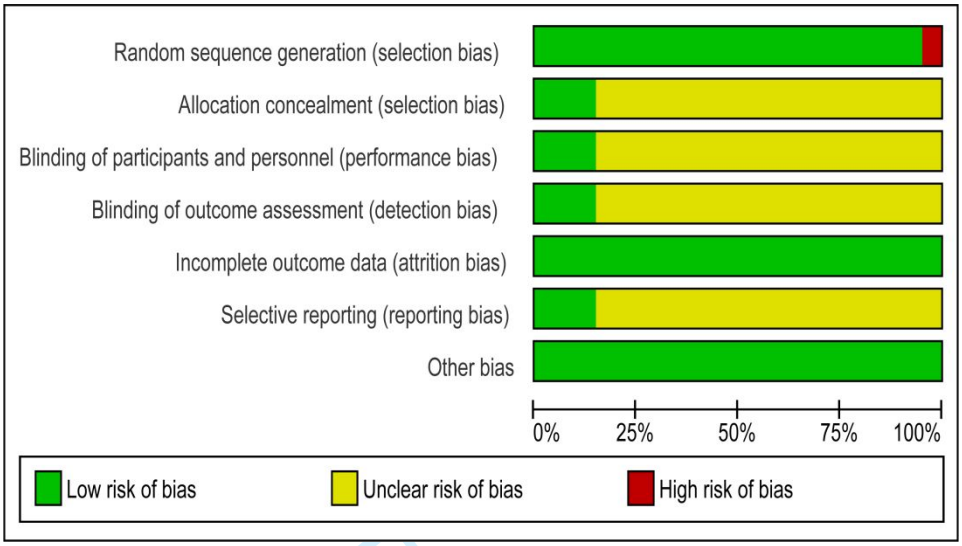

Figure S2. Risk of bias graph

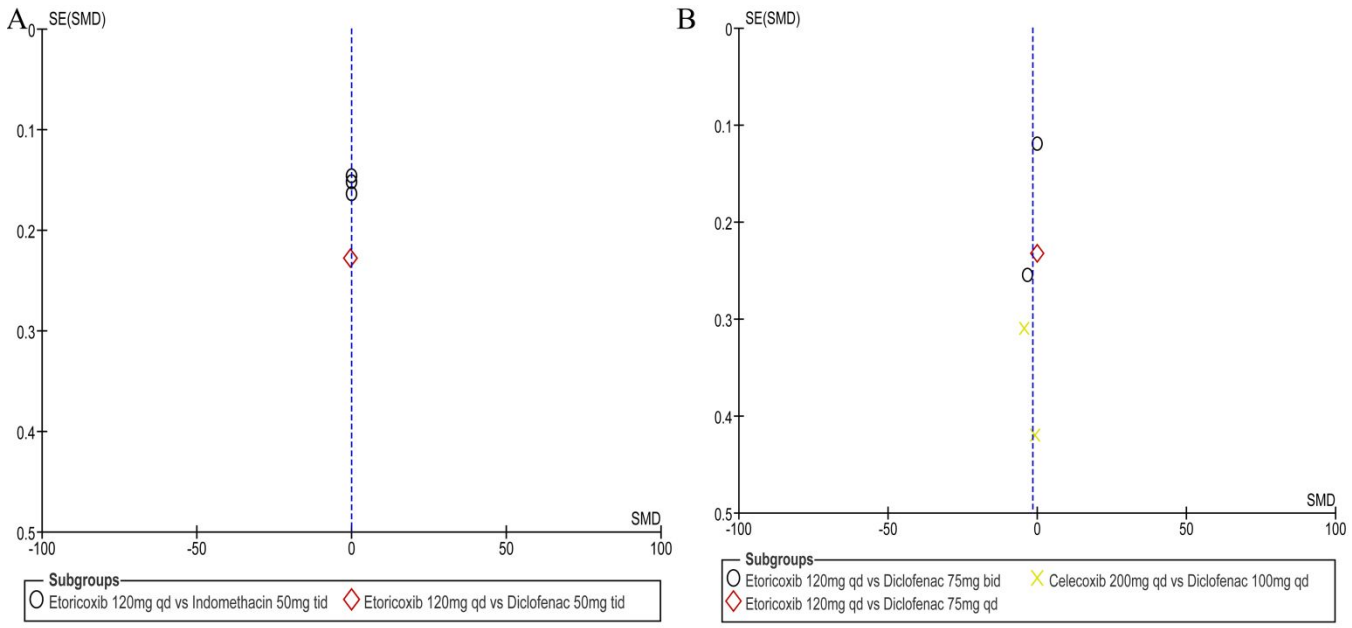

Figure S3. Funnel plots of primary outcomes: COXIBs versus traditional NSAIDs.

Pain Likert scale for days 2–8 (A); pain VAS score for days 2–8 (B). VAS, visual analog scale

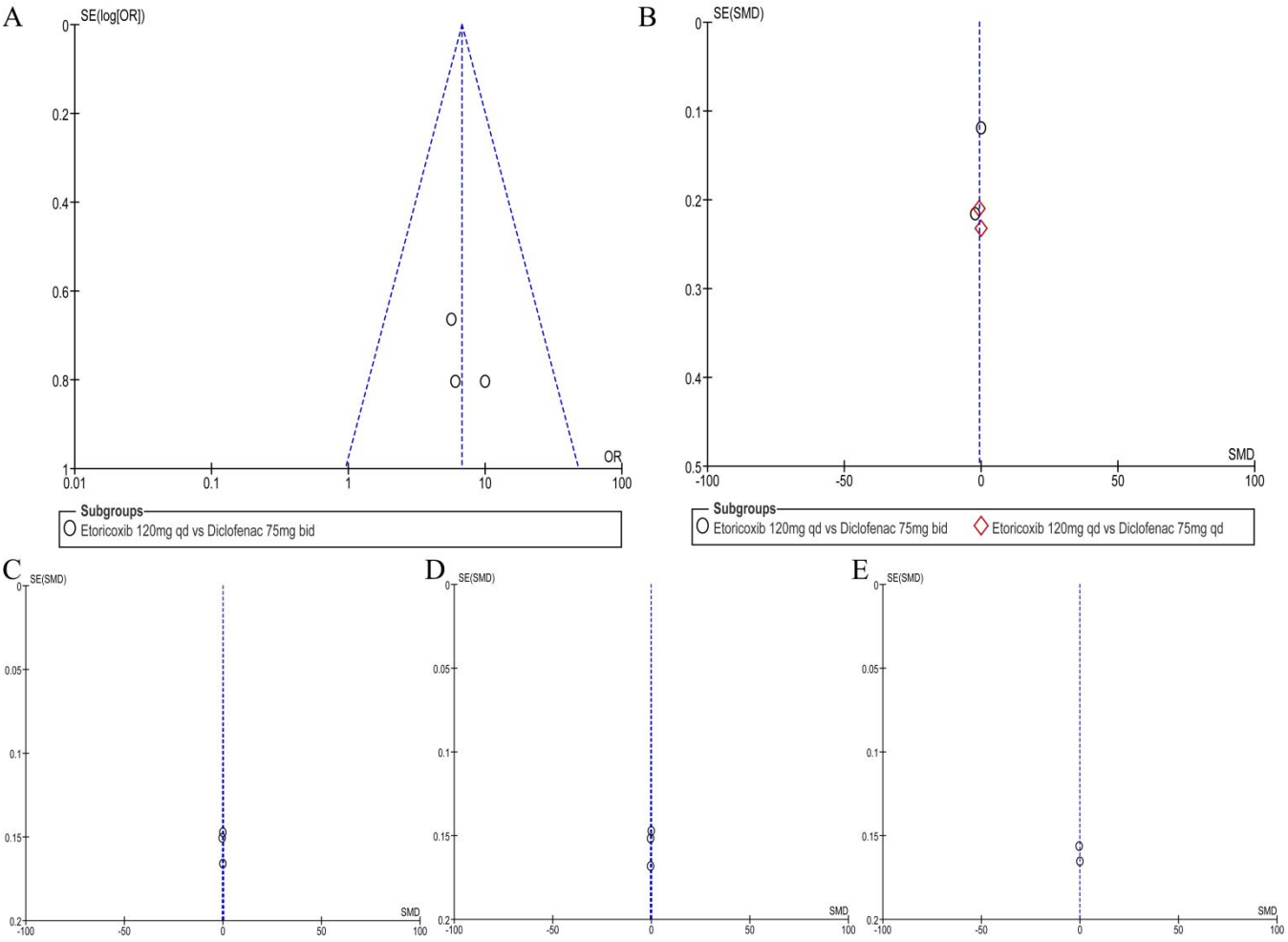

Figure S4. Funnel plots of secondary outcomes: COXIBs versus traditional NSAIDs

Response rate for days 2–8 (A); C-reactive protein (B); patient's global assessment (C); investigator's global assessment (D); and inflammatory swelling (E).

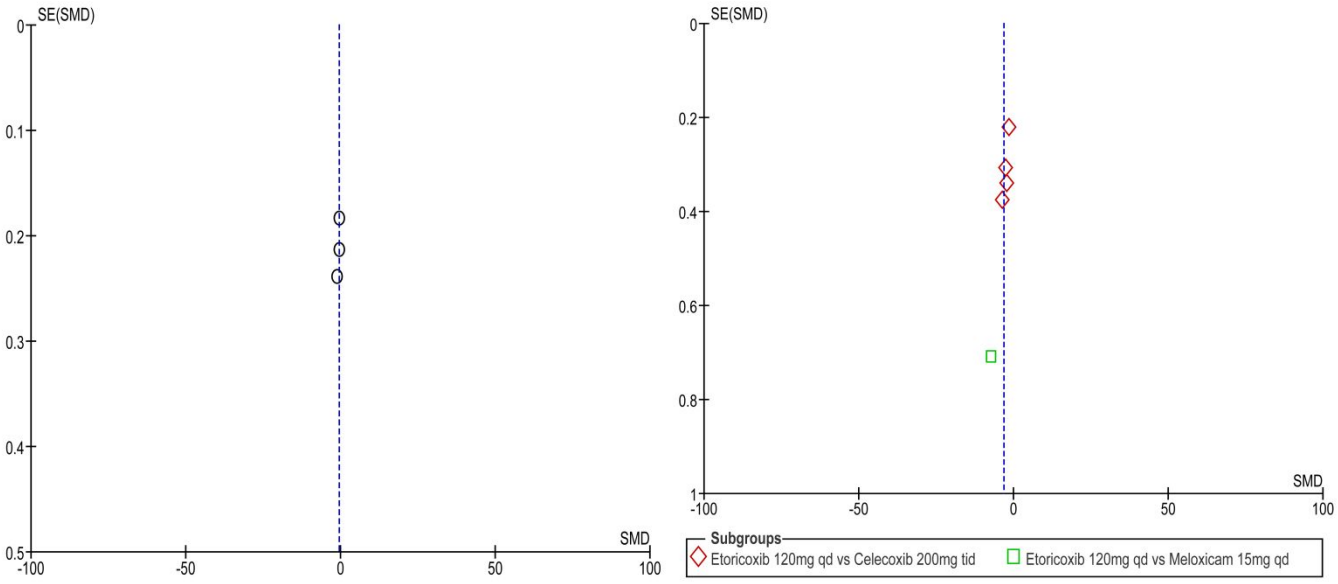

Figure S5. Funnel plots of primary outcomes: comparative efficacy of various COXIBs

Pain Likert scale for days 2–8 (A); Pain VAS scale for days 2–8 (B). VAS, visual analog scale

Table S1: GRADE framework: COXIBs vs traditional NSAIDs for acute gout

Certainty assessment							Summary of findings				
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With traditional NSAIDs	With COXIBs		Risk with traditional NSAIDs	Risk difference with COXIBs
Pain Likert scale											
593 (4 RCTs)	not serious	not serious	not serious	not serious	none	HIGH	290	303	-	-	SMD 0.15 SD lower (0.31 lower to 0.01 higher)
Pain Likert scale – etoricoxib 120 mg qd vs indomethacin 50 mg tid											
513 (3 RCTs)	not serious	not serious	not serious	not serious	none	HIGH	250	263	-	-	SMD 0.09 lower (0.27 lower to 0.08 higher)
Pain Likert scale – etoricoxib 120 mg qd vs diclofenac 50 mg tid											
80 (1 RCT)	serious [a]	not serious	not serious	not serious	none	◯ MODERATE	40	40	-	-	SMD 0.53 lower (0.98 lower to 0.09 lower)
Pain VAS											
661 (5 RCTs)	serious [a]	not serious	not serious	not serious	none	◯ MODERATE	306	355	-	-	SMD 1.64 lower (3.24 lower to 0.03 lower)
Pain VAS – etoricoxib 120 mg qd vs diclofenac 75 mg bid											
426 (2RCTs)	serious [a]	not serious	not serious	not serious	none	◯ MODERATE	191	235	-	-	SMD 1.63 lower (4.60 lower to 1.34 higher)

Certainty assessment							Summary of findings				
Pain VAS – etoricoxib 120 mg qd vs diclofenac 75 mg qd											
75 (1RCTs)	serious [a]	not serious	not serious	not serious	none	◯ MODERATE	35	40	-	-	SMD 0.12 lower (0.58 lower to 0.33 higher)
Pain VAS – celecoxib 200 mg qd vs diclofenac 100 mg qd											
160 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	◯ MODERATE	80	80	-	-	SMD 2.41 lower (5.91 lower to 1.09 higher)
Response rate											
382 (3 RCTs)	not serious	serious [a]	not serious	not serious	none	◯ MODERATE	136/169 (80.5%)	206/213 (96.7%)	OR 6.71 (2.88 to 15.64)	805 per 1,000	160 more per 1,000 (118 more to 180 more)
C-reactive protein											
595 (4 RCTs)	not serious	serious [a]	not serious	not serious	none	◯ MODERATE	273	322	-	-	SMD 0.76 lower (1.63 lower to 0.12 higher)
C-reactive protein – etoricoxib 120 mg qd vs diclofenac 75 mg bid											
426 (2 RCTs)	not serious	serious [a]	not serious	not serious	none	◯ MODERATE	191	235	-	-	SMD 1.15 lower (3.09 lower to 0.79 higher)
C-reactive protein – etoricoxib 120 mg qd vs diclofenac 75 mg qd											
169 (2RCTs)	not serious	serious [a]	not serious	not serious	none	◯ MODERATE	82	87	-	-	SMD 0.38 lower (0.77 lower to 0.02 higher)

Certainty assessment							Summary of findings				
Patient's global assessment of response											
511 (3 RCTs)	not serious	not serious	not serious	not serious	none	HIGH	247	264	-	-	SMD 0.1 SD lower (0.27 lower to 0.07 higher)
Investigator's global assessment of response											
509 (3 RCTs)	not serious	not serious	not serious	not serious	none	HIGH	246	263	-	-	SMD 0.29 SD lower (0.46 lower to 0.11 lower)
Inflammatory swelling											
321 (2 RCTs)	not serious	not serious	not serious	not serious	none	HIGH	146	175	-	-	SMD 0.25 lower (0.74 lower to 0.24 higher)
Onset of efficacy (h) – etoricoxib 120 mg qd vs diclofenac 75 mg qd											
113 (1 RCT)	not serious	serious [a]	not serious	not serious	none	◯ MODERATE	56	57	-	-	SMD 0.94 lower (1.33 lower to 0.55 lower)

CI: Confidence interval; SMD: Standardized mean difference; OR: Odds ratio

Explanations

a. Unclear risk of allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and selective reporting

Table S2: GRADE framework: one COXIB vs another COXIB for acute gout

Certainty assessment							Summary of findings				
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With one COXIBs	With another COXIBs		Risk with one COXIBs	Risk difference with another COXIBs
Pain Likert scale											
292 (3 RCTs)	serious [a]	not serious	not serious	not serious	none	◯ MODERATE	140	152	-	-	SMD 0.56 lower (1.1 lower to 0.02 lower)
Pain VAS											
376 (5 RCTs)	serious [a]	not serious	not serious	not serious	none	◯ MODERATE	188	188	-	-	SMD 3.24 lower (4.61 lower to 1.86 lower)
Pain VAS – etoricoxib 120 mg qd vs celecoxib 200 mg tid											
312 (4 RCTs)	serious [a]	not serious	not serious	not serious	none	◯ MODERATE	156	156	-	-	SMD 2.36 lower (3.36 lower to 1.37 lower)
Pain VAS – etoricoxib 120 mg qd vs meloxicam 15 mg qd											
64 (1 RCT)	serious [a]	not serious	not serious	not serious	none	◯ MODERATE	32	32	-	-	SMD 7.25 lower (8.63 lower to 5.86 lower)
Response rate – etoricoxib 120 mg qd vs celecoxib 200 mg bid											

Certainty assessment							Summary of findings				
76 (1 RCT)	serious [a]	not serious	not serious	not serious	none	◯ MODERATE	27/38 (71.1%)	34/38 (89.5%)	OR 3.46 (0.99 to 12.10)	711 per 1,000	184 more per 1,000 (2 fewer to 257 more)
Onset of efficacy (h) – etoricoxib 120 mg qd vs meloxicam 15 mg qd											
84 (1 RCT)	serious [a]	not serious	not serious	not serious	none	◯ MODERATE	36	48	-	-	SMD 1.57 lower (2.07 lower to 1.08 lower)

CI: Confidence interval; SMD: Standardized mean difference; OR: Odds ratio

Explanations

a. Unclear risk of allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and selective reporting.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	#1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	#2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	#5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	#5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	#6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	#6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	#6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	#7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	#7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	#7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	#8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	#8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	#8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	#8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	#8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	#9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	#9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	#10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	#10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	#10-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	#10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	#10-12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	#12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	#15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	#15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	#16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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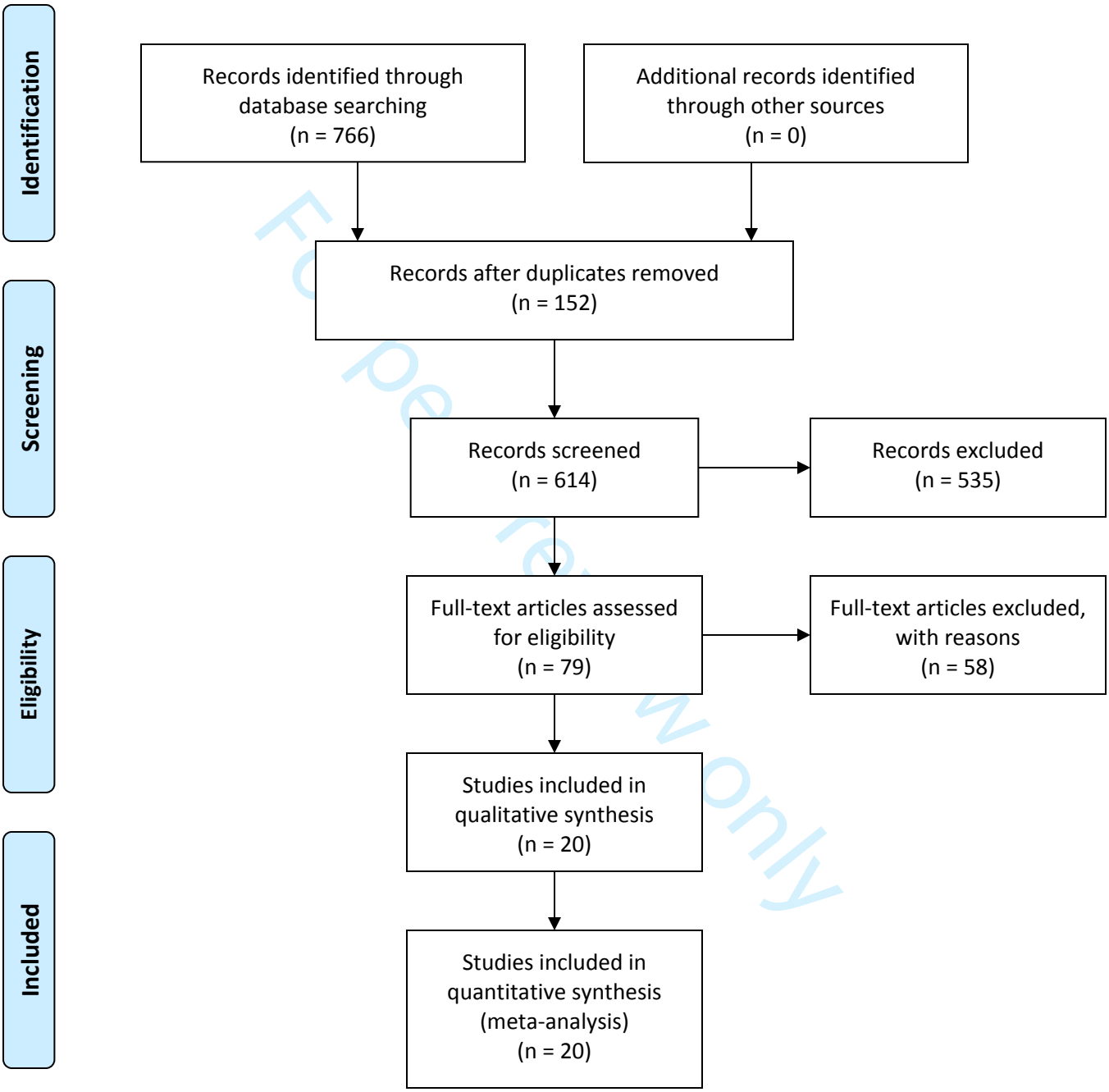

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Comparative efficacy of traditional non-selective NSAIDs and selective cycloxygenase-2 inhibitors in patients with acute gout: a systematic review and meta-analysis

Running title: NSAIDs for acute gout

Mengtao Li, PhD[1], Chen Yu, PhD[1], Xiaofeng Zeng, PhD[1*]

[1]Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

***Address correspondence and reprint requests to**

Xiaofeng Zeng, PhD

Address: Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China

E-mail: zengxfpumc@163.com

Tel: +8613501069845

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Abstract

Objective: To assess comparative efficacy of traditional non-steroidal anti-inflammatory drugs and selective cycloxygenase-2 inhibitor (COXIB) for patients with acute gout.

Design: Systematic review and meta-analysis.

Data sources: Medline, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang Data published as of 04 April 2020.

Methods: We performed meta-analysis of randomized controlled trials (RCTs) of traditional non-selective NSAIDs versus COXIBs and RCTs of various COXIBs in patients with acute gout. The main outcome measures were mean change in pain visual analog scale (VAS) score and 5-point Likert scale score for days 2–8.

Results: Twenty-four trials involving five drugs were evaluated. For pain Likert scale, etoricoxib was comparable to indomethacin (SMD: -0.09, 95% CI: -0.27, 0.08) but better than diclofenac 50 mg tid (SMD: -0.53, 95% CI: -0.98, -0.09). Regarding pain VAS score, etoricoxib was comparable to diclofenac 75 mg bid (SMD: -1.63, 95% CI: -4.60, 1.34) and diclofenac 75 mg qd (SMD: −1.82, 95% CI: −5.18, 1.53), while celecoxib was comparable to diclofenac 100 mg qd (SMD: -2.41, 95% CI: -5.91, 1.09). Etoricoxib have similar patients' global assessment of response (SMD: -0.10, 95% CI: -0.27, 0.07) and swollen joint count (SMD: -0.25, 95% CI: -0.74, 0.24), but better investigator's global assessment of response (SMD: -0.29, 95% CI: -0.46, -0.11) compared with indomethacin. Etoricoxib showed more favorable pain VAS score than celecoxib (SMD: -2.36, 95% CI: -3.36, -1.37), but was comparable to meloxicam (SMD: −4.02, 95% CI: −10.28, 2.24). Etoricoxib showed more favorable pain Likert scale than meloxicam (SMD: -0.56, 95%CI: -1.10, -0.02). Etoricoxib 120 mg qd was more likely to achieve clinical improvement compared with celecoxib 200 mg bid (OR: 4.84, 95% CI: 2.19, 10.72).

Conclusion: Although COXIBs and traditional non-selective NSAIDs may be equally beneficial in terms of pain relief, COXIBs (especially etoricoxib) may confer a greater benefit.

Keywords: acute gout, NSAIDs, selective cycloxygenase-2 inhibitors, efficacy

Strengths and limitations of this study

- The study evaluates available randomized controlled trials comparing the efficacy of traditional non-steroidal anti-inflammatory drugs and selective cycloxygenase-2 inhibitors for patients with acute gout.
- Stringent and sensitive search strategy of the internet databases is used to minimize potential publication bias.
- Most included studies published in Chinese although we do not set specific language restriction in search strategy.
- The main limitations of included trials are relatively few number, small sample size and generally low quality.

Introduction

Gout is a chronic disease characterized by the deposition of monosodium urate crystals in various tissues as a result of elevated serum urate concentration [1]. According to the Global Burden of Disease (GBD) 2010 study, the estimated global prevalence of gout is 0.08% and there is an increasing trend in the burden of gout [2]. Worldwide, the reported prevalence of gout ranges from 0.1% to approximately 10%, and the incidence rates range from 0.3 to 6 cases per 1,000 person-years [3]. The prevalence and incidence of gout is highly variable across various regions of the world. In general, there is a higher prevalence of gout in developed countries than in developing countries [3]. There is no national epidemiological data on the prevalence of gout in China; however, based on data from different local regions at different time points in China, the prevalence of gout is currently 1% to 3% and is steadily increasing every year [4].

Acute gout most frequently begins with the involvement of a single joint in the lower limbs (85–90% of cases) – usually, the first metatarsophalangeal joint [1]. The management of acute gout includes rapid treatment of acute flares and effective long-term therapy [5-9]. The main therapeutic options for an acute flare are colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids [5]. The deposition of monosodium urate microcrystals in the articular and periarticular tissues elicits acute or chronic inflammatory responses that are known as gouty arthritis [1, 10, 11]. There is evidence that monosodium urate microcrystals induce the production of cyclooxygenase-2 (COX-2) in human monocytes [12]. NSAIDs include traditional NSAIDs and selective COX-2 inhibitors (COXIBs) – the former inhibits both COX-1 and -2 enzymes whereas the latter specifically antagonizes COX-2. The efficacy of COXIBs is comparable to that of traditional NSAIDs; however, COXIBs have fewer adverse effects, particularly gastrointestinal adverse effects [13].

In the past decade, NSAIDs have been emphasized as the first-line option for the management of acute gout, in accordance with the 2006 and 2016 European League Against Rheumatism (EULAR) recommendations [5, 8] and American College of Rheumatology guidelines [6, 7]. A meta-analysis found no significant difference between traditional NSAIDs and COXIBs with regard to the pain score, inflammation score, change in patient's global assessment from baseline, and the health-related quality of life (HRQoL) [13]. Another meta-analysis indicated that the efficacy of etoricoxib in acute gout is similar to that of indomethacin and diclofenac; however, etoricoxib showed better performance than indomethacin in terms of the investigator's global assessment of response to therapy and better analgesic efficacy in comparison to diclofenac [14]. Two meta-analyses have assessed whether COXIBs are more effective for acute gout than traditional NSAIDs [13, 14]. However, a comparison between celecoxib and diclofenac [15] was not included.

Given the increasing use of COXIBs and the relatively large number of recent trials, evaluation of the comparative efficacy of various COXIBs is a key imperative – both from the clinical and policy perspectives. After the withdrawal of rofecoxib, lumiracoxib, and valdecoxib, three COXIBs are currently used in clinical practice (etoricoxib, celecoxib, and meloxicam). Meloxicam, an agent synthesized as a traditional NSAID, has a selective inhibitory effect against COX-2 [16]. In four studies, etoricoxib showed better efficacy than meloxicam [17-20]; in another four studies, etoricoxib showed better efficacy than celecoxib [21-24]. Moreover, many studies published in Chinese were not included in previous meta-analyses. Therefore, we conducted a meta-analysis to provide an updated picture of the comparative clinical efficacy of traditional non-selective NSAIDs and COXIBs, as well as that of the three COXIBs in patients with acute gout.

Materials and methods

Literature strategy

This study is registered with the International Platform of Registered Systematic Review and Meta-analysis (INPLASY) Protocols (registration number: INPLASY202040025) (Figure S1). Biomedical databases, including Medline (Pubmed), Web of Science, Embase, China National Knowledge Infrastructure (CNKI), and Wanfang Data were searched for randomized controlled trials (RCTs; published as of April 2018) that investigated the comparative efficacy of traditional non-selective NSAIDs and COXIBs or that of the three COXIBs in patients with acute gout (Table S1). The key words used were: "selective cyclooxygenase-2 inhibitors", "COXIBs", "etoricoxib", "celecoxib", "meloxicam", "acute gout", and "randomized controlled trials". The reference lists of the studies, recent reviews, and meta-analyses retrieved were manually screened to identify additional studies. Two authors independently conducted the literature search; disagreements, if any, were resolved by consensus.

Selection criteria

We included RCTs into the meta-analysis if they met the following criteria. *Study population*: Adult patients (age≥18 years) with a diagnosis of acute gout defined by the American Rheumatology Association diagnostic criteria [25]. *Study design*: RCTs. *Intervention*: Trials that compared COXIBs with traditional non-selective NSAIDs or compared the various COXIBs. *Comparison*: Comparator treatments included one traditional non-selective NSAID or COXIB. *Primary outcomes*: Pain assessed using a visual analog scale (VAS) score and 5-point Likert scale for days 2–8. *Secondary outcomes* were: i) response rate (defined as the proportion of

patients who achieved improvement in clinical symptoms) for days 2–8; ii) onset of efficacy (hours); iii) post-treatment serum C-reactive protein level; iv) patient's global assessment of response; v) investigator's global assessment of response; and vi) inflammatory swelling. The exclusion criteria were: (i) trials that included a mix of people with acute gout and other musculoskeletal pain, unless the results for the acute gout population could be separately analyzed; (ii) trials that investigated obsolete NSAIDs (e.g., rofecoxib, lumiracoxib, valdecoxib); and (iii) trials that compared between traditional non-selective NSAIDs.

Data collection

The titles and abstracts of articles retrieved on database searches were independently screened by two authors to determine the eligibility of the articles according to predetermined selection criteria. The full texts of papers were obtained if more information was required to assess the eligibility for inclusion. Disagreements, if any, were resolved by consensus after review of the full-text article and with the involvement of a third author, if necessary.

Data pertaining to the following variables were independently extracted by two authors by using a standardized data collection form: study design, patient characteristics, treatment details, duration of follow-up, and relevant outcome measures. We extracted the raw data (mean and standard deviation for continuous variables, and frequency of events or participants for dichotomous outcomes). Any differences in data extraction were resolved by referring to the original articles or by consulting a third reviewer author, if required.

Risk of bias assessment

Two authors assessed the risk of bias of the included studies using the methods recommended by the Cochrane Collaboration for the following items [26]. We scored each study on six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias. The risk of bias was graded as high, low, or unclear risk of bias.

Furthermore, the quality of evidence across pooled studies (risk of bias, inconsistency, indirectness, imprecision, and publication bias) was assessed by two researchers as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and using the online version of GRADEpro GDT software (www.gradepro.org, McMaster University, 2016) [27, 28]. Tables of summary of findings were created for every rated outcome in compliance to the Cochrane rules. Disagreements were resolved, first, by discussion and, then, by consulting a third senior author for arbitration.

Statistical analysis

Traditional meta-analyses were conducted for studies that directly compared COXIBs and traditional non-selective NSAIDs and those that compared between etoricoxib, celecoxib, and meloxicam. Odds ratios (OR) and standardized mean difference (SMD) with corresponding 95% confidence intervals (CIs) were used for dichotomous and continuous outcomes, respectively. Heterogeneity was examined by using the Cochran's Q-statistic; *P*-value <0.01 was considered significant. In addition, the I^2 test was used to quantify heterogeneity (range, 0–100%). $P < 0.01$ for Q-test or $I^2 > 50\%$ indicated the existence of heterogeneity among the studies [29]. In case of significant heterogeneity, the random effects model was used; in addition, a subgroup analysis

was conducted to identify the source of heterogeneity. The Review Manager 5 (RevMan 2014) was used for the meta-analysis.

Patient and Public Involvement

There was no patient and public involvement as this was a database research study.

Results

Characteristics of included studies

Of the 1091 articles retrieved on database search, 456 were excluded after a review of titles and abstracts or full-text articles owing to duplication (n=417) or irrelevant efficacy outcomes or measures (n=650) (Figure 1). Finally, 24 trials involving five drugs and six treatment arms (etoricoxib 120 mg qd, indomethacin 50 mg tid, diclofenac 75 mg bid, diclofenac 100 mg qd, celecoxib 200 mg bid, and meloxicam 15 mg qd), with a combined study population of 2513 patients, were included in the meta-analysis [15, 17-24, 30-44]. Three studies were published in English [30, 31, 34] and 21 in Chinese [15, 17-24, 32, 33, 35-44]. The sample size of the included studies ranged from 12 to 140; three of these trials (12.5%) had less than 50 participants (Table 1).

Quality of included studies

Most of the included studies were rated as being of low quality. All studies [15, 17-24, 32-34, 36-40] published in Chinese had an unclear risk of allocation concealment, blinding of participants and personnel, blinding of outcome assessment, or selective reporting. Three studies

showed no risk of bias [30, 31, 34] and one study [19] showed a high risk of random sequence generation (Figure S2, S3).

The quality of evidence was rated as moderate in most comparisons. According to GRADE, the quality of evidence for comparison between traditional NSAIDs and COXIBs was rated as high for pain on the 5-point Likert scale but moderate for pain on the VAS score (Table S2). However, the quality of evidence for comparison between the three COXIBs was rated as moderate for the pain component of both the 5-point Likert scale and the VAS score (Table S3).

Comparative efficacy of traditional non-selective NSAIDs and COXIBs

The efficacy of COXIBs was comparable to that of the traditional NSAIDs in terms of the 5-point Likert scale (SMD: −0.15, 95% CI: −0.31, 0.01) with mild heterogeneity (χ^2 = 3.71, degrees of freedom [df] = 3, P = 0.29, I^2 = 19.0%; Figure 1B). Subgroup analysis indicated comparable efficacy of etoricoxib 120 mg qd and indomethacin 50 mg tid (SMD: −0.09, 95% CI: −0.27, 0.08) with mild heterogeneity (χ^2 = 0.47, df = 2, P = 0.79, I^2 = 0%). One study showed better efficacy of etoricoxib 120 mg qd versus diclofenac 50 mg tid (SMD: −0.53, 95% CI: −0.98, −0.09; Figure 2A).

In general, COXIBs exhibited better efficacy than traditional NSAIDs in terms of the pain VAS score (SMD: −1.95, 95% CI: −3.46, −0.44), but with significant heterogeneity (χ^2 = 294.30, df = 5, P<0.001, I^2 = 98.0%). However, on subgroup analysis, etoricoxib 120 mg qd showed similar efficacy as diclofenac 75 mg bid [(SMD: −1.63, 95% CI: −4.60, 1.34) with significant heterogeneity (χ^2 = 115.35, df = 1, P<0.001, I^2 = 99.0%)] and diclofenac 75 mg qd [(SMD: −1.82, 95% CI: −5.18, 1.53) with significant heterogeneity (χ^2 = 62.83, df = 1, P<0.001, I^2 = 98.0%)]. Besides, celecoxib 200 mg bid showed comparable effect to that of diclofenac 100 mg

qd (SMD: −2.41, 95% CI: −5.91, 1.09) with significant heterogeneity (χ^2 = 47.05, df = 1, P<0.001, I^2 = 98.0%) in regard to the pain VAS score (Figure 2B).

A significantly greater proportion of patients who received etoricoxib 120 mg qd (OR: 6.71, 95% CI: 2.88, 15.64) showed clinical improvement, compared to those who received diclofenac 75 mg bid. There was mild heterogeneity among the included studies in this respect (χ^2 = 0.33, df = 2, P = 0.85, I^2 = 0%; Figure 3A). However, the effect of etoricoxib 120 mg qd on C-reactive protein was comparable to that of diclofenac 75 mg bid (SMD: -1.15, 95% CI: -3.09, 0.79), but superior to that of diclofenac 75 mg qd (SMD: −0.69, 95% CI: −1.35, -0.04) (Figure 3B).

With regard to the global assessment of response in patients, the efficacy of etoricoxib 120 mg qd was comparable to that of indomethacin 50 mg tid (SMD: −0.10, 95% CI: −0.27, 0.07) with mild heterogeneity (χ^2 = 1.75, df = 2, P = 0.42, I^2 = 0%; Figure 3C). However, etoricoxib 120 mg qd showed better efficacy than indomethacin 50 mg tid in terms of the investigator's global assessment of response (SMD: −0.29, 95% CI: −0.46, −0.11) with mild heterogeneity (χ^2 = 2.11, df = 2, P =0.35, I^2 = 5%; Figure 3D). The effect of etoricoxib 120 mg qd on joint swelling was comparable to that of indomethacin 50 mg tid (SMD: −0.25, 95% CI: −0.74, 0.24); there was marked heterogeneity among the studies included in the meta-analysis in this respect (χ^2 = 4.80, df = 1, P = 0.03, I^2 = 79%; Figure 3E). Etoricoxib 120 mg qd had a shorter time to onset of therapeutic effect than diclofenac 75 mg qd (SMD: −0.94, 95% CI: −1.33, −0.55) [35].

Comparative efficacy of COXIBs

With regard to the pain Likert scale score, etoricoxib 120 mg qd was better than meloxicam 15 mg qd (SMD: −0.56, 95% CI: −1.10, −0.02); there was marked heterogeneity among the included studies in this regard (χ^2 = 10.16, df = 2, P = 0.006, I^2 = 80%; Figure 4A). In terms of

the effect on the pain VAS score, etoricoxib was generally better than the other two COXIBs (SMD: −2.82, 95% CI: −4.01, −1.62); there was marked heterogeneity among the included studies in this respect (χ^2 = 106.63, df = 5, P<0.001, I^2 = 95%). Subgroup analysis revealed better efficacy of etoricoxib 120 mg qd compared to celecoxib 200 mg tid (SMD: −2.36, 95% CI: −3.36, −1.37), but comparable to meloxicam 15 mg qd (SMD: −4.02, 95% CI: −10.28, 2.24; Figure 4B). Moreover, the onset time for etoricoxib 120 mg qd was significantly shorter than that for meloxicam 15 mg qd (SMD: −1.57, 95%CI: −2.07, −1.08) [20].

Patients receiving etoricoxib 120 mg qd were more likely to achieve clinical improvement compared with those receiving celecoxib 200 mg bid (OR: 4.84, 95% CI: 2.19, 10.72; Figure 5A). Besides , a greater proportion of patients who received etoricoxib 120 mg qd (89.47%) experienced improvement in clinical symptoms compared to those who received celecoxib 200 mg bid (71.05%) [24]. However, etoricoxib 120 mg qd was comparable to celecoxib 200 mg bid in terms of C-reactive protein (SMD: −1.98, 95% CI: −4.90, 0.95; Figure 5B).

Discussion

Main findings

In this meta-analysis, we evaluated the clinical outcomes of patients with acute gout treated with various NSAIDs. The results showed comparable performance of COXIBs and traditional NSAIDs with regard to the effect on the pain Likert score and pain VAS scores; however, COXIBs showed better efficacy than traditional NSAIDS with regard to several secondary outcomes, including the response rate and the investigator's global assessment of response. Therefore, we were unable to conclude that COXIBs clearly outperform the traditional NSAIDS. However, we found that etoricoxib 120 mg qd offers a clear advantage over celecoxib 200 mg tid

in terms of pain VAS scores and clinical improvement, and over meloxicam in terms of pain Likert scale score.

We exclusively assessed evidence from available studies that compared the efficacy of currently used non-selective NSAIDs and COXIBs in patients with acute gout. Our meta-analysis incorporated all of the clinical outcomes of the available studies; however, most outcomes showed no difference, and several outcomes revealed that COXIBs performed better. Therefore, there was no conclusive evidence of the comparative efficacy of non-selective NSAIDs and COXIBs. However, our study revealed that etoricoxib may perform better in the management of patients with acute gout than either celecoxib or meloxicam. With regard to Likert scores, COXIBs showed better efficacy than non-selective NSAIDs; however, a subgroup analysis revealed no significant difference between the two groups of drugs. The inconsistency in the results between the pooled and subgroup analyses may be attributable to significant heterogeneity between subgroups, and we draw our conclusions on the basis of the results of subgroup analyses.

Implication and strength

Our study has clinical implications. The prevalence of gout has increased in both developed and developing countries, presumably due to lifestyle changes [45]. Of all the 291 conditions studied in the GBD 2010 study, gout ranked 138th in terms of disability, and 173rd in terms of overall burden [2]. NSAIDs have gradually been established as the first-line therapeutic option for acute gout [5, 7, 8]; therefore, a comparison of the efficacy of NSAIDs is of much clinical relevance. Finally, we concluded that COXIBs are comparable to traditional NSAIDs with regard to pain relief, but are preferable to traditional NSAIDs in terms of clinical symptoms and investigator's global assessment of response. Etoricoxib may be the best option when COXIBs are indicated.

Our study has considerable strengths. We designed the meta-analysis according to the PRISMA guidelines and took meticulous care to minimize errors and ensure the validity of findings from all relevant studies. Our meta-analysis thoroughly addresses two key questions – that is, the comparative efficacy of traditional NSAIDs and COXIB and the comparative efficacy of the three COXIBs in terms of various clinical outcomes. Our findings may facilitate the selection of drugs for acute gout in clinical settings.

Safety

Several studies have revealed that COXIBs are preferable to traditional non-selective NSAIDs in terms of safety in patients with acute gout [13, 14] or other pain conditions [46]. Moreover, analysis of VIGOR and two capsule endoscopy studies showed significantly less distal gastrointestinal blood loss with COXIBs than with non-selective NSAIDs [47]. The rates of upper gastrointestinal adverse clinical events were lower with etoricoxib than with diclofenac [48]. When compared with traditional NSAIDs at standard dosages, celecoxib -at dosages greater than those indicated clinically - was associated with a lower incidence of symptomatic ulcers, ulcer-related complications, as well as other clinically important toxic effects [49]. Gout and renal disorders are common comorbidities affecting elderly adults, leading to frequently administration of concomitant analgesics, especially NSAIDs. Several studies showed that COXIBs have a better or similar renal safety profile than ibuprofen or other traditional NSAIDs [50, 51]. It may be hypothesized that COXIBs may decrease renal adverse effects relative to nonselective NSAIDs, as the kidney and vasculature express both COX-1 and -2. However, COXIBs, similar to traditional NSAIDs, must be used cautiously in patients with predisposing renal diseases [52].

The currently prevalent belief is that both traditional NSAIDs and COXIBs are associated with an increased cardiovascular risk, with the probable exception of naproxen [53]. However, the landmark PRECISION study seemingly refutes this widely held idea [54, 55]. Also, there is no clear-cut conclusion of whether COXIBs pose a higher cardiovascular risk when comparing traditional NSAIDs. The MEDAL study revealed similar rates of thrombotic cardiovascular events between long-term etoricoxib and diclofenac treatment in patients with arthritis [48]. In addition to efficacy, care must be exercised to consider gastrointestinal, cardiovascular, and renal conditions when choosing between NSAIDs and COXIBs.

Colchine and naproxen

The study focuses on NSAIDs for acute flares. Colchicine and corticosteroids are also the main therapeutic options; however, owing to their different mechanisms of action and absence of direct comparative evidence, these drugs were excluded from the purview of this study. Several trials that compared traditional NSAIDS with oral corticosteroids (another recommended first-line options for acute flares) were excluded since these trials did not qualify the inclusion criteria for the present study. Naproxen is a traditional NSAID that is used worldwide; however, it was not included in the meta-analysis due to the absence of trials comparing naproxen with COXIBs. In a double-blind, randomized trial in patients with crystal-proven gout, naproxen was found to be as effective as prednisolone for acute flares [56]. Similarly, a double-blind, parallel-group study revealed comparable efficacy of etodolac and naproxen in alleviating symptoms of acute gouty arthritis [57]. Naproxen and phenylbutazone also showed comparable efficacy in the management of acute gout, with few and relatively mild adverse events [58].

Limitations

Nevertheless, there are several limitations of our study. First, a relatively strict search strategy was used in the present study to achieve our goal; this limited the number of included RCTs. There are relatively few recent RCTs that investigated the effect of NSAIDs in acute gout. Moreover, most of these were published in Chinese. The relatively small number of studies and the small sample size in the studies included in the meta-analysis are the major limitations of our study. We did not evaluate the funnel plots as the number of studies was less than 10 for all outcome measures. Besides, most of the included studies published in Chinese were of low quality. Moreover, confounding factors such as the underlying disease and the use of other drugs may have affected the analysis. However, our review emphasizes the potential importance of COXIBs for acute gout. Given the clinical importance and acute nature of a gout flare, more trials focusing on clinically relevant outcomes are essential, especially in those patients who really need care.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Authors' contributions

MTL, CY, and XFZ were responsible for the conception and design of the study. MTL and CY did the analysis and interpreted the analysis. MTL and CY wrote the first draft of the manuscript. All authors critically revised the manuscript and have approved the final version.

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Conflict of Interest

The authors declare that they have no conflict of interests.

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Table

Table 1. Main characteristics of the studies included in this meta-analysis

Author	Year	Language	Treatment arms	N	Male	Age	Follow-up (d)
Schumacher H	2002	English	Etoricoxib 120 mg qd	75	73	48.5 (13.29)	8
			Indomethacin 50 mg tid	75	69	49.5 (13.71)	
Rubin B	2004	English	Etoricoxib 120 mg qd	103	98	51.1 (13)	8
			Indomethacin 50 mg tid	86	79	52.2 (12)	
Ye Q	2010	Chinese	Etoricoxib 120 mg qd	40	33	45.12 (12.48)	7
			Diclofenac 75 mg qd	35	32	38.20 (15.51)	
Zhang J	2012	Chinese	Etoricoxib 120 mg qd	48	48	63.4 (12)	8
			Meloxicam 15 mg qd	36	36	64.1 (11)	
Gao Q	2013	Chinese	Etoricoxib 120 mg qd	140	89	41.78 (12.57)	7
			Diclofenac 75 mg bid	140	92	42.48 (13.23)	
Hong J	2013	Chinese	Etoricoxib 120 mg qd	50	38	42.1 (9.8)	7
			Celecoxib 200 mg tid	50	40	41.5 (7.8)	
Li T	2013	English	Etoricoxib 120 mg qd	89	85	52 (15)	5
			Indomethacin 75 mg bid	89	81	53 (14)	
Guo D	2014	Chinese	Etoricoxib 120 mg qd	60	96	44.3 (15.6)	8
			Meloxicam 15 mg qd	60			
Guo M	2014	Chinese	Etoricoxib 120 mg qd	57	56	40.52 (11.27)	5
			Diclofenac 75 mg qd	56	54	43.03 (13.02)	
Lu J	2014	Chinese	Etoricoxib 120 mg qd	95	89	48.9 (2.3)	7
			Diclofenac 50 mg tid	51	49	46.7 (3.4)	
Kuang L	2015	Chinese	Etoricoxib 120 mg qd	40	29	42.8 (10.3)	7
			Diclofenac 50 mg tid	40	31	43.7 (11.2)	
Liu C	2015	Chinese	Etoricoxib 120 mg qd	32	21	45 (3.74)	7
			Meloxicam 15 mg qd	32	13	44 (3.53)	
Xia H	2015	Chinese	Etoricoxib 120 mg qd	40	27	50.17 (25.13)	7
			Celecoxib 200 mg tid	40	25	50.09 (25.34)	
Zhu H	2015	Chinese	Etoricoxib 120 mg qd	50	48	46.3 (6.9)	7

			Diclofenac 50 mg tid	50	49	46.5 (6.1)	
Cui M	2016	Chinese	Diclofenac 100 mg qd	12	11	41.5 (3.8)	5
			Celecoxib 200 mg qd	12	10	43.2 (4.2)	
Li S	2016	Chinese	Etoricoxib 120 mg qd	47	22	41.8 (11.3)	5
			Diclofenac 75 mg qd	47	21	40.5 (10.1)	
Ming H	2016	Chinese	Etoricoxib 120 mg qd	38	22	52.64 (12.28)	7
			Celecoxib 200 mg bid	38	23	52.79 (12.35)	
Pan Q	2016	Chinese	Etoricoxib 120 mg qd	68	126	43.2 (13.6)	7
			Diclofenac 50 mg tid	68			
Zhou S	2016	Chinese	Etoricoxib 120 mg qd	28	16	53.37 (11.32)	7
			Celecoxib 200 mg tid	28	14	52.13 (10.13)	
Li Y	2017	Chinese	Etoricoxib 120 mg qd	44	68	44.67 (14.99)	8
			Meloxicam 15 mg qd	44			
Gao C	2018	Chinese	Celecoxib 200 mg bid	40	29	58.4 (2. 8)	7
			Etoricoxib 120 mg qd	40	30	56.7 (2. 2)	
Lan T	2018	Chinese	Celecoxib 200 mg bid	30	24	52.21 (1.25)	7
			Etoricoxib 120 mg qd	30	25	52.26 (1.24)	
Sheng J	2019	Chinese	Etoricoxib 120 mg qd	42	82	39.17 (10.28)	7
			Diclofenac 75 mg qd	38			
Wu L	2019	Chinese	Etoricoxib 120 mg qd	30	23	45.98 (6.65)	7
			Meloxicam 15 mg qd	30	21	45.21 (7.20)	

N = number, age presented as mean (standard deviation).

Figure legends

Figure 1. Schematic illustration of literature search and study selection

Figure 2. Forest plots of primary outcomes: COXIBs versus traditional NSAIDs.

Pain Likert scale for days 2–8) (A); pain VAS score for days 2–8 (B).

VAS, visual analog scale

Figure 3. Forest plots of secondary outcomes: COXIBs versus traditional NSAIDs

Response rate for days 2–8 (A); C-reactive protein (B); patient's global assessment (C); investigator's global assessment (D); and inflammatory swelling (E)

Figure 4. Forest plots of primary outcomes: comparative efficacy of various COXIBs

Pain Likert scale score for days 2–8 (A); Pain VAS score for days 2–8 (B).

VAS, visual analog scale

Figure 5. Forest plots of secondary outcomes: comparative efficacy of various COXIBs

Response rate for days 2–8 (A); C-reactive protein (B)

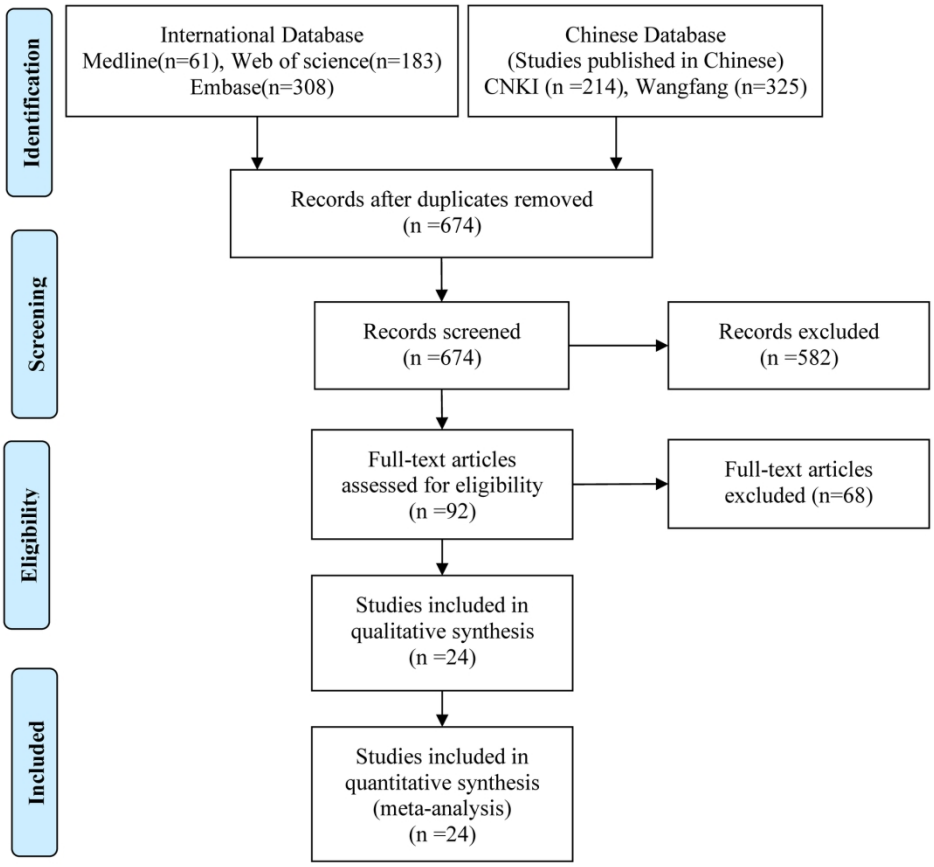

Figure 1. Schematic illustration of literature search and study selection

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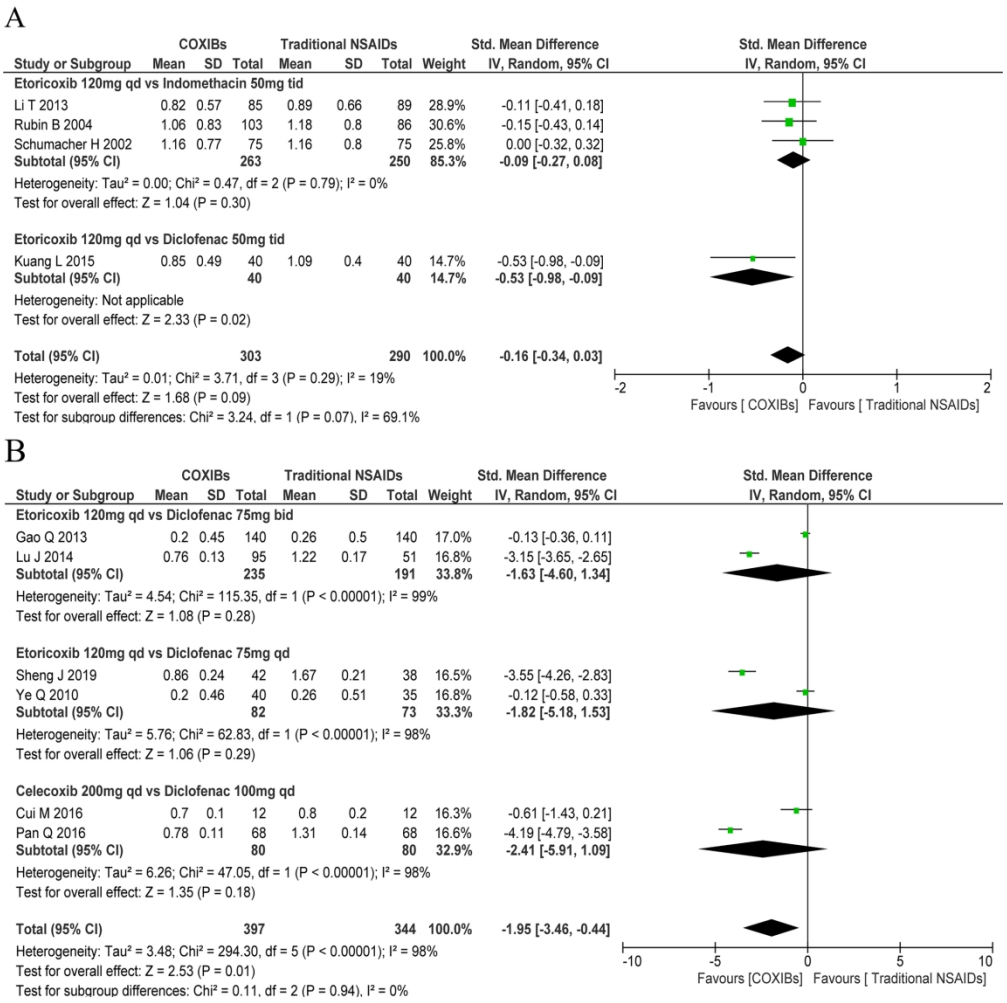

Figure 2. Forest plots of primary outcomes: COXIBs versus traditional NSAIDs. Pain Likert scale for days 2–8) (A); pain VAS score for days 2–8 (B). VAS, visual analog scale

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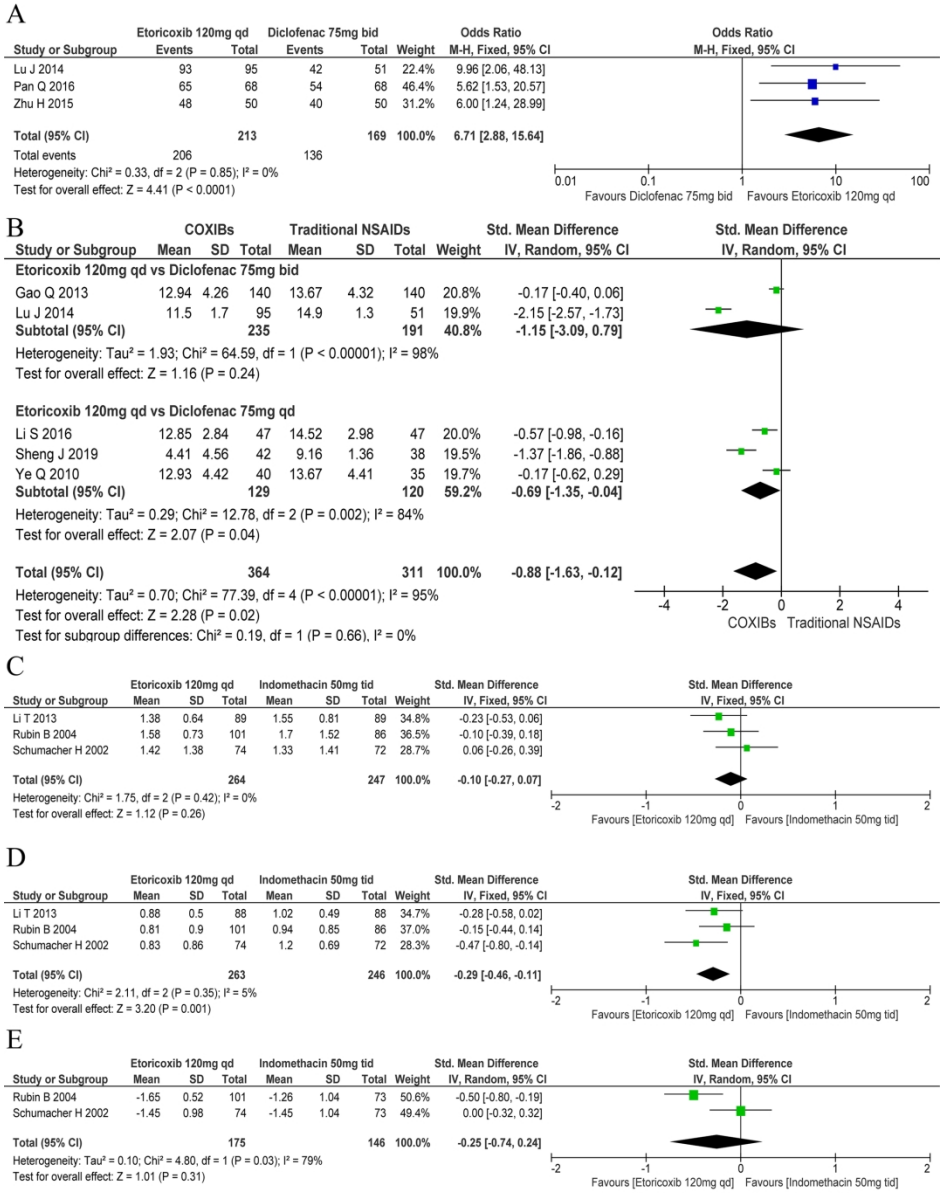

Figure 3. Forest plots of secondary outcomes: COXIBs versus traditional NSAIDs Response rate for days 2–8 (A); C-reactive protein (B); patient's global assessment (C); investigator's global assessment (D); and inflammatory swelling (E)

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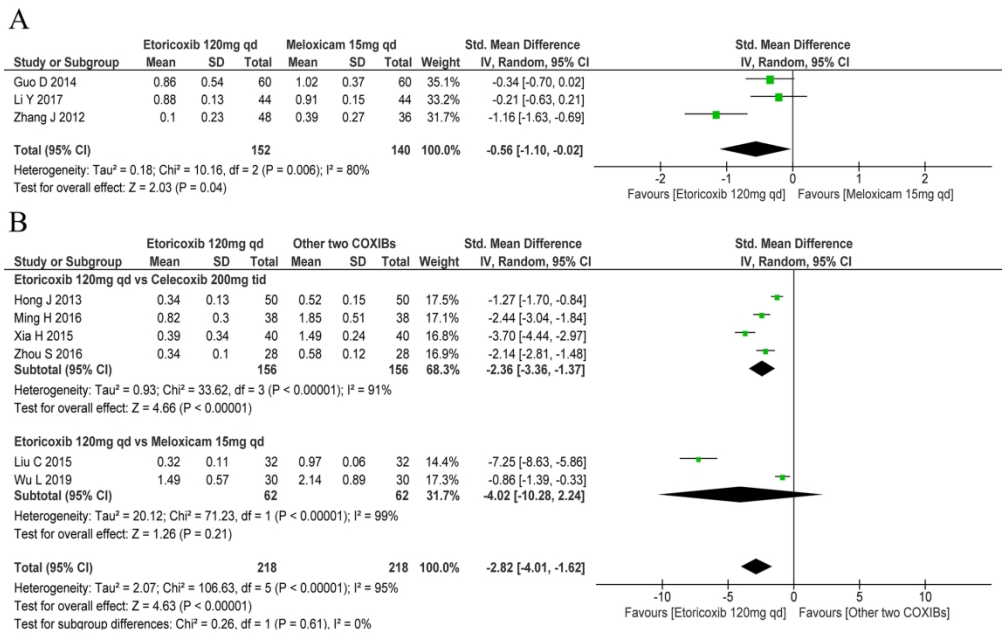

Figure 4. Forest plots of primary outcomes: comparative efficacy of various COXIBs Pain Likert scale score for days 2–8 (A); Pain VAS score for days 2–8 (B). VAS, visual analog scale

190x120mm (300 x 300 DPI)

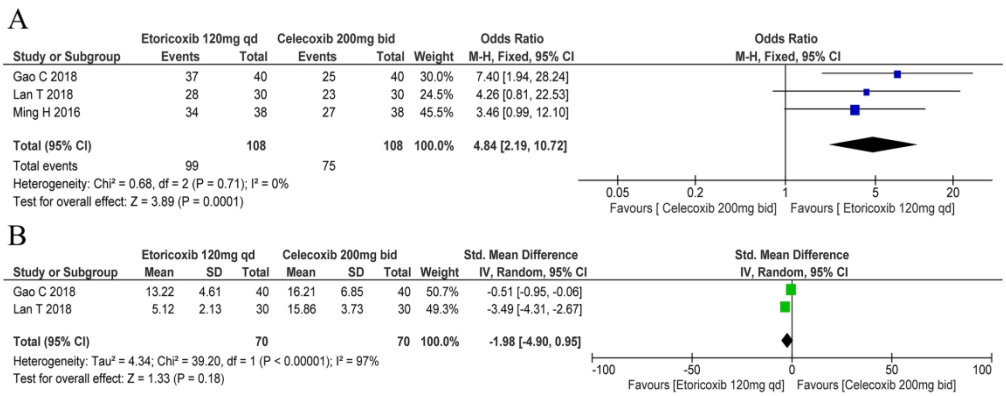

Figure 5. Forest plots of secondary outcomes: comparative efficacy of various COXIBs Response rate for days 2–8 (A); C-reactive protein (B)

190x77mm (300 x 300 DPI)

Supplementary Material for: "Comparative efficacy of traditional non-selective NSAIDs and selective cycloxygenase-2 inhibitor in patients with acute gout: a systematic review and meta-analysis"

Journal: BMJ Open

Authors: Mengtao Li, PhD, Chen Yu, PhD, Xiaofeng Zeng, PhD

Corresponding author: Prof Xiaofeng Zeng, Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Table of content

International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY PROTOCOL

To cite: Li et al. Comparative efficacy of traditional non-selective NSAIDs and selective cycloxygenase-2 inhibitor in patients with acute gout: a systematic review and meta-analysis. Inplasy protocol 20204001925. doi: 10.37766/inplasy2020.4.0025

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Corresponding author:
Xiaofeng Zeng

zengxfpumc@163.com

Author Affiliation:
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The authors declare no conflict of interest.

Comparative efficacy of traditional non-selective NSAIDs and selective cycloxygenase-2 inhibitor in patients with acute gout: a systematic review and meta-analysis

Mengtao Li[1], Chen Yu[2], Xiaofeng Zeng[3].

Review question / Objective: **To assess the comparative efficacy of traditional non-steroidal anti-inflammatory drugs and selective cycloxygenase-2 inhibitor (COXIB) for patients with acute gout.**
Condition being studied: **Acute gout most frequently begins with the involvement of a single joint in the lower limbs (85–90% of cases) – usually, the first metatarsophalangeal joint. The management of acute gout includes rapid treatment of acute flares and effective long-term therapy. The main therapeutic options for an acute flare are colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids. The deposition of monosodium urate microcrystals in the articular and periarticular tissues elicits acute or chronic inflammatory responses that are known as gouty arthritis.There is evidence that monosodium urate microcrystals induce the production of cyclooxygenase-2 (COX-2) in human monocytes. NSAIDs include traditional NSAIDs and selective COX-2 inhibitors (COXIBs) – the former inhibits both COX-1 and -2 enzymes whereas the latter specifically antagonizes COX-2. The efficacy of COXIBs is comparable to that of traditional NSAIDs; however, COXIBs have fewer adverse effects, particularly gastrointestinal adverse effects.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 April 2020 and was last updated on 04 April 2020 (registration number INPLASY202040025).

INTRODUCTION

Review question / Objective: **To assess the comparative efficacy of traditional non-steroidal anti-inflammatory drugs and selective cycloxygenase-2 inhibitor (COXIB) for patients with acute gout.**

Condition being studied: **Acute gout most frequently begins with the involvement of a single joint in the lower limbs (85–90% of cases) – usually, the first metatarsophalangeal joint. The management of acute gout includes rapid treatment of acute flares and effective long-term therapy. The main therapeutic options for an acute flare are colchicine,**

Figure S1 International Platform of Registered Systematic Review and Meta-analysis (INPLASY) Protocol (continued)

non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids. The deposition of monosodium urate microcrystals in the articular and periarticular tissues elicits acute or chronic inflammatory responses that are known as gouty arthritis.There is evidence that monosodium urate microcrystals induce the production of cyclooxygenase-2 (COX-2) in human monocytes. NSAIDs include traditional NSAIDs and selective COX-2 inhibitors (COXIBs) – the former inhibits both COX-1 and -2 enzymes whereas the latter specifically antagonizes COX-2. The efficacy of COXIBs is comparable to that of traditional NSAIDs; however, COXIBs have fewer adverse effects, particularly gastrointestinal adverse effects.

METHODS

Participant or population: Adult patients (age≥18 years) with a diagnosis of acute gout defined by the American Rheumatology Association diagnostic criteria.

Intervention: Traditional non-selective NSAIDs or selective cycloxygenase-2 inhibitor.

Comparator: Traditional non-selective NSAIDs or selective cycloxygenase-2 inhibitor.

Study designs to be included: Randomized controlled trial.

Eligibility criteria: Trials that compared COXIBs with traditional non-selective NSAIDs or compared the various COXIBs.

Information sources: Biomedical databases, including Medline, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang Data

Main outcome(s): Primary outcomes: Pain assessed using a visual analog scale (VAS) score and 5-point Likert scale for days 2–8. Secondary outcomes were: i) response rate (defined as the proportion of patients who achieved improvement in clinical symptoms) for days 2–8; ii) onset of efficacy (hours); iii) post-treatment serum C-reactive protein level; iv) patient's global assessment of response; v) investigator's global assessment of response; and vi) inflammatory swelling.

Quality assessment / Risk of bias analysis: Two authors assessed the risk of bias of the included studies using the methods recommended by the Cochrane Collaboration for the following items. We scored each study on six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias. The risk of bias was graded as high, low, or unclear risk of bias. Furthermore, the quality of evidence across pooled studies (risk of bias, inconsistency, indirectness, imprecision, and publication bias) was assessed by two researchers as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and using the online version of GRADEpro GDT software (www.gradepro.org, McMaster University, 2016). Disagreements were resolved, first, by discussion and, then, by consulting a third senior author for arbitration.

Strategy of data synthesis: Traditional meta-analyses were conducted for studies that directly compared COXIBs and traditional non-selective NSAIDs and those that compared between etoricoxib, celecoxib, and meloxicam. Odds ratios (OR) and standardized mean difference (SMD) with corresponding 95% confidence intervals (CIs) were used for dichotomous and continuous outcomes, respectively.

Subgroup analysis: Comparative efficacy of traditional non-selective NSAIDs and COXIBs. Comparative efficacy of COXIBs

Sensibility analysis: In order to check the stability of the result, sensitivity analysis was performed by sequential delete single study if suitable.

Countries involved: China

Keywords: Acute gout, NSAIDs, selective cycloxygenase-2 inhibitors, efficacy.

Figure S1 International Platform of Registered Systematic Review and Meta-analysis (INPLASY) Protocol

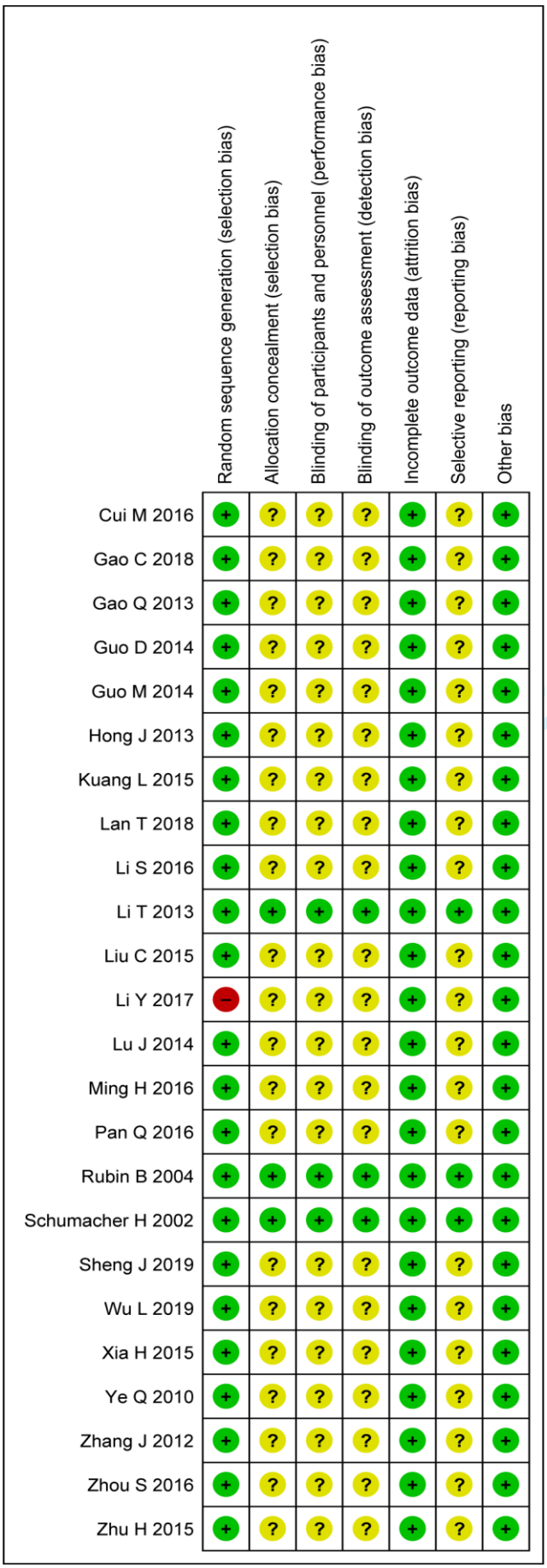

Figure S2. Risk of bias summary

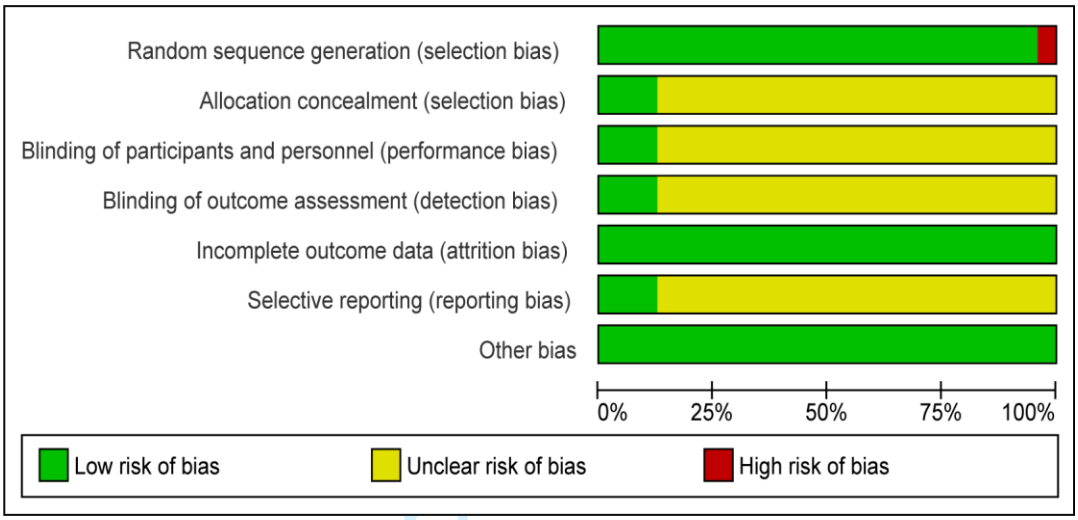

Figure S3. Risk of bias graph

Table S1. Detailed search strategy

PubMed		
Search	Query	Number
#3	Search ((((gout) OR gouty arthritis) OR acute gout)) AND (((Etoricoxib) OR Celecoxib) OR Meloxicam)	61
#2	Search ((gout) OR gouty arthritis) OR acute gout	18847
#1	Search ((Etoricoxib) OR Celecoxib) OR Meloxicam	9404
Web of Science		
# 3	#2 AND #1 Databases = WOS, BIOSIS, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO. Timespan=All years; Search language=Auto	183
# 2	TOPIC: (gout) OR TOPIC: (gouty arthritis) OR TOPIC: (acute gout) Databases = WOS, BIOSIS, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO. Timespan=All years; Search language=Auto	36,548
# 1	TOPIC: (Etoricoxib) OR TOPIC: (Celecoxib) OR TOPIC: (Meloxicam) Databases = WOS, BIOSIS, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO. Timespan=All years; Search language=Auto	19,277
Embase		
# 3	#2 AND #3	308
# 2	'gout'/exp OR gout OR 'gouty arthritis'/exp OR 'gouty arthritis' OR (gouty AND ('arthritis'/exp OR arthritis)) OR 'acute gout'/exp OR 'acute gout' OR (acute AND ('gout'/exp OR gout))	28,967
# 1	'etoricoxib'/exp OR etoricoxib OR 'celecoxib'/exp OR celecoxib OR 'meloxicam'/exp OR meloxicam	29,285
CNKI		
	(依托考昔 and 痛风）OR (塞来昔布 and 痛风) OR (美洛昔康 and 痛风)	214
	(Etoricoxib and Gout) OR (Celecoxib and Gout) OR (Meloxicam and Gout)	214
Wangfang		
	主题:(痛风)*主题:(美洛昔康) Etoricoxib and Gout	97
	主题:(痛风)*主题:(塞来昔布) Celecoxib and Gout	121
	主题:(痛风)*主题:(依托考昔) Meloxicam and Gout	107
	(依托考昔 and 痛风）OR (塞来昔布 and 痛风) OR (美洛昔康 and 痛风)	325
	(Etoricoxib and Gout) OR (Celecoxib and Gout) OR (Meloxicam and Gout)	325

Table S2: Summary of Findings table: COXIBs vs traditional NSAIDs for acute gout

COXIBs compared to traditional NSAIDs for acute gout

Patient or population: acute gout

Setting:

Intervention: COXIBs

Comparison: traditional NSAIDs

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with traditional NSAIDs	Risk difference with COXIBs
Pain Likert scale	593 (4 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.15 SD lower** (0.31 lower to 0.01 higher)
Pain Likert scale - Etoricoxib 120 mg qd vs Indomethacin 50 mg tid	513 (3 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.09 lower** (0.27 lower to 0.08 higher)
Pain Likert scale - Etoricoxib 120 mg qd vs Diclofenac 75 mg qd	80 (1 RCT)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.53 lower** (0.98 lower to 0.09 lower)
Pain VAS scale	741 (6 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **1.95 SD lower** (3.46 lower to 0.044 lower)
Pain VAS scale - Etoricoxib 120 mg qd vs Diclofenac 75 mg bid	426 (2 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **1.63 SD lower** (460 lower to 1.34 higher)

COXIBs compared to traditional NSAIDs for acute gout

Patient or population: acute gout

Setting:

Intervention: COXIBs

Comparison: traditional NSAIDs

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with traditional NSAIDs	Risk difference with COXIBs
Pain VAS scale - Etoricoxib 120 mg qd vs Diclofenac 75 mg qd	155 (2 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **1.82 SD lower** (5.18 lower to 1.53 higher)
Pain VAS scale - Celecoxib 200 mg qd vs Diclofenac 100 mg qd	160 (2 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **2.41 lower** (5.91 lower to 1.09 higher)
Response rate	382 (3 RCTs)	⨁⨁⨁⨁ HIGH	**OR 6.71** (2.88 to 15.64)	805 per 1,000	**160 more per 1,000** (118 more to 180 more)
C reactive protein	674 (5 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **0.88 SD lower** (1.63 lower to 0.12 lower)
C reative protein-Pain VAS scale - Etoricoxib 120 mg qd vs Diclofenac 75 mg bid	426 (2 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **1.15 SD lower** (3.09 lower to 0.79 higher)

COXIBs compared to traditional NSAIDs for acute gout

Patient or population: acute gout

Setting:

Intervention: COXIBs

Comparison: traditional NSAIDs

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with traditional NSAIDs	Risk difference with COXIBs
C reative protein-Pain VAS scale - Etoricoxib 120 mg qd vs Diclofenac 75 mg qd	249 (3 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.69 SD lower** (1.35 lower to 0.04 lower)
Patient's global assessment of response	511 (3 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.1 SD lower** (0.27 lower to 0.07 higher)
Investigator's global assessment of response	509 (3 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.29 SD lower** (0.46 lower to 0.11 lower)
Inflammation swelling	321 (2 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.25 lower** (0.74 lower to 0.24 higher)
Onset of efficacy(h) - Etoricoxib 120 mg qd vs Diclofenac 75 mg qd	113 (1 RCT)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.94 lower** (1.33 lower to 0.55 lower)

COXIBs compared to traditional NSAIDs for acute gout

Patient or population: acute gout

Setting:

Intervention: COXIBs

Comparison: traditional NSAIDs

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with traditional NSAIDs	Risk difference with COXIBs

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **SMD:** Standardised mean difference; **OR:** Odds ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table S3: Summary of Findings table: one COXIB vs another COXIB for acute gout

Another COXIBs compared to one COXIBs for acute gout

Patient or population: acute gout

Setting:

Intervention: another COXIBs

Comparison: one COXIBs

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with one COXIBs	Risk difference with another COXIBs
Pain Likert scale	292 (3 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.56 lower** (1.1 lower to 0.02 lower)
Pain VAS scale	436 (6 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **2.82 SD lower** (4.01 lower to 1.62 lower)
Pain VAS scale - Etoricoxib 120 mg qd vs Celecoxib 200 mg tid	312 (4 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **2.36 lower** (3.36 lower to 1.37 lower)
Pain VAS scale - Etoricoxib 120 mg qd vs Meloxicam 15 mg qd	124 (2 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **4.02 SD lower** (10.28 lower to 2.24 higher)
Response rate-Etoricoxib 120 mg qd vs Celecoxib 200 mg bid	216 (3 RCTs)	⊕⊕⊕⊕ HIGH	**OR 4.84** (2.19 to 10.72)	694 per 1,000	**222 more per 1,000** (138 more to 266 more)

Another COXIBs compared to one COXIBs for acute gout

Patient or population: acute gout

Setting:

Intervention: another COXIBs

Comparison: one COXIBs

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with one COXIBs	Risk difference with another COXIBs
C-reactive protein	140 (2 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **1.98 SD lower** (4.9 lower to 0.95 higher)
Onset of efficacy(h)-Etoricoxib 120 mg qd vs Meloxicam 15 mg qd	84 (1 RCT)	⨁⨁⨁⨁ HIGH	-	-	SMD **1.57 lower** (2.07 lower to 1.08 lower)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **SMD:** Standardised mean difference; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	#1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	#2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	#5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	#5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	#6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	#6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	#6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	#7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	#7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	#7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	#8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	#8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	#8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	#8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	#8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	#9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	#9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	#10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	#10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	#10-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	#10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	#10-12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	#12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	#15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	#15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	#16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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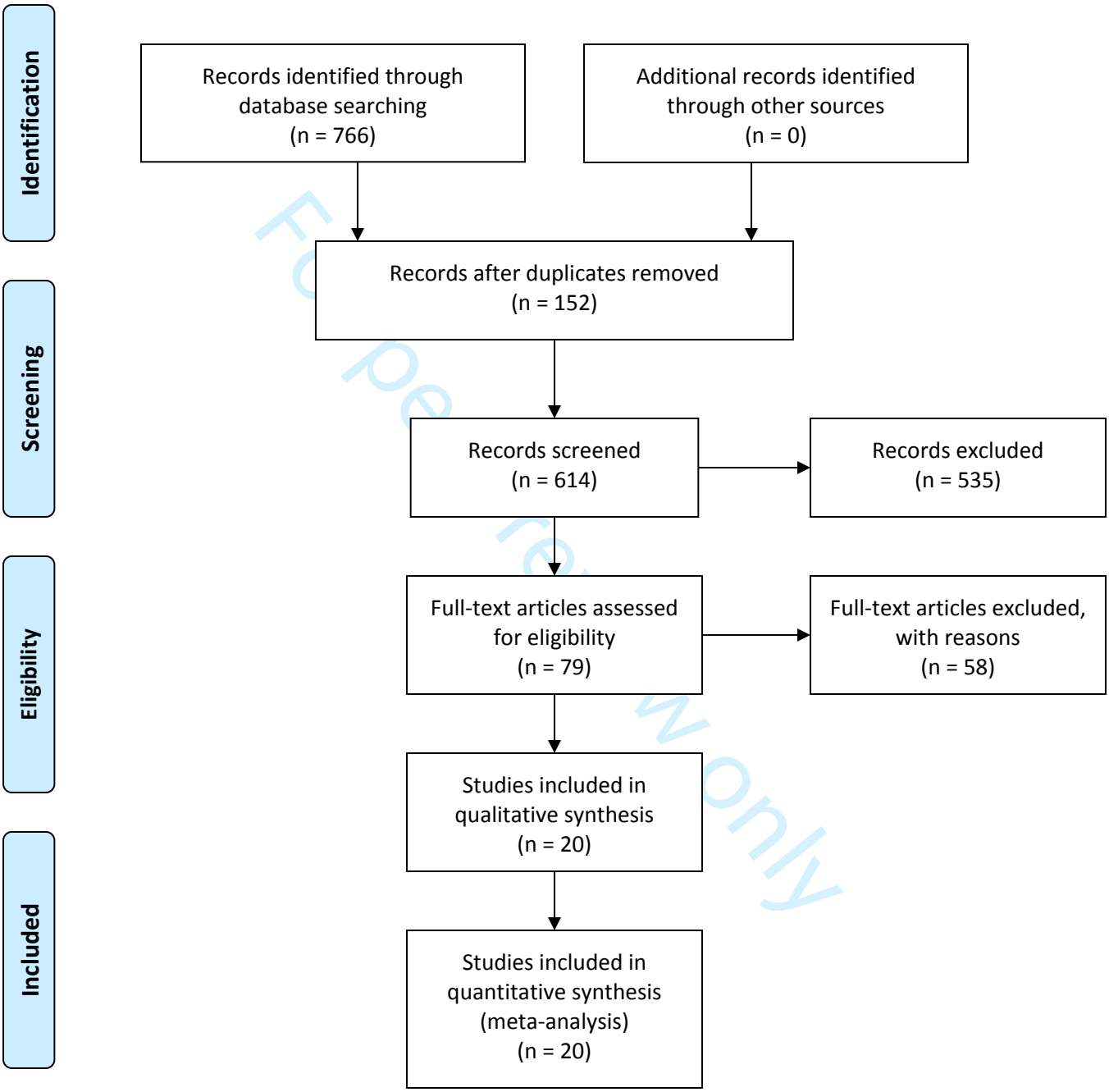
PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Comparative efficacy of traditional non-selective NSAIDs and selective cycloxygenase-2 inhibitors in patients with acute gout: a systematic review and meta-analysis

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Comparative efficacy of traditional non-selective NSAIDs and selective cycloxygenase-2 inhibitors in patients with acute gout: a systematic review and meta-analysis

Running title: NSAIDs for acute gout

Mengtao Li, PhD[1], Chen Yu, PhD[1], Xiaofeng Zeng, PhD[1*]

[1]Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

***Address correspondence and reprint requests to:**

Xiaofeng Zeng, PhD

Address: Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China

E-mail: zengxfpumc@163.com

Tel: +8613501069845

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Abstract

Objective: To assess the comparative efficacy of traditional non-steroidal anti-inflammatory drugs and selective cycloxygenase-2 inhibitors (COXIBs) in patients with acute gout.

Design: Systematic review and meta-analysis.

Data sources: Medline, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang Data published as of 04 April 2020.

Methods: We performed meta-analysis of randomized controlled trials (RCTs) of traditional non-selective NSAIDs versus COXIBs and RCTs of various COXIBs in patients with acute gout. The main outcome measures were mean change in pain visual analog scale (VAS) score and 5-point Likert scale score on days 2–8.

Results: Twenty-four trials involving five drugs were evaluated. For pain Likert scale, etoricoxib was comparable to indomethacin (SMD: -0.09, 95% CI: -0.27, 0.08) but better than diclofenac 50 mg tid (SMD: -0.53, 95% CI: -0.98, -0.09). Regarding pain VAS score, etoricoxib was comparable to diclofenac 75 mg bid (SMD: -1.63, 95% CI: -4.60, 1.34) and diclofenac 75 mg qd (SMD: −1.82, 95% CI: −5.18, 1.53), while celecoxib was comparable to diclofenac 100 mg qd (SMD: -2.41, 95% CI: -5.91, 1.09). Etoricoxib showed similar patients' global assessment of response (SMD: -0.10, 95% CI: -0.27, 0.07) and swollen joint count (SMD: -0.25, 95% CI: -0.74, 0.24), but better investigator's global assessment of response (SMD: -0.29, 95% CI: -0.46, -0.11) compared with indomethacin. Etoricoxib showed more favorable pain VAS score than celecoxib (SMD: -2.36, 95% CI: -3.36, -1.37), but was comparable to meloxicam (SMD: −4.02, 95% CI: −10.28, 2.24). Etoricoxib showed more favorable pain Likert scale than meloxicam (SMD: -0.56, 95%CI: -1.10, -0.02). Etoricoxib 120 mg qd was more likely to achieve clinical improvement than celecoxib 200 mg bid (OR: 4.84, 95% CI: 2.19, 10.72).

Conclusion: Although COXIBs and traditional non-selective NSAIDs may be equally beneficial in terms of pain relief, COXIBs (especially etoricoxib) may confer a greater benefit.

Keywords: acute gout, NSAIDs, selective cycloxygenase-2 inhibitors, efficacy

Strengths and limitations of this study

- We evaluated data from randomized controlled trials that compared the efficacy of traditional non-steroidal anti-inflammatory drugs and selective cycloxygenase-2 inhibitors in patients with acute gout.
- A stringent search strategy was employed to minimize the influence of publication bias.
- Most of the included studies were published in Chinese, although no language restriction was imposed during literature search.
- Inclusion of relatively few trials, small sample size in the included trials, and generally low quality are the main limitations.

Introduction

Gout is a chronic disease characterized by the deposition of monosodium urate crystals in various tissues as a result of elevated serum urate concentration [1]. According to the Global Burden of Disease (GBD) 2010 study, the estimated global prevalence of gout is 0.08% and there is an increasing trend in the burden of gout [2]. Worldwide, the reported prevalence of gout ranges from 0.1% to approximately 10%, and the incidence rates range from 0.3 to 6 cases per 1,000 person-years [3]. The prevalence and incidence of gout is highly variable across various regions of the world. In general, the prevalence of gout in developed countries is higher than that in developing countries [3]. There is no national epidemiological data on the prevalence of gout in China; however, based on data from different regions at different time-points, the estimated prevalence of gout in China is 1%–3%; in addition, the prevalence is steadily increasing every year [4].

Acute gout typically begins with the involvement of a single joint in the lower limb (85–90% of cases) – usually the first metatarsophalangeal joint [1]. The management of acute gout includes rapid treatment of acute flares and long-term maintenance therapy [5-9]. The main therapeutic options for an acute flare are colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids [5]. The deposition of monosodium urate microcrystals in the articular and periarticular tissues elicits an acute or chronic inflammatory response, a condition referred to as gouty arthritis [1, 10, 11]. There is evidence that monosodium urate microcrystals induce the production of cyclooxygenase-2 (COX-2) in human monocytes [12]. NSAIDs include traditional NSAIDs and selective COX-2 inhibitors (COXIBs) – the former inhibits both COX-1 and -2 enzymes whereas the latter specifically antagonizes COX-2. The efficacy of COXIBs is

comparable to that of traditional NSAIDs; however, COXIBs have fewer adverse effects, particularly gastrointestinal adverse effects [13].

In the past decade, NSAIDs have been emphasized as the first-line option for the management of acute gout, in accordance with the 2006 and 2016 European League Against Rheumatism (EULAR) recommendations [5, 8] and American College of Rheumatology guidelines [6, 7]. A meta-analysis found no significant difference between traditional NSAIDs and COXIBs with regard to the pain score, inflammation score, change in patient's global assessment from baseline, and the health-related quality of life (HRQoL) [13]. Another meta-analysis indicated that the efficacy of etoricoxib in acute gout is similar to that of indomethacin and diclofenac; however, etoricoxib showed better performance than indomethacin in terms of the investigator's global assessment of response to therapy and better analgesic efficacy in comparison to diclofenac [14]. Two meta-analyses have assessed whether COXIBs are more effective against acute gout than traditional NSAIDs [13, 14]. However, comparison between celecoxib and diclofenac [15] was not included.

Given the increasing use of COXIBs and the relatively large number of recent trials, evaluation of the comparative efficacy of various COXIBs is a key imperative – both from the clinical and policy perspectives. After the withdrawal of rofecoxib, lumiracoxib, and valdecoxib, three COXIBs are currently used in clinical practice (etoricoxib, celecoxib, and meloxicam). Meloxicam, an agent synthesized as a traditional NSAID, has a selective inhibitory effect against COX-2 [16]. In four studies, etoricoxib showed better efficacy than meloxicam [17-20]; in another four studies, etoricoxib showed better efficacy than celecoxib [21-24]. Moreover, many studies published in Chinese were not included in previous meta-analyses. Therefore, we conducted a

meta-analysis to provide an updated picture of the comparative clinical efficacy of traditional non-selective NSAIDs and COXIBs, as well as that of the three COXIBs in patients with acute gout.

Materials and methods

Literature strategy

Biomedical databases, including Medline (Pubmed), Web of Science, Embase, China National Knowledge Infrastructure (CNKI), and Wanfang Data were searched for randomized controlled trials (RCTs; published as of April 2018) that investigated the comparative efficacy of traditional non-selective NSAIDs and COXIBs or that of the three COXIBs in patients with acute gout (Table S1). The key words used were: "selective cyclooxygenase-2 inhibitors", "COXIBs", "etoricoxib", "celecoxib", "meloxicam", "acute gout", and "randomized controlled trials". The reference lists of the studies, recent reviews, and meta-analyses retrieved were manually screened to identify additional studies. Two authors independently conducted the literature search; disagreements, if any, were resolved by consensus.

Selection criteria

We included RCTs into the meta-analysis if they qualified the following criteria. *Study population*: Adult patients (age≥18 years) with a diagnosis of acute gout defined by the American Rheumatology Association diagnostic criteria [25]. *Study design*: RCTs. *Intervention*: Trials that compared COXIBs with traditional non-selective NSAIDs or compared the various COXIBs. *Comparison*: Comparator treatments included one traditional non-selective NSAID or COXIB. *Primary outcomes*: Pain assessed using a visual analog scale (VAS) score and 5-point Likert scale for days 2–8. *Secondary outcomes* were: i) response rate (defined as the proportion of patients who

achieved improvement in clinical symptoms) for days 2–8; ii) onset of efficacy (hours); iii) post-treatment serum C-reactive protein level; iv) patient's global assessment of response; v) investigator's global assessment of response; and vi) inflammatory swelling. The exclusion criteria were: (i) trials that included a mix of people with acute gout and other causes of musculoskeletal pain, unless the results for the acute gout population could be separately analyzed; (ii) trials that investigated obsolete NSAIDs (e.g., rofecoxib, lumiracoxib, valdecoxib); and (iii) trials that compared between traditional non-selective NSAIDs.

Data collection

The titles and abstracts of articles retrieved on database search were independently screened by two authors to determine the eligibility of the articles according to predetermined selection criteria. The full texts of papers were obtained if more information was required to assess the eligibility for inclusion. Disagreements, if any, were resolved by consensus after review of the full-text article and with the involvement of a third author, if necessary.

Data pertaining to the following variables were independently extracted by two authors using a standardized data collection form: study design, patient characteristics, treatment details, duration of follow-up, and relevant outcome measures. We extracted the raw data (mean and standard deviation for continuous variables, and frequency of events or participants for dichotomous outcomes). Any differences in data extraction were resolved by referring to the original articles or by consulting a third reviewer author, if required.

Risk of bias assessment

Two authors assessed the risk of bias of the included studies using the methods recommended by the Cochrane Collaboration for the following items [26]. We scored each study on six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias. The risk of bias was graded as high, low, or unclear.

Furthermore, the quality of evidence across pooled studies (risk of bias, inconsistency, indirectness, imprecision, and publication bias) was assessed by two researchers as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and using the online version of GRADEpro GDT software (www.gradepro.org, McMaster University, 2016) [27, 28]. Tables of summary of findings were created for every rated outcome in compliance to the Cochrane rules. Disagreements were resolved, first, by discussion and, then, by consulting a third senior author for arbitration.

Statistical analysis

Traditional meta-analyses were conducted for studies that directly compared COXIBs and traditional non-selective NSAIDs and those that compared between etoricoxib, celecoxib, and meloxicam. Odds ratios (OR) and standardized mean difference (SMD) with corresponding 95% confidence intervals (CIs) were used for dichotomous and continuous outcomes, respectively. Heterogeneity was examined by using the Cochran's Q-statistic; *P*-value <0.01 was considered significant. In addition, the I^2 test was used to quantify heterogeneity (range, 0–100%). $P < 0.01$ for Q-test or $I^2 > 50\%$ indicated the existence of heterogeneity among the studies [29]. In case of significant heterogeneity, the random effects model was used; in addition, subgroup analysis was conducted to identify the source of heterogeneity. The Review Manager 5 (RevMan 2014) was used for the meta-analysis.

Patient and Public Involvement

There was no patient or public involvement as this was a database research study.

Results

Characteristics of included studies

Of the 1091 articles retrieved on database search, 456 were excluded after a review of titles and abstracts or full-text articles owing to duplication (n=417) or irrelevant efficacy outcomes or measures (n=650) (Figure 1). Finally, 24 trials involving five drugs and six treatment arms (etoricoxib 120 mg qd, indomethacin 50 mg tid, diclofenac 75 mg bid, diclofenac 100 mg qd, celecoxib 200 mg bid, and meloxicam 15 mg qd), with a combined study population of 2513 patients, were included in the meta-analysis [15, 17-24, 30-44]. Three studies were published in English [30, 31, 34] and 21 in Chinese [15, 17-24, 32, 33, 35-44]. The sample size of the included studies ranged from 12 to 140; three of these trials (12.5%) had less than 50 participants (Table 1).

Quality of included studies

Most of the included studies were rated as being of low quality. All studies [15, 17-24, 32-34, 36-40] published in Chinese had an unclear risk of allocation concealment, blinding of participants and personnel, blinding of outcome assessment, or selective reporting. Three studies showed no risk of bias [30, 31, 34] and one study [19] showed a high risk of random sequence generation (Figure S1, S2).

The quality of evidence was rated as moderate in most comparisons. According to GRADE, the quality of evidence for comparison between traditional NSAIDs and COXIBs was rated as high

for pain on the 5-point Likert scale but moderate for pain on the VAS score (Table S2). However, the quality of evidence for comparison between the three COXIBs was rated as moderate for the pain component of both the 5-point Likert scale and the VAS score (Table S3).

Comparative efficacy of traditional non-selective NSAIDs and COXIBs

The efficacy of COXIBs was comparable to that of the traditional NSAIDs in terms of the 5-point Likert scale (SMD: −0.15, 95% CI: −0.31, 0.01) with mild heterogeneity (χ^2 = 3.71, degrees of freedom [df] = 3, P = 0.29, I^2 = 19.0%; Figure 1B). Subgroup analysis indicated comparable efficacy of etoricoxib 120 mg qd and indomethacin 50 mg tid (SMD: −0.09, 95% CI: −0.27, 0.08) with mild heterogeneity (χ^2 = 0.47, df = 2, P = 0.79, I^2 = 0%). One study showed better efficacy of etoricoxib 120 mg qd versus diclofenac 50 mg tid (SMD: −0.53, 95% CI: −0.98, −0.09; Figure 2A).

In general, COXIBs exhibited better efficacy than traditional NSAIDs in terms of the pain VAS score (SMD: −1.95, 95% CI: −3.46, −0.44), but with significant heterogeneity (χ^2 = 294.30, df = 5, P<0.001, I^2 = 98.0%). However, on subgroup analysis, etoricoxib 120 mg qd showed similar efficacy as diclofenac 75 mg bid [(SMD: −1.63, 95% CI: −4.60, 1.34) with significant heterogeneity (χ^2 = 115.35, df = 1, P<0.001, I^2 = 99.0%)] and diclofenac 75 mg qd [(SMD: −1.82, 95% CI: −5.18, 1.53) with significant heterogeneity (χ^2 = 62.83, df = 1, P<0.001, I^2 = 98.0%)]. Besides, celecoxib 200 mg bid showed comparable effect to that of diclofenac 100 mg qd (SMD: −2.41, 95% CI: −5.91, 1.09) with significant heterogeneity (χ^2 = 47.05, df = 1, P<0.001, I^2 = 98.0%) in regard to the pain VAS score (Figure 2B).

A significantly greater proportion of patients who received etoricoxib 120 mg qd (OR: 6.71, 95% CI: 2.88, 15.64) showed clinical improvement, compared to those who received diclofenac

75 mg bid. There was mild heterogeneity among the included studies in this respect (χ^2 = 0.33, df = 2, P = 0.85, I^2 = 0%; Figure 3A). However, the effect of etoricoxib 120 mg qd on C-reactive protein was comparable to that of diclofenac 75 mg bid (SMD: -1.15, 95% CI: -3.09, 0.79), but superior to that of diclofenac 75 mg qd (SMD: −0.69, 95% CI: −1.35, -0.04) (Figure 3B).

With regard to the global assessment of response in patients, the efficacy of etoricoxib 120 mg qd was comparable to that of indomethacin 50 mg tid (SMD: −0.10, 95% CI: −0.27, 0.07) with mild heterogeneity (χ^2 = 1.75, df = 2, P = 0.42, I^2 = 0%; Figure 3C). However, etoricoxib 120 mg qd showed better efficacy than indomethacin 50 mg tid in terms of the investigator's global assessment of response (SMD: −0.29, 95% CI: −0.46, −0.11) with mild heterogeneity (χ^2 = 2.11, df = 2, P =0.35, I^2 = 5%; Figure 3D). The effect of etoricoxib 120 mg qd on joint swelling was comparable to that of indomethacin 50 mg tid (SMD: −0.25, 95% CI: −0.74, 0.24); there was marked heterogeneity among the studies included in the meta-analysis in this respect (χ^2 = 4.80, df = 1, P = 0.03, I^2 = 79%; Figure 3E). Etoricoxib 120 mg qd had a shorter time to onset of therapeutic effect than diclofenac 75 mg qd (SMD: −0.94, 95% CI: −1.33, −0.55) [35].

Comparative efficacy of COXIBs

With regard to the pain Likert scale score, etoricoxib 120 mg qd was better than meloxicam 15 mg qd (SMD: −0.56, 95% CI: −1.10, −0.02); there was marked heterogeneity among the included studies in this regard (χ^2 = 10.16, df = 2, P = 0.006, I^2 = 80%; Figure 4A). In terms of the effect on the pain VAS score, etoricoxib was generally better than the other two COXIBs (SMD: −2.82, 95% CI: −4.01, −1.62); there was marked heterogeneity among the included studies in this respect (χ^2 = 106.63, df = 5, P < 0.001, I^2 = 95%). Subgroup analysis revealed better efficacy of etoricoxib 120 mg qd compared to celecoxib 200 mg tid (SMD: −2.36, 95% CI: −3.36, −1.37), but

comparable to meloxicam 15 mg qd (SMD: −4.02, 95% CI: −10.28, 2.24; Figure 4B). Moreover, the onset time for etoricoxib 120 mg qd was significantly shorter than that for meloxicam 15 mg qd (SMD: −1.57, 95%CI: −2.07, −1.08) [20].

Patients receiving etoricoxib 120 mg qd were more likely to achieve clinical improvement compared with those receiving celecoxib 200 mg bid (OR: 4.84, 95% CI: 2.19, 10.72; Figure 5A). Besides, a greater proportion of patients who received etoricoxib 120 mg qd (89.47%) experienced improvement in clinical symptoms compared to those who received celecoxib 200 mg bid (71.05%) [24]. However, etoricoxib 120 mg qd was comparable to celecoxib 200 mg bid in terms of C-reactive protein (SMD: −1.98, 95% CI: −4.90, 0.95; Figure 5B).

Discussion

Main findings

In this meta-analysis, we evaluated the clinical outcomes of patients with acute gout who were treated with various NSAIDs. The results showed comparable performance of COXIBs and traditional NSAIDs with regard to the effect on the pain Likert score and pain VAS scores; however, COXIBs showed better efficacy than traditional NSAIDS with regard to several secondary outcomes, including the response rate and the investigator's global assessment of response. Therefore, we were unable to conclude that COXIBs clearly outperform the traditional NSAIDS. However, we found that etoricoxib 120 mg qd offers a clear advantage over celecoxib 200 mg tid in terms of pain VAS scores and clinical improvement, and over meloxicam in terms of pain Likert scale score.

We exclusively assessed evidence from available studies that compared the efficacy of currently used non-selective NSAIDs and COXIBs in patients with acute gout. Our meta-analysis incorporated all of the clinical outcomes of the available studies; however, most outcomes showed

no difference, and several outcomes revealed that COXIBs performed better. Therefore, there was no conclusive evidence of the comparative efficacy of non-selective NSAIDs and COXIBs. However, our study revealed that etoricoxib may perform better in the management of patients with acute gout than either celecoxib or meloxicam. With regard to Likert scores, COXIBs showed better efficacy than non-selective NSAIDs; however, on subgroup analysis, no significant difference were observed between the two groups of drugs. The inconsistency in the results between the pooled and subgroup analyses may be attributable to significant heterogeneity between the subgroups; we draw our conclusions based on the results of subgroup analyses.

Implication and strength

Our study has clinical implications. The prevalence of gout has increased in both developed and developing countries, presumably due to lifestyle changes [45]. Of all the 291 conditions studied in the GBD 2010 study, gout ranked 138th in terms of disability, and 173rd in terms of overall burden [2]. NSAIDs have gradually been established as the first-line therapeutic option for acute gout [5, 7, 8]; therefore, a comparison of the efficacy of NSAIDs is of much clinical relevance. Finally, we concluded that COXIBs are comparable to traditional NSAIDs with regard to pain relief, but are preferable to traditional NSAIDs in terms of clinical symptoms and investigator's global assessment of response. Etoricoxib may be the best option when COXIBs are indicated.

Our study has considerable strengths. We designed the meta-analysis according to the PRISMA guidelines and took meticulous care to minimize errors and ensure the validity of findings from all relevant studies. Our meta-analysis thoroughly addresses two key questions – that is, the comparative efficacy of traditional NSAIDs and COXIB and the comparative efficacy of the three COXIBs in terms of various clinical outcomes. Our findings may facilitate the selection of drugs for acute gout in clinical settings.

Safety

Several studies have revealed a better safety profile of COXIBs compared to traditional non-selective NSAIDs in patients with acute gout [13, 14] or other pain conditions [46]. Moreover, analysis of VIGOR and two capsule endoscopy studies showed significantly less distal gastrointestinal blood loss with COXIBs than with non-selective NSAIDs [47]. The rates of upper gastrointestinal adverse clinical events were lower with etoricoxib than with diclofenac [48]. When compared with traditional NSAIDs at standard dosages, treatment with celecoxib -at dosages greater than those indicated clinically - was associated with a lower incidence of symptomatic ulcers, ulcer-related complications, as well as other clinically important toxic effects [49]. Gout and renal disorders are common comorbidities in elderly adults, leading to frequent administration of concomitant analgesics, especially NSAIDs. Several studies have shown that COXIBs have a better or similar renal safety profile than ibuprofen or other traditional NSAIDs [50, 51]. It may be hypothesized that COXIBs decrease the renal adverse effects relative to nonselective NSAIDs, as the kidney and vasculature express both COX-1 and -2. However, similar to traditional NSAIDs, due caution should be exercised while prescribing COXIBs to patients with underlying renal diseases [52].

The currently prevalent belief is that both traditional NSAIDs and COXIBs are associated with an increased cardiovascular risk, with the probable exception of naproxen [53]. However, the landmark PRECISION study seemingly refutes this widely held notion [54, 55]. In addition, there is no definitive evidence that COXIBs pose a higher cardiovascular risk as compared to the traditional NSAIDs. The MEDAL study revealed similar rates of thrombotic cardiovascular events between long-term etoricoxib and diclofenac treatment in patients with arthritis [48]. In addition

to efficacy, care must be exercised to consider gastrointestinal, cardiovascular, and renal conditions when choosing between NSAIDs and COXIBs.

Colchine and naproxen

The study focuses on NSAIDs for acute flares. Colchicine and corticosteroids are also the main therapeutic options; however, owing to their different mechanisms of action and absence of direct comparative evidence, these drugs were not included in this meta-analysis. Several trials have compared traditional NSAIDS with oral corticosteroids (another recommended first-line options for acute flares); however, these trials did not qualify the inclusion criteria for this meta-analysis. Naproxen is a traditional NSAID that is used worldwide; however, it was not included in the meta-analysis due to the absence of trials comparing naproxen with COXIBs. In a double-blind, randomized trial in patients with crystal-proven gout, naproxen was found to be as effective as prednisolone for acute flares [56]. Similarly, a double-blind, parallel-group study revealed comparable efficacy of etodolac and naproxen in alleviating symptoms of acute gouty arthritis [57]. Naproxen and phenylbutazone also showed comparable efficacy in the management of acute gout, with few and relatively mild adverse events [58].

Limitations

Nevertheless, there are several limitations of our study. First, a relatively strict search strategy was used in the present study to achieve our objective; this limited the number of included RCTs. There are relatively few recent RCTs that investigated the effect of NSAIDs in acute gout. Moreover, most of these were published in Chinese. The relatively small number of studies and the small sample size in the studies included in the meta-analysis are the major limitations of our study. We did not evaluate publication bias using funnel plots because the number of studies was less than 10 for all outcome measures. Besides, most of the included studies published in Chinese

were of low quality. Moreover, confounding factors such as the underlying disease and the use of other drugs may have affected the analysis. However, our review emphasizes the potential importance of COXIBs for acute gout. Given the clinical importance and acute nature of a gout flare, more trials focusing on clinically relevant outcomes are essential, especially in those patients who really need care.

Conclusion

Although COXIBs and traditional non-selective NSAIDs may be equally beneficial in terms of pain relief, COXIBs (especially etoricoxib) may confer a greater benefit.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Authors' contributions

MTL, CY, and XFZ were responsible for the conception and design of the study. MTL and CY performed data analysis and interpretation. MTL and CY wrote the first draft of the manuscript. All authors critically revised the manuscript and have approved the final version.

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Conflict of Interest

The authors declare that they have no conflict of interests.

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Table

Table 1. Main characteristics of the studies included in this meta-analysis

Author	Year	Language	Treatment arms	N	Male	Age	Follow-up (d)
Schumacher H	2002	English	Etoricoxib 120 mg qd	75	73	48.5 (13.29)	8
			Indomethacin 50 mg tid	75	69	49.5 (13.71)	
Rubin B	2004	English	Etoricoxib 120 mg qd	103	98	51.1 (13)	8
			Indomethacin 50 mg tid	86	79	52.2 (12)	
Ye Q	2010	Chinese	Etoricoxib 120 mg qd	40	33	45.12 (12.48)	7
			Diclofenac 75 mg qd	35	32	38.20 (15.51)	
Zhang J	2012	Chinese	Etoricoxib 120 mg qd	48	48	63.4 (12)	8
			Meloxicam 15 mg qd	36	36	64.1 (11)	
Gao Q	2013	Chinese	Etoricoxib 120 mg qd	140	89	41.78 (12.57)	7
			Diclofenac 75 mg bid	140	92	42.48 (13.23)	
Hong J	2013	Chinese	Etoricoxib 120 mg qd	50	38	42.1 (9.8)	7
			Celecoxib 200 mg tid	50	40	41.5 (7.8)	
Li T	2013	English	Etoricoxib 120 mg qd	89	85	52 (15)	5
			Indomethacin 75 mg bid	89	81	53 (14)	
Guo D	2014	Chinese	Etoricoxib 120 mg qd	60	96	44.3 (15.6)	8
			Meloxicam 15 mg qd	60			
Guo M	2014	Chinese	Etoricoxib 120 mg qd	57	56	40.52 (11.27)	5
			Diclofenac 75 mg qd	56	54	43.03 (13.02)	
Lu J	2014	Chinese	Etoricoxib 120 mg qd	95	89	48.9 (2.3)	7
			Diclofenac 50 mg tid	51	49	46.7 (3.4)	
Kuang L	2015	Chinese	Etoricoxib 120 mg qd	40	29	42.8 (10.3)	7
			Diclofenac 50 mg tid	40	31	43.7 (11.2)	
Liu C	2015	Chinese	Etoricoxib 120 mg qd	32	21	45 (3.74)	7
			Meloxicam 15 mg qd	32	13	44 (3.53)	
Xia H	2015	Chinese	Etoricoxib 120 mg qd	40	27	50.17 (25.13)	7
			Celecoxib 200 mg tid	40	25	50.09 (25.34)	
Zhu H	2015	Chinese	Etoricoxib 120 mg qd	50	48	46.3 (6.9)	7

			Diclofenac 50 mg tid	50	49	46.5 (6.1)	
Cui M	2016	Chinese	Diclofenac 100 mg qd	12	11	41.5 (3.8)	5
			Celecoxib 200 mg qd	12	10	43.2 (4.2)	
Li S	2016	Chinese	Etoricoxib 120 mg qd	47	22	41.8 (11.3)	5
			Diclofenac 75 mg qd	47	21	40.5 (10.1)	
Ming H	2016	Chinese	Etoricoxib 120 mg qd	38	22	52.64 (12.28)	7
			Celecoxib 200 mg bid	38	23	52.79 (12.35)	
Pan Q	2016	Chinese	Etoricoxib 120 mg qd	68	126	43.2 (13.6)	7
			Diclofenac 50 mg tid	68			
Zhou S	2016	Chinese	Etoricoxib 120 mg qd	28	16	53.37 (11.32)	7
			Celecoxib 200 mg tid	28	14	52.13 (10.13)	
Li Y	2017	Chinese	Etoricoxib 120 mg qd	44	68	44.67 (14.99)	8
			Meloxicam 15 mg qd	44			
Gao C	2018	Chinese	Celecoxib 200 mg bid	40	29	58.4 (2. 8)	7
			Etoricoxib 120 mg qd	40	30	56.7 (2. 2)	
Lan T	2018	Chinese	Celecoxib 200 mg bid	30	24	52.21 (1.25)	7
			Etoricoxib 120 mg qd	30	25	52.26 (1.24)	
Sheng J	2019	Chinese	Etoricoxib 120 mg qd	42	82	39.17 (10.28)	7
			Diclofenac 75 mg qd	38			
Wu L	2019	Chinese	Etoricoxib 120 mg qd	30	23	45.98 (6.65)	7
			Meloxicam 15 mg qd	30	21	45.21 (7.20)	

N = number; age presented as mean (standard deviation).

Figure legends

Figure 1. Schematic illustration of literature search and study selection

Figure 2. Forest plots of primary outcomes: COXIBs versus traditional NSAIDs.

Pain Likert scale for days 2–8 (A); pain VAS score for days 2–8 (B).

VAS, visual analog scale

Figure 3. Forest plots of secondary outcomes: COXIBs versus traditional NSAIDs

Response rate for days 2–8 (A); C-reactive protein (B); patient's global assessment (C); investigator's global assessment (D); and inflammatory swelling (E)

Figure 4. Forest plots of primary outcomes: comparative efficacy of various COXIBs

Pain Likert scale score for days 2–8 (A); Pain VAS score for days 2–8 (B).

VAS, visual analog scale

Figure 5. Forest plots of secondary outcomes: comparative efficacy of various COXIBs

Response rate for days 2–8 (A); C-reactive protein (B)

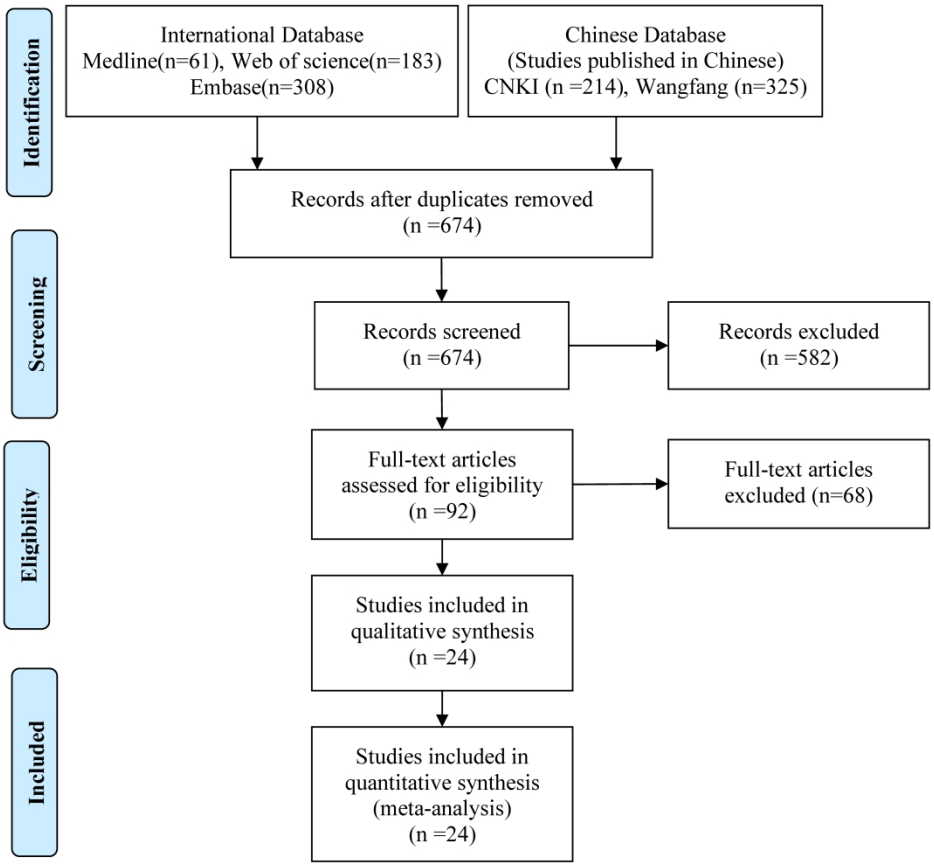


Figure 1. Schematic illustration of literature search and study selection

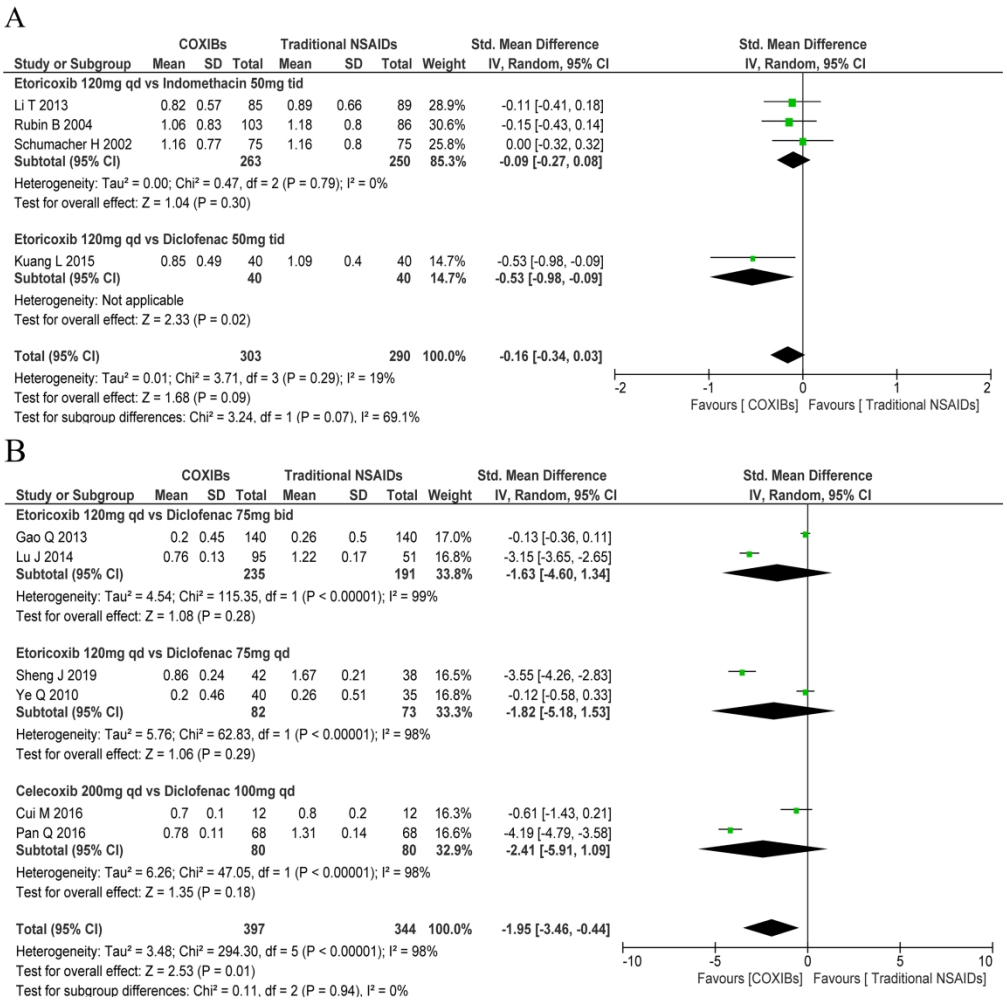


Figure 2. Forest plots of primary outcomes: COXIBs versus traditional NSAIDs. Pain Likert scale for days 2–8) (A); pain VAS score for days 2–8 (B). VAS, visual analog scale

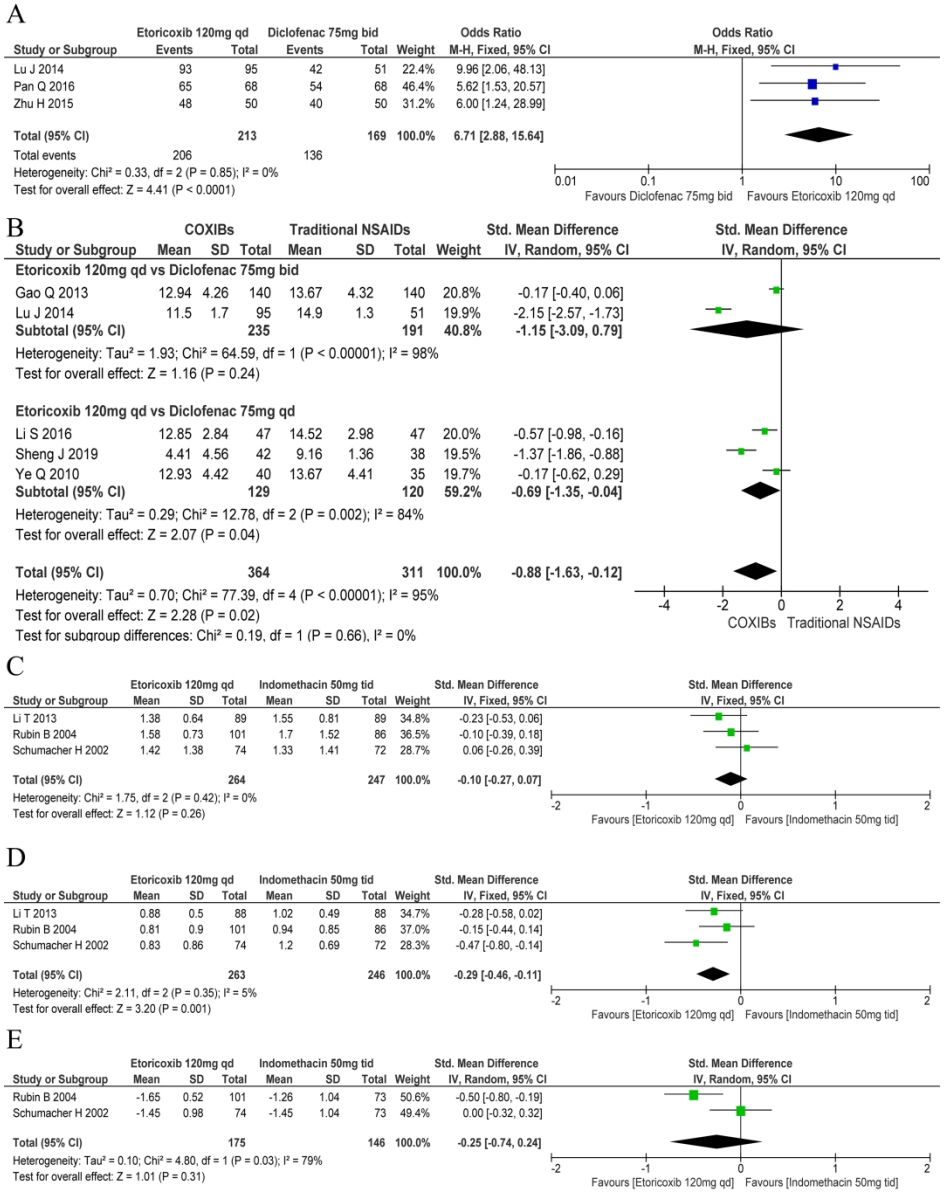


Figure 3. Forest plots of secondary outcomes: COXIBs versus traditional NSAIDs Response rate for days 2–8 (A); C-reactive protein (B); patient's global assessment (C); investigator's global assessment (D); and inflammatory swelling (E)

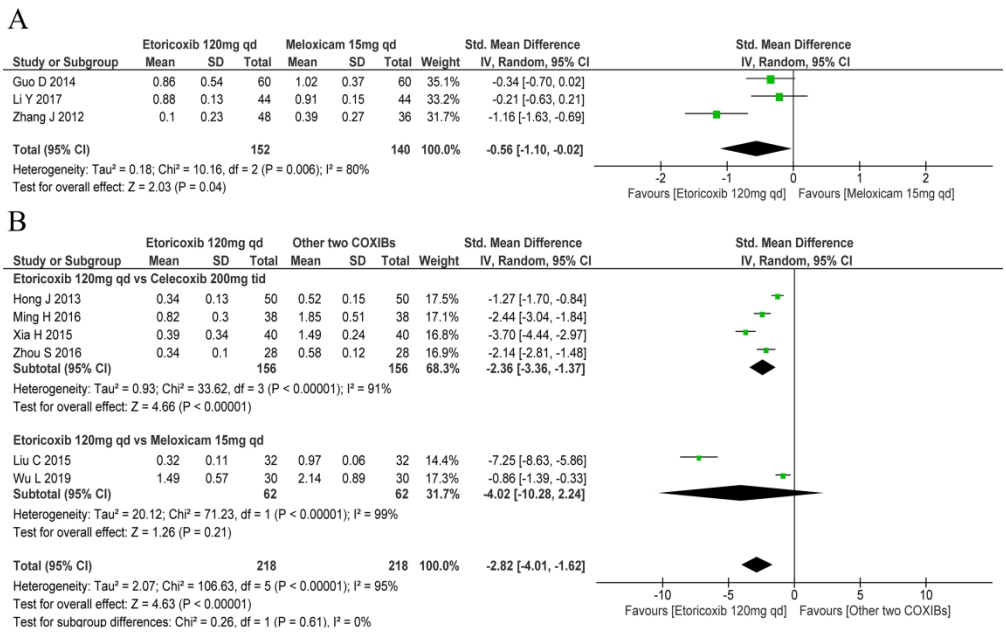


Figure 4. Forest plots of primary outcomes: comparative efficacy of various COXIBs Pain Likert scale score for days 2–8 (A); Pain VAS score for days 2–8 (B). VAS, visual analog scale

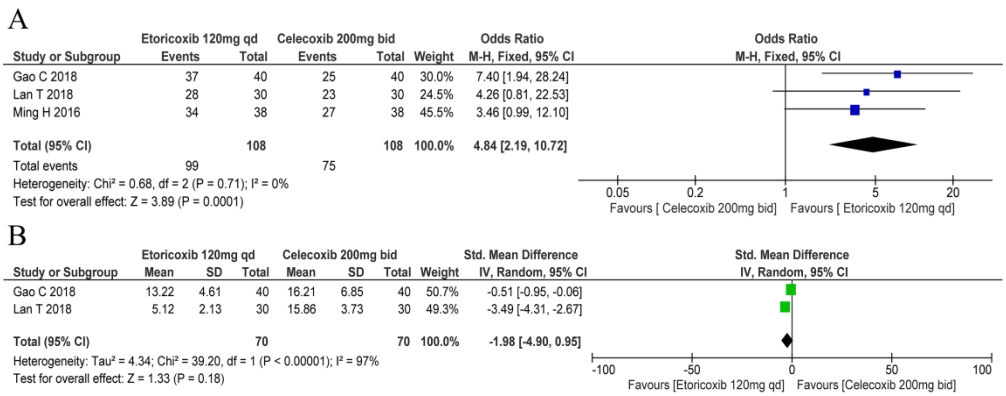


Figure 5. Forest plots of secondary outcomes: comparative efficacy of various COXIBs Response rate for days 2–8 (A); C-reactive protein (B)

Supplementary Material for: "Comparative efficacy of traditional non-selective NSAIDs and selective cycloxygenase-2 inhibitor in patients with acute gout: a systematic review and meta-analysis"

Journal: BMJ Open

Authors: Mengtao Li, PhD, Chen Yu, PhD, Xiaofeng Zeng, PhD

Corresponding author: Prof Xiaofeng Zeng, Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Table of content

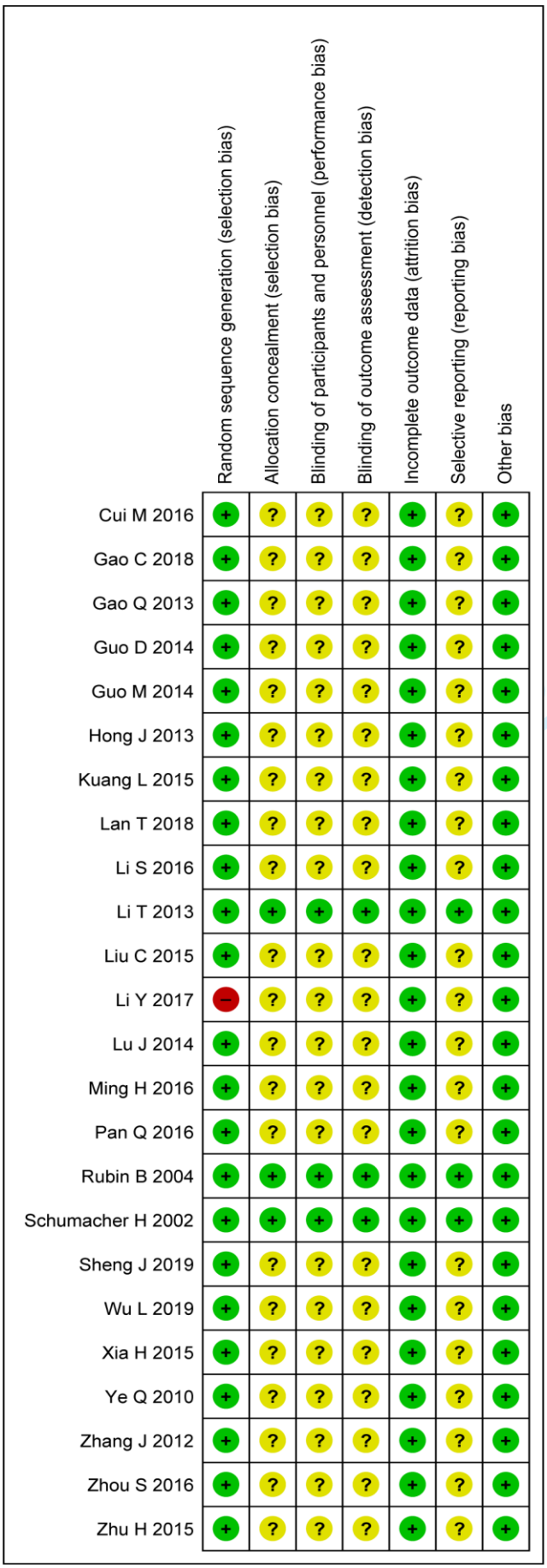


Figure S1. Risk of bias summary

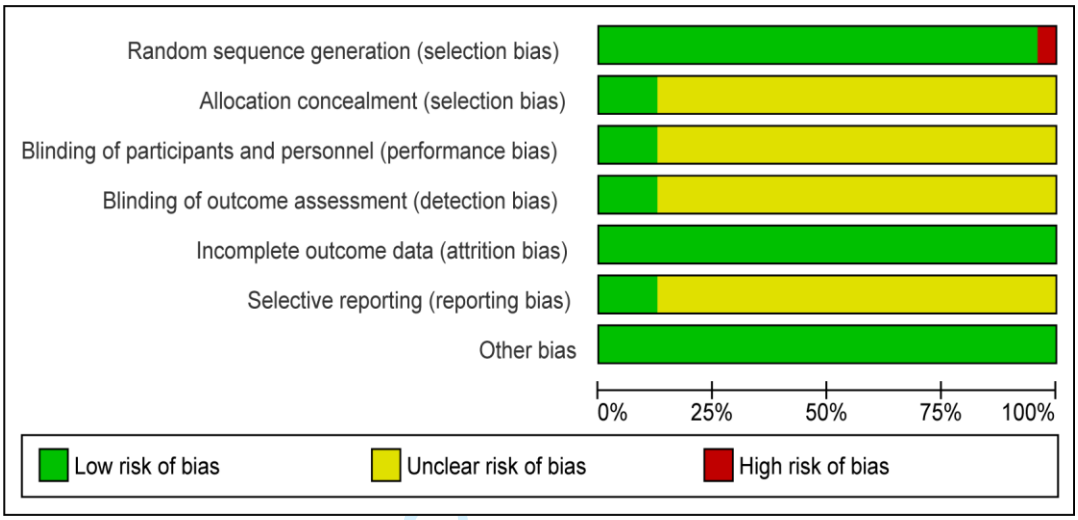


Figure S2. Risk of bias graph

Table S1. Detailed search strategy

PubMed		
Search	Query	Number
#3	Search ((((gout) OR gouty arthritis) OR acute gout)) AND (((Etoricoxib) OR Celecoxib) OR Meloxicam)	61
#2	Search ((gout) OR gouty arthritis) OR acute gout	18847
#1	Search ((Etoricoxib) OR Celecoxib) OR Meloxicam	9404
Web of Science		
# 3	#2 AND #1 Databases = WOS, BIOSIS, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO. Timespan=All years; Search language=Auto	183
# 2	TOPIC: (gout) OR TOPIC: (gouty arthritis) OR TOPIC: (acute gout) Databases = WOS, BIOSIS, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO. Timespan=All years; Search language=Auto	36,548
# 1	TOPIC: (Etoricoxib) OR TOPIC: (Celecoxib) OR TOPIC: (Meloxicam) Databases = WOS, BIOSIS, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO. Timespan=All years; Search language=Auto	19,277
Embase		
# 3	#2 AND #3	308
# 2	'gout'/exp OR gout OR 'gouty arthritis'/exp OR 'gouty arthritis' OR (gouty AND ('arthritis'/exp OR arthritis)) OR 'acute gout'/exp OR 'acute gout' OR (acute AND ('gout'/exp OR gout))	28,967
# 1	'etoricoxib'/exp OR etoricoxib OR 'celecoxib'/exp OR celecoxib OR 'meloxicam'/exp OR meloxicam	29,285
CNKI		
	(依托考昔 and 痛风）OR (塞来昔布 and 痛风) OR (美洛昔康 and 痛风)	214
	(Etoricoxib and Gout) OR (Celecoxib and Gout) OR (Meloxicam and Gout)	214
Wangfang		
	主题:(痛风)*主题:(美洛昔康) Etoricoxib and Gout	97
	主题:(痛风)*主题:(塞来昔布) Celecoxib and Gout	121
	主题:(痛风)*主题:(依托考昔) Meloxicam and Gout	107
	(依托考昔 and 痛风）OR (塞来昔布 and 痛风) OR (美洛昔康 and 痛风)	325
	(Etoricoxib and Gout) OR (Celecoxib and Gout) OR (Meloxicam and Gout)	325

Table S2: Summary of findings: COXIBs vs traditional NSAIDs for acute gout

COXIBs compared to traditional NSAIDs for acute gout

Patient or population: acute gout

Setting:

Intervention: COXIBs

Comparison: traditional NSAIDs

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with traditional NSAIDs	Risk difference with COXIBs
Pain Likert scale	593 (4 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **0.15 SD lower** (0.31 lower to 0.01 higher)
Pain Likert scale - Etoricoxib 120 mg qd vs Indomethacin 50 mg tid	513 (3 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **0.09 lower** (0.27 lower to 0.08 higher)
Pain Likert scale - Etoricoxib 120 mg qd vs Diclofenac 75 mg qd	80 (1 RCT)	⨁⨁⨁⨁ HIGH	-	-	SMD **0.53 lower** (0.98 lower to 0.09 lower)
Pain VAS scale	741 (6 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **1.95 SD lower** (3.46 lower to 0.044 lower)
Pain VAS scale - Etoricoxib 120 mg qd vs Diclofenac 75 mg bid	426 (2 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **1.63 SD lower** (460 lower to 1.34 higher)

COXIBs compared to traditional NSAIDs for acute gout

Patient or population: acute gout

Setting:

Intervention: COXIBs

Comparison: traditional NSAIDs

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with traditional NSAIDs	Risk difference with COXIBs
Pain VAS scale - Etoricoxib 120 mg qd vs Diclofenac 75 mg qd	155 (2 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **1.82 SD lower** (5.18 lower to 1.53 higher)
Pain VAS scale - Celecoxib 200 mg qd vs Diclofenac 100 mg qd	160 (2 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **2.41 lower** (5.91 lower to 1.09 higher)
Response rate	382 (3 RCTs)	⨁⨁⨁⨁ HIGH	**OR 6.71** (2.88 to 15.64)	805 per 1,000	**160 more per 1,000** (118 more to 180 more)
C-reactive protein	674 (5 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **0.88 SD lower** (1.63 lower to 0.12 lower)
C-reactive protein-Pain VAS scale - Etoricoxib 120 mg qd vs Diclofenac 75 mg bid	426 (2 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **1.15 SD lower** (3.09 lower to 0.79 higher)

COXIBs compared to traditional NSAIDs for acute gout

Patient or population: acute gout

Setting:

Intervention: COXIBs

Comparison: traditional NSAIDs

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with traditional NSAIDs	Risk difference with COXIBs
C-reactive protein-Pain VAS scale - Etoricoxib 120 mg qd vs Diclofenac 75 mg qd	249 (3 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.69 SD lower** (1.35 lower to 0.04 lower)
Patient's global assessment of response	511 (3 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.1 SD lower** (0.27 lower to 0.07 higher)
Investigator's global assessment of response	509 (3 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.29 SD lower** (0.46 lower to 0.11 lower)
Inflammation swelling	321 (2 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.25 lower** (0.74 lower to 0.24 higher)
Onset of efficacy (h) - Etoricoxib 120 mg qd vs Diclofenac 75 mg qd	113 (1 RCT)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.94 lower** (1.33 lower to 0.55 lower)

COXIBs compared to traditional NSAIDs for acute gout

Patient or population: acute gout

Setting:

Intervention: COXIBs

Comparison: traditional NSAIDs

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with traditional NSAIDs	Risk difference with COXIBs

*__The risk in the intervention group__ (and the associated 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and the associated 95% CI).

CI: Confidence interval; **SMD:** Standardized mean difference; **OR:** Odds ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table S3: Summary of findings: one COXIB vs another COXIB for acute gout

Another COXIBs compared to one COXIBs for acute gout

Patient or population: acute gout

Setting:

Intervention: another COXIBs

Comparison: one COXIBs

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with one COXIBs	Risk difference with another COXIBs
Pain Likert scale	292 (3 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.56 lower** (1.1 lower to 0.02 lower)
Pain VAS scale	436 (6 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **2.82 SD lower** (4.01 lower to 1.62 lower)
Pain VAS scale - Etoricoxib 120 mg qd vs Celecoxib 200 mg tid	312 (4 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **2.36 lower** (3.36 lower to 1.37 lower)
Pain VAS scale - Etoricoxib 120 mg qd vs Meloxicam 15 mg qd	124 (2 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **4.02 SD lower** (10.28 lower to 2.24 higher)
Response rate-Etoricoxib 120 mg qd vs Celecoxib 200 mg bid	216 (3 RCTs)	⊕⊕⊕⊕ HIGH	**OR 4.84** (2.19 to 10.72)	694 per 1,000	**222 more per 1,000** (138 more to 266 more)

Another COXIBs compared to one COXIBs for acute gout

Patient or population: acute gout

Setting:

Intervention: another COXIBs

Comparison: one COXIBs

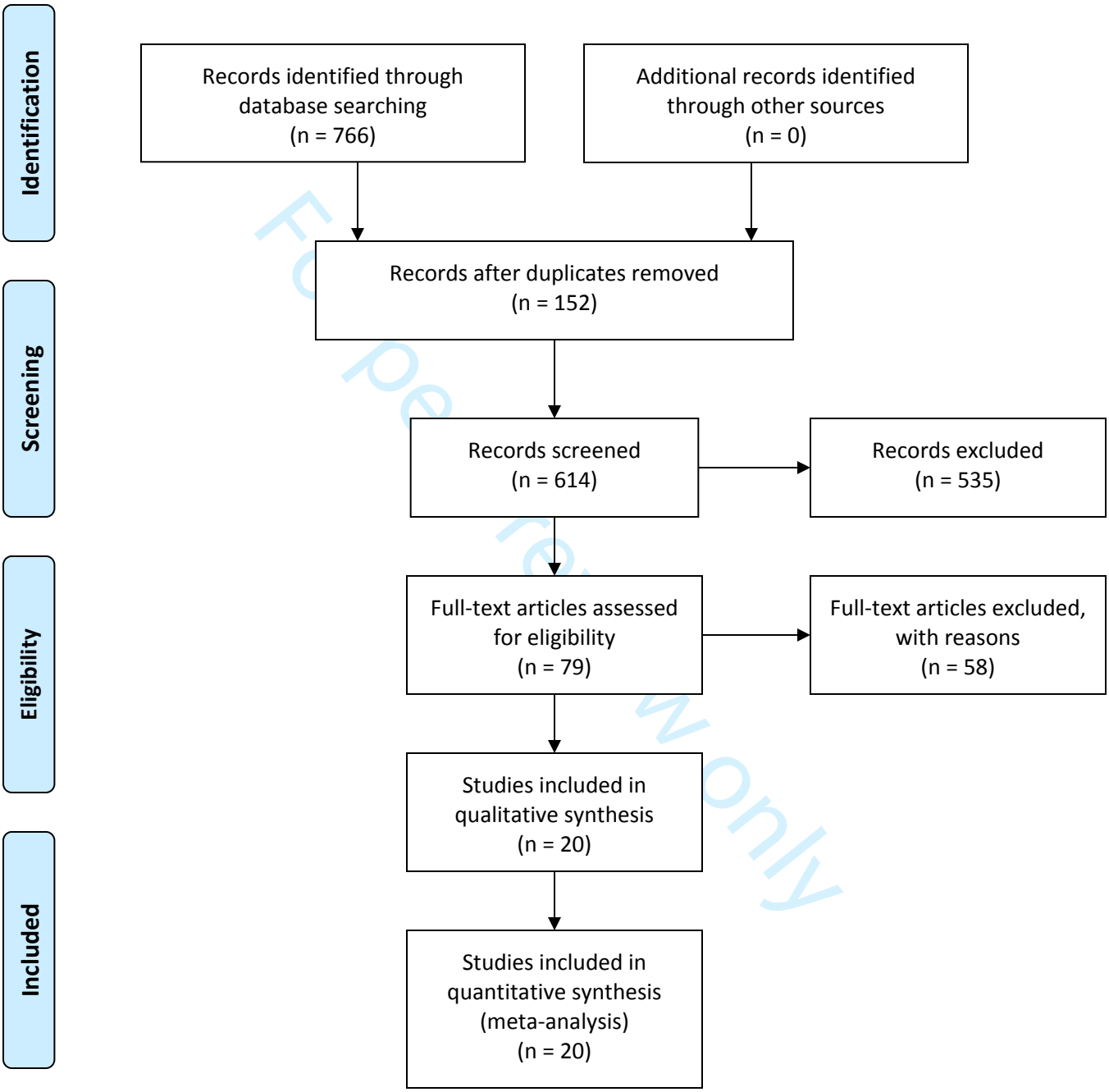
Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with one COXIBs	Risk difference with another COXIBs
C-reactive protein	140 (2 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **1.98 SD lower** (4.9 lower to 0.95 higher)
Onset of efficacy (h)-Etoricoxib 120 mg qd vs Meloxicam 15 mg qd	84 (1 RCT)	⨁⨁⨁⨁ HIGH	-	-	SMD **1.57 lower** (2.07 lower to 1.08 lower)

***The risk in the intervention group** (and the associated 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and the associated 95% CI).

CI: Confidence interval; **SMD:** Standardized mean difference; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	#1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	#2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	#5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	#5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	INPLASY 202040025
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	#6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	#6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	#6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	#7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	#7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	#7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	#8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	#8

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	#8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	#8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	#8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	#9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	#9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	#10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	#10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	#10-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	#10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	#10-12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	#12-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	#15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	#16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	#17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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