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Network Meta-Analysis Comparing Relatively Selective COX-2 Inhibitors Versus Coxibs for the Prevention of NSAID-Induced Gastrointestinal Injury

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Abstract: Currently 2 difference classes of cyclooxygenase (COX)-2 inhibitors, coxibs and relatively selective COX-2 inhibitors, are available for patients requiring nonsteroidal anti-inflammatory drug (NSAID) therapy; their gastroprotective effect is hardly directly compared.

The aim of this study was to compare the gastroprotective effect of relatively selective COX-2 inhibitors with coxibs.

MEDLINE, EMBASE, and the Cochrane Library (from their inception to March 2015) were searched for potential eligible studies.

We included randomized controlled trials comparing coxibs (celecoxib, etoricoxib, parecoxib, and lumiracoxib), relatively selective COX-2 inhibitors (nabumetone, meloxicam, and etodolac), and nonselective NSAIDs with a study duration ≥4 weeks.

Comparative effectiveness and safety data were pooled by Bayesian network meta-analysis. The primary outcomes were ulcer complications and symptomatic ulcer. Summary effect-size was calculated as risk ratio (RR), together with the 95% confidence interval (CI).

This study included 36 trials with a total of 112,351 participants. Network meta-analyses indicated no significant difference between relatively selective COX-2 inhibitors and coxibs regarding ulcer complications (RR, 1.38; 95% CI, 0.47–3.27), symptomatic ulcer (RR, 1.02; 95% CI, 0.09–3.92), and endoscopic ulcer (RR, 1.18; 95% CI, 0.37–2.96). Network meta-analyses adjusting potential influential factors (age, sex, previous ulcer disease, and follow-up time), and sensitivity analyses did not reveal any major change to the main results. Network meta-analyses suggested that relatively selective COX-2 inhibitors and coxibs were associated with comparable incidences of total adverse events (AEs) (RR, 1.09; 95% CI, 0.93–1.31), gastrointestinal AEs (RR, 1.04; 95% CI, 0.87–1.25), total withdrawals (RR, 1.00; 95% CI, 0.74–1.33), and gastrointestinal AE-related withdrawals (RR, 1.02; 95% CI, 0.57–1.74).

Relatively selective COX-2 inhibitors appear to be associated with similar gastroprotective effect and tolerability as coxibs. Owing to the indirectness of the comparisons, future research is required to confirm the study conclusion.

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Abbreviations: AE = adverse event, CI = confidence interval, COX = cyclooxygenase, NSAID = nonsteroidal anti-inflammatory drug, RCT = randomized controlled trial, RR = risk ratio.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most highly prescribed drugs, commonly used for musculoskeletal conditions such as rheumatoid arthritis and osteoarthritis. However, the use of NSAIDs is often limited by the gastrointestinal toxicity.[1,2] It has been reported that NSAID-induced gastrointestinal complications such as ulcer bleeding, perforation, and obstruction may occur in approximately 2% to 4% of NSAID users.[3,4] Worse still, NSAIDs lead to considerable mortality worldwide. In the United States[5,6] and the United Kingdom,[7] NSAIDs are thought to cause at least 7000 and 1000 deaths every year, respectively.

It has been recognized that both the efficacy and toxicity of NSAIDs result from their inhibition of cyclooxygenase (COX), which primarily has 2 structurally and functionally distinct isoforms, COX-1 and COX-2.[8,9] COX-1 is the constitutive isoform expressed throughout the body and plays an important role in gastrointestinal protection and platelet aggregation.[8,9] While COX-2 is an inducible COX that is involved in the inflammatory response.[9,10] The discovery of COX-2 has led to the important development of therapeutic COX-2 inhibitors. Strong evidence indicates that COX-2 inhibitors are associated with significantly lower incidence of gastrointestinal adverse effects than nonselective NSAIDs.[11,12]

Currently there are 2 classes of COX-2 inhibitors, including coxibs and relatively selective COX-2 inhibitors, available for prescription.[9,11] Coxibs, including celecoxib, etoricoxib, parecoxib, and lumiracoxib, are a relatively new class of NSAIDs and their gastrointestinal safety has been systematically evaluated.[10,11] Clinical guidelines now recommend coxibs for patients with high gastrointestinal and low cardiovascular risk.[13] However, coxibs are much more expensive than conventional NSAIDs.[9,14,15] In contrast, relatively selective COX-2 inhibitors, including nabumetone, meloxicam, and etodolac, are a group of traditional NSAIDs that were retrospectively found to have COX-2 selectivity.[9,11] They are structurally dissimilar with coxibs and cheaper, but their selective COX-2 properties have not been rigorously evaluated. So far a large number of clinical trials have been performed to evaluate the

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gastroprotective effectiveness of coxibs and relatively selective COX-2 inhibitors; however, these studies often took nonselective NSAIDs as control and there are hardly any trials directly compared the 2 different classes of COX-2 inhibitors. Network meta-analysis, in the context of a systematic review, is a meta-analysis in which multiple treatments are compared using both direct comparisons of interventions within trials and indirect comparisons across trials based on a common comparator.[16,17] In this study, we carried out a network meta-analysis to indirectly compare the gastroprotective effect of relatively selective COX-2 inhibitors with coxibs

METHODS

This study was carried out according to the Cochrane handbook for systematic reviews of interventions,[18] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[19] Because this is a secondary literature based study, ethic approval is not necessary.

Literature Search

We searched the Cochrane Library, MEDLINE, and EMBASE from their inception to March 2015. The search strategy included the following combined texts and MeSH terms: ''Nonsteroidal anti-inflammatory drugs,'' ''coxibs,'' ''COX-2 inhibitors,'' ''celecoxib,'' ''etoricoxib,'' ''parecoxib,'' ''lumiracoxib,'' ''nabumetone,'' ''meloxicam,'' ''etodolac,'' ''peptic ulcer,'' ''bleeding,'' ''perforation,'' ''obstruction,'' ''randomized controlled trial,'' and ''clinical trial.'' All searches were restricted to human studies and there was no limitation on publication language. We manually searched reference lists of the included studies and related review articles to identify additional trials.

Study Selection

We included randomized controlled trials (RCTs) comparing coxibs (celecoxib, etoricoxib, parecoxib, and lumiracoxib), relatively selective COX-2 inhibitors (nabumetone, meloxicam, and etodolac), and nonselective NSAIDs in patients with chronic musculoskeletal conditions or health people. The classification of NSAIDs in this study is as same as previous reports.[9,20] Some selective COX-2 inhibitors which have been withdrawn from the market, like rofecoxib, valdecoxib, and nimesulide, were not included. Eligible studies should report at least 1 outcome for this systematic review and the follow-up time should be equal or longer than 4 weeks.

Two investigators independently selected the potentially eligible studies and extracted the data, disagreement was resolved by discussion. Duplicate citations were removed by reference management software, and the remaining records were evaluated by examining the titles, abstracts, and full articles sequentially. We only included the publication with the most relevant data if 2 or more papers were published for a same trial.

Data Extraction and Quality Assessment

Data from eligible studies were extracted using a standard form for this study. The data extracted from eligible studies included study information, patient characteristics, intervention, outcomes, and study methods. We consulted the authors of original studies to collect missing information as necessary. The methodological quality of the included studies was evaluated using the Jadad scale.[21] The Jadad scale provides an overall evaluation of the methodological quality by assessing the risk of bias in randomization, blinding, and withdrawals/dropouts. Data extraction and quality assessment were independently carried out by 2 authors, and disagreements were resolved by discussion with a third author.

Outcome

The primary outcomes for this systematic review included ulcer complications (bleeding, perforation, and obstruction) and symptomatic ulcers. Secondary outcomes included endoscopic ulcers, gastrointestinal adverse events (AEs), total AEs, total withdrawals, and withdrawals due to gastrointestinal AEs.

Statistical Analysis

In order to account for the expected clinical and methodological heterogeneity, we used Bayesian random-effects models to evaluate the effect between coxibs and relatively selective COX-2 inhibitors. Summary effect-size was presented as risk ratio (RR) together with the 95% confidence intervals (CIs). Comparisons between coxibs and relatively selective COX-2 inhibitors were indirectly calculated through nonselective NSAIDs which is a common reference for both of the 2 different COX-2 inhibitors in original trials.

Like traditional meta-analysis, network meta-analysis also holds the assumption of heterogeneity across studies in the available direct comparisons. We tested the heterogeneity by Q-statistic and I^2-index statistic.[18] In addition, network meta-analyses require that a valid indirect comparison of 2 treatments by way of 2 direct comparisons with common reference must include trials that are sufficiently similar in important clinical and methodological characteristics.[22,23] This assumption ensures that indirect comparisons from network meta-analysis are not influenced by potential effect modifiers. In our study, the assumption of similarity was tested using meta-regression analyses by adding potential effect modifiers as covariates to the network meta-analysis models.[22,23] The potential effect modifiers assessed in our data analysis included average age, proportion of females, proportion of patients with previous ulcer disease, and length of follow-up. We would plan to evaluate other factors including *Helicobacter pylori* infection and ulcer risk, but such analyses were not performed due to insufficient data. Lastly, network meta-analyses assume that the direct and indirect estimated effects should be consistent when both are available in the network meta-analysis.[24] Because direct comparison between coxibs and relatively selective COX-2 inhibitors were not available for all study outcomes, a test for assumption of consistency was not required in our study.

The primary results reported in our study were based on the network meta-analyses including all available trial data. In addition, we also reported the results from the network meta-analyses which adjusted other potential effect modifiers. Sensitivity analyses were performed for the primary outcomes by excluding small studies with <100 participants, excluding studies with poor mythological quality (Jadad <3), and excluding studies of diclofenac. Data analysis was carried out by RevMan version 5.3 and WinBUGS version 1.4.

RESULTS

Study Characteristics and Risk of Bias

Our search strategy identified 503 citations from electronic databases and 62 citations from other resources. We excluded 497 citations after excluding duplicates and screening titles/abstracts. The full texts of the remaining 68 records were screened and 36 trials including 112,351 participants from 35

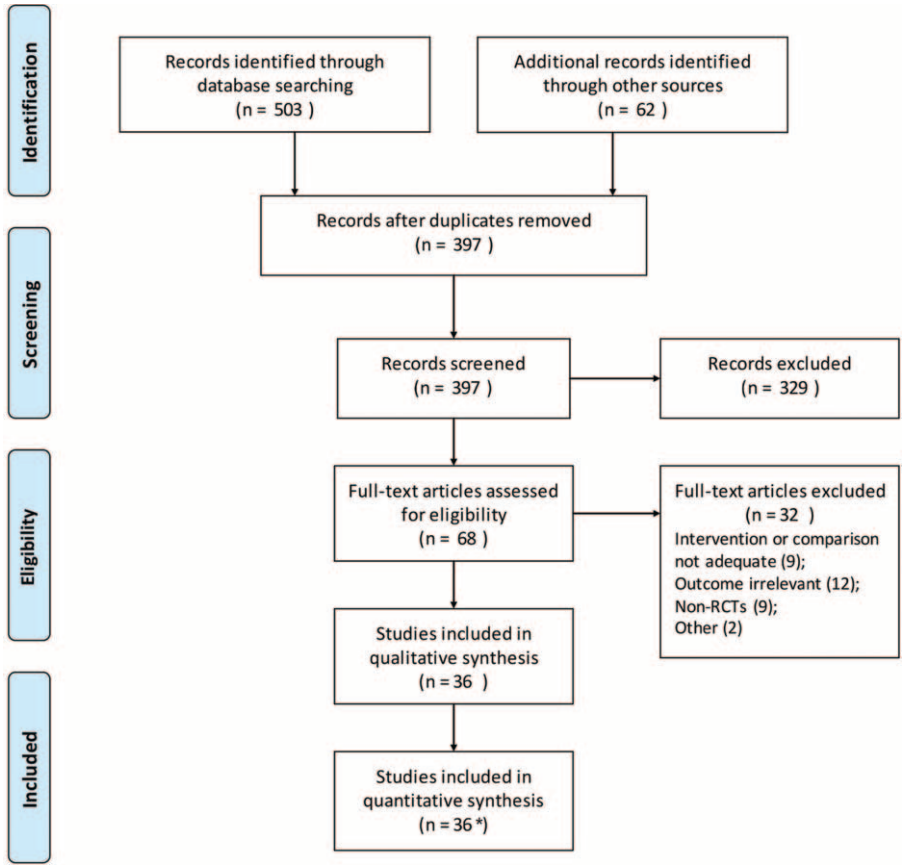

FIGURE 1. Flowchart of study selection. *One publication reported 2 trials in the same paper.

publications were finally included[3,25–58] (there are 2 trials reported in a same paper,[28] see the flowchart of study selection in Figure 1).

Table 1 presents the characteristics and risk of bias of included studies. Of 36 included RCTs, 18 trials[25–41] compared relatively selective COX-2 inhibitors with nonselective NSAIDs, 18 trials[3,42–58] compared coxibs with nonselective NSAIDs. We did not find any study directly compared coxibs with relatively selective COX-2 inhibitors. Thirty-five included trials were performed in patients with chronic musculoskeletal conditions and 1[35] included healthy people. The mean age of studies ranged from 36 to 72 years (median: 61.4 years). The study duration ranged from 4 to 156 weeks (median: 12 weeks). The mythological quality of most included trials was assessed as moderate or high. Eighteen studies had a Jadad scale >4 points, 16 studies had 3 points, and 3 studies had 2 points.

Ulcer Complications

Twenty studies including 59,717 participants and 145 events contributed to the analyses of ulcer complications. Pairwise meta-analyses comparing relatively selective COX-2 inhibitors with nonselective NSAIDs (10 trials; $P = 0.46$, $I^2 = 0\%$), and comparing coxibs with nonselective NSAIDs (10 trials; $P = 0.48$, $I^2 = 0\%$) showed no significant heterogeneity across included studies. Network meta-regression analyses testing the assumption of similarity did not reveal any prespecified factors that significantly modified the estimated effects (Supplemental digital content—Table S1, http://links.lww.com/MD/A428).

Network meta-analysis indicated that the event probability was 0.13% (95% CI, 0.04–0.32) for relatively selective COX-2 inhibitors and 0.15% (95% CI, 0.05–0.34) for coxibs. There was no significant difference between relatively selective COX-2 inhibitors and coxibs (RR, 1.38; 95% CI, 0.47–3.27) (Table 2). Network meta-analysis adjusting for the prespecified factors showed very similar RRs as the primary estimated effect (Table 3).

Symptomatic Ulcer

Sixteen trials including 34,991 participants and 66 events contributed to the analyses of symptomatic ulcer. Pairwise meta-analyses comparing relatively selective COX-2 inhibitors with nonselective NSAIDs (11 trials; $P = 0.86$, $I^2 = 0\%$), and comparing coxibs with nonselective NSAIDs (5 trials; $P = 0.95$, $I^2 = 0\%$) showed no significant heterogeneity across included trials. Network meta-regression analyses testing the assumption of similarity did not reveal any prespecified factors that significantly modified the estimated effects (Supplemental digital content—Table S1, http://links.lww.com/MD/A428).

Network meta-analysis indicated that the event probability was 0.21% (95% CI, 0.04–0.62) for relatively selective COX-2 inhibitors and 0.18% (95% CI, 0.01–0.74) for coxibs. There was no significant difference between relatively selective COX-2 inhibitors and coxibs (RR, 1.02; 95% CI, 0.09–3.92)

TABLE 1. Characteristics of Included Studies

Author, year	Location	NSAID, Dosage (Number of Participants)	Age, yr	Female, n (%)	Previous Peptic Ulcers, n (%)	Study Duration, wk	Jadad Score
Lindén 1996[32]	Europe	Meloxicam 15 mg (128); Piroxicam 20 mg (127)	67.2	161 (62.9%)	NA	6	3
Wojtulewski 1996[25]	Multinational	Meloxicam 7.5 mg (199); Naproxen 750 mg (180)	NA	NA	NA	26	3
Lightfoot 1997[33]	Europe, USA	Etodolac 400 mg (140); Etodolac 600 mg (147); Piroxicam 20 mg (139)	57	304 (71.4%)	NA	12	3
Taha 1990[27]	UK	Etodolac 600 mg (16); Naproxen 1000 mg (13)	NA	19 (70.4%)	NA	4	2
Taha 1989[26]	UK	Etodolac 600 mg (16); Naproxen 1000 mg (13)	53.5	21 (70.0%)	0 (0%)	4	3
Hawkey 1998[36]	Europe	Meloxicam 7.5 mg (4635); Diclofenac 100 mg (4688)	61.6	6240 (67.1%)	471 (5.1%)	5	3
Laine 1995[35]	USA	Etodolac 800 mg (17); Naproxen 1000 mg (18)	36	14 (40%)	0 (0%)	4	3
Hawkey 1998[36]	Europe	Meloxicam 7.5 mg (4635); Diclofenac 100 mg (4688)	61.6	6240 (67.1%)	471 (5.1%)	5	3
Dequeker 1998[39]	Europe	Meloxicam 15 mg (4320); Piroxicam 20 mg (4336)	61.4	5842 (67.5%)	519 (6.0%)	4	3
Filipowicz 1997[37]	NA	Nabumetone (59); Diclofenac (53)	59.9	33 (28.0%)	NA	NA	3
Eversmeyer 1993[38]	USA	Nabumetone 1000–2000 mg (3315); nsNSAID (1096)	NA	NA	457 (10.3%)	12	2
Roth 1994[29]	USA	Nabumetone 1000 mg (20); Naproxen 500 mg (20)	61.4	32 (80.0%)	17 (42.5%)	12	3
Bellamy 1995[41]	Canada	Nabumetone 1000–1500 mg (191); Diclofenac 100 mg (189)	62	268 (74.4%)	NA	26	3
Li 2001[34]	Mainland China	Nabumetone 1000 mg (64); Diclofenac 75 mg (61)	44	NA	NA	12	4
Roth 1987[30]	USA	Nabumetone 1000 mg (20); Naproxen 500 mg (20)	61.4	32 (80%)	0 (0.0%)	12	3
Bianchi 1995[40]	Italy	Nabumetone 2000 mg (30); Naproxen 1000 mg (30)	51.7	43 (71.2%)	10 (16.7%)	24	3
Scott 2000 (study 1)[28]	USA	Nabumetone 1500 mg (200); Diclofenac 100 mg (199)	63.5	226 (63%)	11 (3%)	4	4
Scott 2000 (study 2)[28]	USA	Nabumetone 1500–2000 mg (148); Piroxicam 20–30 mg (147)	63	142 (55%)	10 (9%)	4	4
Morgan 2001[31]	USA	Nabumetone 1000 mg (167); Diclofenac 100 mg (168)	72	236 (71.0%)	35 (10.5%)	12	3
Dougados 2001[53]	Europe	Celecoxib 200 mg (80); Ketoprofen 200 mg (90)	38.5	57 (31.8%)	0 (0%)	6	3
Bensen 1999[57]	Canada	Celecoxib 100 mg (203); Celecoxib 200 mg (197); Celecoxib 400 mg (202); Naproxen 1000 mg (198)	62.2	570 (71.2%)	0 (0%)	12	4

TABLE 1. *Continued*

Author, year	Location	NSAID, Dosage (Number of Participants)	Age, yr	Female, n (%)	Previous Peptic Ulcers, n (%)	Study Duration, wk	Jadad Score
Simon 1999[43]	USA	Celecoxib 200–800 mg (692); Naproxen 1000 mg (225)	54.2	668 (73.0%)	0 (0%)	12	4
Laine 2007[45]	USA	Etoricoxib 60 or 90 mg (17412); Diclofenac 150 mg (17289)	63.2	25,784 (74.0%)	6.5%	156	5
Emery 1999[52]	Multinational	Celecoxib 400 mg (326); Diclofenac 150 mg (329)	55.2	481 (73.4%)	55 (8.5%)	24	5
Singh 2006[42]	Multinational	Celecoxib 400 mg (8800); Diclofenac 100 mg or Naproxen 1000 mg BID (4394)	62.2	10,007 (75.8%)	535 (4%)	12	5
Sieper 2008[44]	Germany	Celecoxib 400 mg (150); Celecoxib 200 mg (153); Diclofenac 150 mg (155)	44.8	141 (31%)	0 (0%)	12	3
Hunt 2003[47]	USA, Canada	Etoricoxib 120 mg (251); Naproxen 1000 mg (244)	53.5	413 (83.5%)	47 (9.5%)	4	5
Hawkey 2004[49]	UK	Celecoxib 200 mg (258); Ibuprofen 2400 mg (260)	58.9	797 (76.5%)	355 (34.6%)	13	4
Hunt 2003[48]	USA, Canada	Etoricoxib 120 mg (221); Ibuprofen 2400 mg (226)	61.6	324 (72.5%)	36 (7.5%)	12	2
Baraf 2007[58]	USA	Etoricoxib 90 mg (3593); Diclofenac 150 mg (3518)	63.7	5099 (71.7%)	290 (4.1%)	36	5
Silverstein 2000[3]	USA, Canada	Celecoxib 800 mg (3987); Ibuprofen 2400 mg/Diclofenac150 mg (3981)	59.5	5418 (68%)	654 (8.2%)	26	5
Cryer 2013[55]	USA	Celecoxib 200 mg (4035); nsNSAID (4032)	63.3	6113 (75.8%)	0 (0%)	26	5
Collantes 2002[56]	Multinational	Etoricoxib 90 mg (353); Naproxen 1000 mg (181)	52.3	436 (81.6%)	NA	12	5
Dahlberg 2009[54]	Sweden, Norway	Celecoxib 200 mg (463); Diclofenac 100 mg (364)	71	635 (68.6%)	0 (0%)	52	5
Kivitz 2004[46]	Multinational	Lumiracoxib 800 mg (227); Lumiracoxib 400 mg (227); Celecoxib 400 mg (223); Ibuprofen 2400 mg (216)	51.7	705 (78.9%)	363 (40.6%)	13	3
Goldstein 2001[50]	USA	Celecoxib 400 mg (270); Naproxen 1000 mg (267)	57.2	360 (67%)	41 (7.6%)	12	5
Goldstein 2000[51]	USA	Celecoxib 50–800 mg (6376); nonselective NSAIDs (2768)	59.3	6387 (69.8%)	1045 (11.5%)	12	4

NA = not available; NSAID = nonsteroidal anti-inflammatory drugs.

TABLE 2. Network Meta-Analyses Comparing Coxibs With Relatively Selective Cyclooxygenase-2 Inhibitors in Preventing Ulcer Complications, Symptomatic Ulcer, and Endoscopic Ulcer

		Event Probability (95% CI)		
Outcome	Study (Participant)	Coxibs	Relatively Selective COX-2 Inhibitors	RR (95% CI)
Ulcer complications	20 (59,717)	0.15% (0.05%, 0.34%)	0.13% (0.04%, 0.32%)	1.17 (0.88, 1.56)
Symptomatic ulcer	16 (34,991)	0.18% (0.01%, 0.74%)	0.21% (0.04%, 0.62%)	1.06 (0.84, 1.34)
Endoscopic ulcer	11 (3903)	4.30% (2.01%, 7.88%)	4.70% (1.35%, 11.13%)	1.00 (0.74, 1.33)

CI = confidence interval; COX = cyclooxygenase; RR = risk ratio.

(Table 2). The crude RR was consistent with those from network meta-analyses adjusting for the prespecified factors (Table 3).

Endoscopic Ulcer

Network meta-analyses evaluating the risk of endoscopic ulcer involved 3903 participants and 465 events from 11 trials. Pairwise meta-analysis comparing relatively selective COX-2 inhibitors with nonselective NSAIDs show no significant heterogeneity across included trials (5 trials; $P = 0.91$, $I^2 = 0\%$), while substantial heterogeneity was shown in the meta-analysis comparing coxibs with nonselective NSAIDs (6 trials; $P = 0.006$, $I^2 = 69\%$). Meta-regression indicated that average age, proportion of females, and study duration did not significantly modify the estimated effects (Supplemental digital content—Table S1, http://links.lww.com/MD/A428).

Network meta-analysis indicated that the event probability was 4.70% (95% CI, 1.35–11.13) for relatively selective COX-2 inhibitors and 4.30% (95% CI, 2.01–7.88) for coxibs. There was no significant difference between relatively selective COX-2 inhibitors and coxibs (RR, 1.18; 95% CI, 0.37–2.92) (Table 2). The crude RR was consistent with those from network meta-analyses adjusting for the prespecified factors (Table 3).

Overall Safety and Tolerability

Table 4 presents the network meta-analyses about the safety of relatively selective COX-2 inhibitors and coxibs taking nonselective NSAIDs as the reference. Network meta-analysis indicated that relatively selective COX-2 inhibitors and coxibs were associated with comparable incidences of total AEs (RR, 1.09; 95% CI, 0.93–1.31), gastrointestinal AEs (RR, 1.04; 95% CI, 0.87–1.25), total withdrawals (RR, 1.00; 95% CI, 0.74–1.33), and gastrointestinal AE-related withdrawals (RR, 1.02; 95% CI, 0.57–1.74).

Sensitivity Analysis

The results of sensitivity analyses are presented in Supplemental digital content-Table S2, http://links.lww.com/MD/A428. The estimated effects for ulcer complications, symptomatic ulcer, and endoscopic ulcer were robust and we did not indicate any major influence to the estimated effects between relatively selective COX-2 inhibitors and coxibs by sensitivity analyses.

DISCUSSION

It has been widely accepted that the NSAIDs with COX-2 selectivity are associated with less gastrointestinal harms. However, the comparative gastroprotective effect of relatively selective COX-2 inhibitors and coxibs remains unclear due to lack of head-to-head trail. In this systematic review, we indirectly compared the gastroprotective effect of relatively selective COX-2 inhibitors and coxibs by Bayesian network meta-analysis. Our study suggested that relatively selective COX-2 inhibitors were associated with comparable risk of ulcer complications, symptomatic ulcer, and endoscopic ulcer as compared with coxibs. Additionally, these 2 different classes of COX-2 inhibitors also showed a similar safety and tolerability profile. These findings provide evidence supporting the use of selective COX-2 inhibitors as an alternative strategy to reduce the gastrointestinal adverse effects in patients requiring NSAID therapy.

TABLE 3. Network Meta-Analyses Comparing Coxibs With Relatively Selective Cyclooxygenase-2 Inhibitors After Adjusting for Potential Influential Factors

	Ulcer Complications		Symptomatic Ulcer		Endoscopic Ulcer	
Adjusted Factor	Study (Participant)	RR (95% CI)	Study (Participant)	RR (95% CI)	Study (Participant)	RR (95% CI)
Average age	18 (55,277)	1.18 (0.35, 3.14)	13 (30,172)	0.75 (0.05, 3.19)	11 (3903)	1.30 (0.33, 3.80)
Proportion of females	19 (55,306)	1.22 (0.32, 3.57)	14 (30,201)	0.71 (0.06, 2.85)	11 (3903)	1.23 (0.36, 3.01)
Proportion of patients with previous peptic ulcers	16 (58,472)	1.40 (0.36, 3.88)	11 (33,521)	0.87 (0.02, 4.96)	NA	NA
Follow-up time	20 (59,717)	1.21 (0.28, 3.49)	16 (34,991)	1.23 (0.10, 4.85)	11 (3903)	1.25 (0.37, 3.26)

CI = confidence interval; NA = not available; RR = risk ratio.

TABLE 4. Network Meta-Analysis Comparing the Safety and Tolerability of Coxibs vs Relatively Selective Cyclooxygenase-2 Inhibitors

Outcome	Study (Participant)	Event Probability (95% CI)		RR (95% CI)
		Coxibs	Relatively Selective COX-2 Inhibitors	
Total AEs	22 (32,630)	45.97% (25.66%, 67.24%)	42.49% (22.86%, 64.27%)	1.09 (0.93, 1.31)
Gastrointestinal AEs	24 (26,550)	24.54% (13.02%, 39.94%)	23.7% (12.28%, 39.15%)	1.04 (0.87, 1.25)
Total withdrawals	24 (12,532)	19.61% (9.04%, 34.90%)	19.42% (9.07%, 34.21%)	1.00 (0.74, 1.33)
Gastrointestinal AE-related withdrawals	15 (24,657)	5.37% (2.14%, 11.01%)	5.22% (2.18%, 10.44%)	1.02 (0.57, 1.74)

AE = adverse event; CI = confidence interval; COX = cyclooxygenase; RR = risk ratio.

Based on the predefined criteria, we did not identify any eligible study directly compared selective COX-2 inhibitors with coxibs. Some trials comparing selective COX-2 inhibitors with coxibs were excluded because the time of follow-up was <4 weeks,[59,60] and the evaluated coxibs (rofecoxib, which has been withdrawn from market) was not covered by this systematic review.[61] Results from these studies suggested that selective COX-2 inhibitors and coxibs were well tolerated[59–61] and showed comparable tolerability profile,[61] which are consistent with our findings. In addition, the study by Truitt et al[61] also suggested that rofecoxib and nabumeton were associated with similar risk of serious gastrointestinal complications, but the estimate effect was based on only 1 event and 289 participants.[11,61]

Since selective COX-2 inhibitors and coxibs showed comparable gastrointestinal safety, the costs and cardiovascular safety become the primary influential factors for selecting the most suitable COX-2 inhibitors for patients. The high cost is still a limitation for coxibs.[9,14,15] Data from the Irish General Medical Services Prescription Database suggested that coxibs were up to 10-fold more expensive, with a median monthly costs of €34.61 for coxibs, compared to €3.26 for nonselective NSAIDs.[15] In addition, coxibs may be associated with increased risk of cardiovascular adverse events, and this has led to the withdrawal of many coxibs, including rofecoxib and valdecoxib. However, not only COX-2 inhibitors but also traditional NSAIDs are associated with increased cardiovascular adverse events. US FDA has announced warnings about cardiovascular safety for COX-2 selective and most nonselective NSAIDs.[62] Future research is expected to directly compare the cost-effectiveness and cardiovascular safety between these agents.

Our study only considered nonselective NSAIDs as the comparator for network meta-analysis because they are the most common control used in the related original trails. Theoretically it is possible to consider other gastroprotective strategies as the comparators in the network meta-analysis models, but including more nodes may increase the complexity and risk of inconsistency in network. Our estimated effects of selective COX-2 inhibitors and coxibs as compared with nonselective NSAID were consistent with previous meta-analyses.[11,14,63]

To the best of our knowledge, this is the first network meta-analysis evaluating the gastroprotective effectiveness between selective COX-2 inhibitors and coxibs. Network meta-analysis provides a coherent and methodologically robust evaluation of comparative effectiveness for multiple interventions, which may help guide clinicians and patients to make informed treatment decisions.[64] This is particularly important as direct comparison between the 2 difference classes of COX2-inhibitors is lacking so clinicians and patients have to make clinical decision based on indirect evidence. In addition, the sample size of this study is large, which make it possible to get a precise estimation of important but rare clinical outcomes, and to control potential influential factors. Lastly, low level of heterogeneity, consistent results from different models adjusting for various influential factors, and stable sensitivity analyses further increased our confidence in the results.

This study need to be explained with caution due to some limitations. Firstly, clinical outcomes like ulcer complications and symptomatic ulcer were sparsely reported and often obtained from drug safety information in the original trials. The definition of clinical outcomes might not be consistent across included studies. Secondly, indirect comparisons from network meta-analyses are observational in nature, which may be biased due to study-level confounding factors.[65,66] Though we have controlled age, sex, patients with previous ulcer disease, and length of follow-up, other factors including *H pylori* infection and ulcer risk were not adjusted due to insufficient data. Lastly, the results may be affected as the mythological quality of some original trials is low. However, the potential influence is unlikely to be substantial because sensitivity analyses by study quality did not show major change to the primary estimated effects.

In conclusion, this systematic review suggested that relatively selective COX-2 inhibitors appear to have a similar gastroprotective effect and tolerability as coxibs. Relatively selective COX-2 inhibitors may be used as an alternative strategy to reduce the gastrointestinal adverse effects in patients requiring NSAID therapy. Because our findings are based on indirect comparisons, future research, particularly head-to-head trials, is required to confirm the conclusion.

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