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Title: Systematic review with meta-analysis: the gastrointestinal benefit of COX-2 selective inhibitors with concomitant use of low-dose aspirin

Running title: Coxib gastrointestinal benefit with aspirin use

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SUMMARY

Background It is uncertain whether concurrent use of low-dose aspirin removes the gastrointestinal benefit displayed by COX-2 selective inhibitors (coxibs) when compared to traditional nonsteroidal anti-inflammatory drugs (NSAIDs).

Aim To evaluate the gastrointestinal risks associated with coxibs and traditional NSAIDs and the interaction with concurrent use of low-dose aspirin.

Methods We searched MEDLINE, EMBASE, and the Cochrane Library through April 2016 to identify randomized trials comparing the gastrointestinal risk between coxibs and traditional NSAIDs in patients taking or not taking low-dose aspirin. Results were combined using random effects meta-analysis. Subgroup analyses by concurrent use of aspirin were undertaken.

Results Eleven trials (84,150 participants) were included. The overall relative risk (RR) of coxibs vs. traditional NSAIDs for complicated gastrointestinal events was 0.54 (95% confidence interval [CI] 0.32 to 0.92), with a significant subgroup difference ($P=0.04$) according to concurrent use of aspirin (Used: $RR=0.96$, 95% CI 0.66 to 1.24; Not used: $RR=0.33$, 95% CI 0.14 to 0.83). The overall RR for clinical gastrointestinal events was 0.59 (95% CI 0.47 to 0.75), with a significant subgroup difference according to aspirin usage ($P=0.008$; Used: $RR=0.77$, 95% CI 0.62 to 0.95; Not used: $RR=0.50$, 95% CI 0.39 to 0.64). Overall coxibs were associated with significantly lower risk of symptomatic ulcers ($RR=0.60$, 95% CI 0.50 to 0.72) and endoscopic ulcers ($RR=0.29$, 95% CI 0.16 to 0.53) than traditional NSAIDs; a significant subgroup difference was shown for endoscopic ulcers ($P=0.05$) but not for symptomatic ulcers ($P=0.27$).

Conclusions Concomitant use of low-dose aspirin reduces but does not completely eliminate the gastrointestinal benefit of coxibs over traditional NSAIDs.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed medicines, commonly used for arthritis and a variety of clinical conditions.¹ Unfortunately, the use of NSAIDs is limited due to gastrointestinal toxicity, ranging in severity from mild dyspepsia to serious ulcer complications like bleeding.^{1, 2} It has been reported that clinical gastrointestinal complications may occur in approximately 2–4% of chronic NSAID users every year.^{3–6} In the United States, NSAIDs are thought to cause about 7000 to 16500 deaths every year.^{7, 8}

It has been recognized that both efficacy and toxicity of NSAIDs result from their inhibition of cyclooxygenase (COX), which primarily has two functionally distinct isoforms, COX-1 and COX-2.^{9, 10} The discovery of COX-2 has led to the important development of COX-2 selective inhibitors (coxibs), which are superior in terms of displaying significantly lower gastrointestinal toxicity than traditional NSAIDs.^{11–13} Aspirin is unique among NSAIDs for its antithrombotic properties, which are beneficial for patients with high risk of thromboembolic cardiovascular events.¹⁴ Low-dose aspirin (75–325 mg q.d) is now widely used for primary and secondary prevention of cardiovascular events.^{15, 16}

Patients with chronic pain and high risk of cardiovascular events often require concurrent administration of NSAIDs and low-dose aspirin. A telephone survey of 325 coxib users indicated that 48.1% of the participants also received aspirin therapy.¹⁷ In large clinical trials of NSAIDs for rheumatoid arthritis or osteoarthritis, approximately 20% to 35% of the participants received low-dose aspirin in addition to NSAIDs.^{18–20} Though the evidence about the gastrointestinal benefit of coxibs, as compared to traditional NSAIDs, is well es-

established, it remains unclear whether the benefit persists in the setting of low-dose aspirin treatment.¹⁴ The CLASS study compared celecoxib with traditional NSAIDs in 8059 patients, subgroup analyses in 1645 patients taking low-dose aspirin indicated no differences between groups²⁰ and these results were consistent with another similar study.¹⁹ However, the MEDAL programme demonstrated that coxibs were associated with significantly fewer uncomplicated gastrointestinal events than traditional NSAIDs in patients receiving low-dose aspirin.¹⁸ Many studies examining endoscopically detected ulcers have also shown conflicting results.²¹⁻²³ Owing to the inconsistency in current evidence, clinicians often face a dilemma whether to prescribe coxibs instead of traditional NSAIDs for patients who require low-dose aspirin treatment. The aim of this meta-analysis was to evaluate the gastrointestinal benefit of coxibs compared to traditional NSAIDs and the interaction with low-dose aspirin treatment.

METHODS

This systematic review and meta-analysis was performed according to the Cochrane handbook for systematic reviews of interventions²⁴ and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).²⁵

Inclusion and exclusion criteria

This systematic review included randomized control trials (RCTs) comparing coxibs (celecoxib, etoricoxib, parecoxib, rofecoxib, valdecoxib, and lumiracoxib) vs. traditional NSAIDs (naproxen, diclofenac, piroxicam, tenoxicam, ibuprofen, etodolac, nabumetone, flurbiprofen, ketoprofen, tiaprofenic, piroxica, piroxen, sulindac, tolmetin, indomethacin, loxoprofen, diflunisal, meloxicam, nimesulide) in patients requiring NSAID treatment. Eli-

gible studies should perform subgroup analysis by concomitant use of low-dose aspirin or have the raw subgroup data.

Data Sources and Searches

The Cochrane Library, MEDLINE and EMBASE were searched through May 2015 to identify potentially eligible studies. The search strategy included terms for gastrointestinal events, NSAIDs, coxibs, and clinical trials using the following combined text and MeSH terms: '*ulcer*', '*bleeding*', '*obstruction*', '*perforation*', '*non-steroidal anti-inflammatory drugs*', '*cyclooxygenase-2-selective inhibitor*', and '*randomized controlled trial*' (see full search strategy in *Supplement-Table S1*). All searches were restricted to human studies and there was no limitation on publication language. We searched Clinical Trials and WHO International Clinical Trials Registry Platform for ongoing studies. Reference lists of the included studies and related review articles were checked for additional studies. The search of electronic databases was updated in April 2016.

Study selection and data extraction

Duplicate records from different databases were initially removed by reference management software. We then evaluated the eligibility of the remaining citations by examining the titles, abstracts and full articles sequentially. If the population in different studies were overlapped, we only included the largest study or the one with the most comprehensive analysis. Two authors (J.Y and M.Y) independently selected studies and extracted data. Disagreements were resolved by discussion with a third author (C.M)..The data extracted for this systematic review include study information, patient characteristics, intervention/control, outcomes, and study methods. We contacted the authors of original studies by email to collect missing

information when necessary.

Quality Assessment

Two investigators (J.Y and C.M) independently evaluated the risk of bias of the included studies using the Cochrane Collaboration's tool.²⁴ This tool evaluated the risk of bias due to random sequence generation, concealment of allocation, blinding, incomplete outcome data, selective reporting, and other sources of bias. The strength of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation system (GRADE).²⁶ The quality of evidence was graded as 'High', 'Moderate', 'Low' and 'Very low' based on the fundamental study design and additional methodological factors.²⁶

Outcome measures

The primary outcome for this review was complicated gastrointestinal events (bleeding, perforation, or obstruction). Clinical gastrointestinal events (bleeding, perforation, obstruction, or symptomatic ulcer), symptomatic ulcer, and endoscopic ulcer were considered as the secondary outcomes. Studies define endoscopic ulcer as any lesion ≥ 3 mm (or 5 mm) with unequivocal depth.

Data Synthesis and Analysis

Meta-analyses were performed with a random effects model which accounts for both within and between-study variability to provide more conservative estimates.²⁷ The summary effect size was calculated as a relative risk (RR), together with its 95% confidence intervals (95% CI). Heterogeneity among studies was assessed with the Q-test and the I^2 -index statistic.²⁸ A value for I^2 greater than 50% accompanied by $p < 0.10$ for the Q-test was regarded as being indicative of moderate-to-high heterogeneity.²⁴ If an outcome of interest achieved statistical

significance, then the number needed to treat (NNT) was calculated based on the summary RR and assumed control risk of included studies.²⁴ To calculate the assumed control risk we used the annualised incidence in the traditional NSAID group reported in included studies. Two studies reported the annualized incidence in the traditional NSAID group,^{5, 20} and we used the data reported by Silverstein and colleagues because the treatment duration was longer and the time-to-event data for participants taking aspirin was larger.²⁰

We evaluated the gastrointestinal effects of coxibs vs. traditional NSAIDs including all participants and the subgroup effect by concurrent use of low-dose aspirin. Because subgroup analyses may suffer bias through confounding by other study-level characteristics,²⁴ we also pooled the within-trial covariate interaction.²⁹ The interaction of concurrent low-dose aspirin use was measured as the ratio of relative risk (RRR) with the method reported by Altman and Bland.³⁰

We evaluated the presence of small-study effect with funnel plots and Egger's test if ten or more studies were included in meta-analyses.^{24, 31} Sensitivity analyses were performed according to sample size (excluding the studies with <400 participants) and risk of bias (excluding the studies with high risk of bias on one or more domain, or with unclear risk of bias on three or more domains). All tests were two sided and used a significance level of $P < 0.05$. The results were presented with "Summary of Findings" tables.²⁴ We presented the results by subgroups to show the estimated effects of individual groups. Data analyses were undertaken using RevMan 5.3 (The Cochrane Collaboration, Copenhagen).

RESULTS

Study characteristics

The search strategy identified 592 potentially eligible citations, of which 231 duplicate citations were excluded. A total of 308 records were excluded after screening the titles/abstracts. We screened the full texts of the 53 remaining studies and 14 studies were considered as potentially eligible.^{5, 18-20, 22, 32-40} Three studies³⁸⁻⁴⁰ were further excluded as their data were totally covered by another study.¹⁸ Finally, 11 studies with 84,150 participants were included in this systematic review (Figure 1).^{5, 18-20, 22, 32-37} No raw subgroup data about concurrent use of low-dose aspirin were available in five studies,^{32-35, 37} so six studies^{5, 18-20, 22, 36} contributed to the final quantitative meta-analysis.

Table 1 presents the characteristics of included studies. Two trials^{22, 34} were performed in the USA and the others were multi-national studies. All studies included patients with chronic musculoskeletal conditions. The average age of participants in included studies ranged from 51.0 to 63.7 years. All studies recruited more females than males (the percentage of female ranged from 67.0% to 83.9%).

Risk of bias

The overall risk of bias of individual trials was low for most included studies. The randomization was adequate in eight trials^{5, 18-20, 22, 32, 35, 37} and the allocation was adequately concealed in six studies.^{5, 18-20, 32, 37} All included studies used double-blinding. The risk of bias due to incomplete outcome data was assessed as low in eleven studies^{5, 18-20, 22, 32, 34-37} and four studies were considered at low risk of selective outcome reporting bias.^{5, 18, 36, 37} A detailed assessment of the risk of bias was presented in the *Supplement-Table S2*. The evaluation of the quality of evidence for study outcomes was presented in Table 2.

Complicated gastrointestinal events

Five studies^{5, 18-20, 22} (74,532 participants) contributed to the meta-analysis of complicated

gastrointestinal events (Figure 2, Table 2). The RR with coxibs vs. traditional NSAIDs, including all participants, was 0.54 (95%CI = 0.32 to 0.92; Heterogeneity: $P=0.001$, $I^2 = 69\%$). Subgroup analysis according to concurrent use of aspirin showed a significant subgroup difference ($P = 0.04$), which was confirmed by the meta-analysis of the interaction term directly retrieved from trials with subgroup analysis data ($RRR = 2.19$, 95%CI = 1.02 to 4.70, *Supplement-Figure 1*). The RR with coxibs vs. traditional NSAIDs was 0.90 (95%CI = 0.66 to 1.24; Heterogeneity: $P=0.94$, $I^2 = 0\%$) in the participants taking low-dose aspirin, and 0.33 (95%CI = 0.14 to 0.83; Heterogeneity: $P=0.002$, $I^2 = 76\%$) in those who did not take low-dose aspirin. The reported annualized incidence of complicated gastrointestinal events in the traditional NSAID group was 0.7% - 1.3% for those who did not take low-dose aspirin.^{5, 20} We estimate 115 (95%CI = 89 to 452) non-aspirin users would need to be treated with coxibs rather than traditional NSAIDs to prevent one complicated gastrointestinal event.

Clinical gastrointestinal events

Five studies^{5, 18-20, 22}(74,532 participants) contributed to the meta-analysis of clinical gastrointestinal events (Figure 3, Table 2). When all results were combined, the RR with coxibs vs. traditional NSAIDs was 0.59 (95%CI = 0.47 to 0.75; Heterogeneity: $P=0.06$, $I^2 = 47\%$). Subgroup analysis by concurrent use of aspirin showed a significant subgroup difference ($P = 0.008$), which was consistent with the meta-analysis of the interaction term ($RRR = 1.63$, 95%CI = 1.22 to 2.17, *Supplement-Figure 1*). The RR with coxibs vs. traditional NSAIDs was 0.77 (95%CI = 0.62 to 0.95; Heterogeneity: $P=0.80$, $I^2 = 0\%$) in the participants taking low-dose aspirin, compared with 0.50 (95%CI = 0.39 to 0.64; Heterogeneity: $P=0.26$, $I^2 = 25\%$) in those who did not take low-dose aspirin. The reported annualized incidence of clinical

cal gastrointestinal events with traditional NSAID use was 6% - 6.6% in patients taking low-dose aspirin and 1.7% - 2.9% in patients not taking low-dose aspirin.^{5, 20} The NNT with coxibs in place of traditional NSAIDs to prevent 1 clinical gastrointestinal event was estimated as 72 (95%CI = 44 to 333) for patients taking low-dose aspirin and 69 (95%CI = 57 to 96) for those who not taking low-dose aspirin.

Symptomatic ulcer

Four studies^{5, 18-20} including 74,107 participants contributed to the meta-analysis of symptomatic ulcer (Figure 4, Table 2). Coxibs were associated with significantly lower risk of symptomatic ulcer than traditional NSAIDs when all data were combined (RR = 0.60, 95%CI = 0.50 to 0.72; Heterogeneity: P=0.87, I² = 0%). Subgroup analysis by concurrent use of aspirin did not show significant between-group difference (P = 0.27), which was consistent with the meta-analyses of the interaction term (RRR = 1.25, 95%CI = 0.86 to 1.82, *Supplement-Figure 1*). The RRs of symptomatic ulcer for coxibs vs. traditional NSAIDs in patients taking, and not taking aspirin were 0.68 (95%CI = 0.51, 0.90; Heterogeneity: P=0.90, I² = 0%) and 0.55 (95%CI = 0.43, 0.69; Heterogeneity: P=0.72, I² = 0%), respectively. The NNT with coxibs in place of traditional NSAIDs to prevent one symptomatic ulcer is 80 (95%CI = 52 to 256) in patients taking low-dose aspirin, compared with 139 (95%CI = 110 to 202) in those not taking aspirin.

Endoscopic ulcer

Two studies^{22, 36} with 1147 participants contributed to the meta-analysis of endoscopic ulcer (Figure 5, Table 2). Both studies defined endoscopic gastric ulcer as any lesion ≥ 3 mm with unequivocal depth. Meta-analysis of all participants indicated that coxibs were associated

with significantly lower risk of endoscopic ulcers (RR = 0.29, 95%CI = 0.16 to 0.53; Heterogeneity: $P = 0.05$, $I^2 = 61\%$). Subgroup analysis suggested that the effect was different according to concurrent use of low-dose aspirin ($P = 0.05$), which was confirmed by meta-analyses of the interaction term (RRR = 2.94, 95%CI = 1.18 to 7.29, *Supplement-Figure 1*). The RR of endoscopic ulcer was 0.46 (95%CI = 0.25 to 0.82; Heterogeneity: $P = 0.41$, $I^2 = 0\%$) in low-dose aspirin users and 0.20 (95%CI = 0.11 to 0.36; Heterogeneity: $P = 0.19$, $I^2 = 41\%$) in non-aspirin users. The NNT with coxibs in place of traditional NSAIDs to prevent one endoscopic ulcer was 6 (95%CI = 4 to 19) for low-dose aspirin users and 5 (95%CI = 4 to 6) for non-aspirin users.

Reporting bias and sensitivity analysis

We did not undertake funnel plot and Egger's test to evaluate reporting bias as the numbers of included studies in meta-analyses were less than ten. Sensitivity analyses according to sample size and risk of bias did not indicate any major influence on the main results (*Supplement-Table S3*).

DISCUSSION

Based on 11 RCTs including a total of 84,150 participants, this study demonstrated that concurrent use of low-dose aspirin reduced but did not completely eliminate the gastrointestinal benefit of coxibs over traditional NSAIDs. There was insufficient evidence that the risk of complicated gastrointestinal events was significantly different between coxibs and traditional NSAIDs in patients taking low-dose aspirin; However, coxibs were associated with significantly lower risk of clinical gastrointestinal events (reduced by 23%), symptomatic ulcer (reduced by 32%), and endoscopic ulcer (reduced by 54%) than traditional

NSAIDs. As the gastrointestinal risk in patients taking NSAIDs and low-dose aspirin is high, the absolute benefits of coxibs are modest to large, 72, 80 and 6 aspirin users would need to be treated with coxibs rather than traditional NSAIDs to prevent one additional clinical gastrointestinal event, symptomatic ulcer, and endoscopic ulcer, respectively.

Of all included studies, 5 studies were not included quantitative meta-analyses. These studies tested the interaction with concurrent use of low-dose aspirin and they generally suggested that low-dose aspirin usage had no effect on the gastrointestinal benefit of coxibs over traditional NSAIDs.^{32-35, 37} However, these tests were generally not powered to be conclusive. In addition to these trials, many other studies have also evaluated the effect of coxibs in aspirin users. In a previous meta-analysis, celecoxib was associated with significantly lower risk of endoscopic ulcer than traditional NSAIDs in patients taking low-dose aspirin (RR = 0.48, NNT = 7.2);⁴¹ however, clinical outcomes were not evaluated in this study. The findings were consistent with two RCTs in healthy adults.^{21, 42} A previous literature review, which included an analysis of coxib vs. traditional NSAID for complicated and clinical events related to low-dose aspirin use, showed similar results as our study;⁴³ however, comparison of results is not possible as no details of their review methods were provided. In a retrospective cohort study of 332,491 patients, Rahme and colleagues suggested that the estimated risk of hospitalization for gastrointestinal bleeding was 6.2/1000 patient-years in celecoxib + aspirin group compared with 8.9/1000 patient-years in non-selective NSAIDs + aspirin group, indicating a significant 38% hazard rate reduction.⁴⁴ In a hospital-based case-control study including 8309 participants, combining aspirin with traditional NSAIDs or coxibs potentiated the risk of bleeding beyond that expected from a simple additive effect

of these agents, the authors concluded that the differences between non-selective NSAIDs and coxibs tend to disappear with concurrent use of low-dose aspirin.⁴⁵ However, traditional NSAIDs and coxibs were not directly compared and the quality of evidence was low.²⁶

The prescription of NSAIDs should be based on both gastrointestinal and cardiovascular safety in clinical practice. Extensive data suggested that both coxibs and traditional NSAIDs (except for naproxen) were associated with an increased risk of cardiovascular events.^{46, 47} To date there are still very few trials showing whether low-dose aspirin remains cardioprotective with concurrent use of other NSAIDs. In a large cohort study, concomitant low-dose aspirin use reversed the increased myocardial infarction risk with coxibs and some non-selective NSAIDs (meloxicam and sulindac), but the risk was not significantly reversed with indomethacin and ibuprofen.⁴⁸ Because the likelihood and severity of gastrointestinal and cardiovascular events differ between patients and agents, quantitative comparison of the harms and benefits would be difficult¹⁴ but warrants further investigation.

Aside from the aforementioned meta-analysis which evaluated the risk of endoscopic ulcer,⁴¹ this is the first systematic review to investigate clinical outcomes and the interaction of concomitant use of low-dose aspirin. The sample size was increased, allowing us to get a more precise estimation of clinical outcomes, than previous studies. Additionally, the methodological quality of included studies and the quality of evidence for the estimated effects was moderate or high, suggesting no major risk of bias in the study results. Our confidence in results is further strengthened by large effects (symptomatic ulcer, endoscopic ulcer), stable sensitivity analyses, low heterogeneity in the subgroup analyses, and consistency with other study results.

A limitation of this study is that most data about coxibs and concurrent use of aspirin were obtained from subgroup data and additional characteristics were often not reported, thus, we were unable to undertake further analysis to investigate the potential influence. The numbers of studies in meta-analyses were generally small so we cannot investigate the potential influence of treatment duration, comorbidities, and other risk factors. In addition, subgroup analyses should be interpreted with caution as they may suffer bias through confounding by other study-level characteristics.⁴⁹ However, the credibility of subgroup analyses is high because (i) concurrent use of aspirin was a pre-specified and the only characteristic to explore in analyses, (ii) the subgroup results were consistent with the meta-analyses of the within-trial covariate interaction, (iii) statistical tests suggest that the significant subgroup differences are unlikely caused by chance, (iv) the direction of subgroup effect is correctly prespecified and consistent across all outcomes, and (v) the subgroup effect is consistent with evidence from other resources.^{41, 44, 50} Moreover, though our meta-analysis greatly increased the sample size, it was still too small to detect a clinically meaningful difference in complicated ulcer events between coxib and traditional NSAID in patients taking low-dose aspirin. However, the large and significant effect on symptomatic and endoscopic ulcers does suggest a real decrease in gastrointestinal harms with coxib use. Lastly, we are unsure if the study results are influenced by publication bias because the numbers of studies included meta-analyses were less than 10 so the funnel plot and Egger's test were not undertaken. However, when small studies were excluded in sensitivity analyses the results were not influenced.

Overall, this study demonstrated consistent evidence that concomitant use of low-dose

aspirin reduces but does not completely eliminate the gastrointestinal benefit of coxibs over traditional NSAIDs. The risk of clinical gastrointestinal events, symptomatic ulcers, and endoscopic ulcers associated with coxibs was significantly lower than it was with traditional NSAIDs in patients taking low-dose aspirin. As the selection of NSAIDs should not only be based on the gastrointestinal safety but also the cardiovascular safety, the benefits and harms need to be assessed on a case-by-case basis. Because the gastrointestinal risk is high in patients taking both aspirin and NSAIDs, use of gastroprotectants, particularly proton pump inhibitors, is important to provide sufficient gastroprotection.¹³ Further trials are needed to clarify whether coxibs are associated with lower risk of complicated gastrointestinal event in patients taking low-dose aspirin and whether the gastrointestinal benefit of coxibs outweighs potential cardiovascular benefits seen with some traditional NSAIDs, such as naproxen.

AUTHORSHIP

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Author contributions: J.Y and C.M contributed to conception and design of the study. J.Y, M.Y, and C.M contributed to acquisition of data; J.Y, C.M contributed to quality assessment; J.Y, J.H and C.M undertook the statistical analysis; J.Y, D.T, and M.Y drafted the report; X.Q, D.Y, J.T, J.H contributed to critical revision of the manuscript for important intellectual content. All authors commented on drafts of the paper and have approved the final draft of the manuscript.

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STATEMENT OF INTERESTS

This study was not funded. The authors declare that there are no conflicts of interest.

SUPPORTING INFORMATION

Additional Supporting Information is available online.

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Figures legends

Figure 1. PRISMA flowchart of study selection.

Figure 2. Meta-analysis of complicated gastrointestinal events stratified by concurrent use of low-dose aspirin.

Coxibs: COX-2 selective inhibitors; NSAID: Non-steroidal anti-inflammatory drug; CI: confidence interval.

Figure 3. Meta-analysis of clinical gastrointestinal events stratified by concurrent use of low-dose aspirin.

Coxibs: COX-2 selective inhibitors; NSAID: Non-steroidal anti-inflammatory drug; CI: confidence interval.

Figure 4. Meta-analysis of symptomatic ulcer stratified by concurrent use of low-dose aspirin.

Coxibs: COX-2 selective inhibitors; NSAID: Non-steroidal anti-inflammatory drug; CI: confidence interval.

Figure 5. Meta-analysis of endoscopic ulcer stratified by concurrent use of low-dose aspirin.

Coxibs: COX-2 selective inhibitors; NSAID: Non-steroidal anti-inflammatory drug; CI: confidence interval.

Table 1. Characteristics of included studies

Author, Year (Study name)	Country	Intervention, dosage (number of patients)	Average age, years	Female, n (%)	Previous peptic ulcers, n (%)	<i>H. pylori</i> infection, n (%)	Concurrent use of low-dose aspirin, n (%)	Study duration
Simon 1999 ³⁷	USA, Canada	Celecoxib 200-800 mg (692); Naproxen 1000 mg (225)	54.2	668(73.0%)	0(0%)	NA	81(8.82%)	12 weeks
Silverstein 2000 (CLASS) ²⁰	USA, Canada	Celecoxib 800 mg (3987); Ibuprofen 2400 mg/Diclofenac 150 mg (3981)	59.5	5418(68%)	654(8.2%)	3020(37.9%)	1645(20.6%)	26 weeks
Goldstein 2001 ²²	USA	Celecoxib 400 mg (270); Naproxen 1000 mg (267)	57.2	360(67%)	41(7.6%)	66(12.3%)	57(10.6%)	12 weeks
Sikes 2002 ³⁶	USA, Canada	Valdecoxib 10 mg (204); Valdecoxib 20 mg (219); Ibuprofen 2400 mg (207); Diclofenac 150 mg (212)	60.1	573(68.1%)	118(14.0%)	343(40.7%)	109(15.1%)	12 weeks
Hunt 2003 ³³	USA, Canada	Etoricoxib 120 mg (221); Ibuprofen 2400 mg (226)	61.6	324(72.5%)	36(7.5%)	257(57.5%)	20(4.47%)	12 weeks
Lisse 2003 ³⁵	USA, Sweden	Rofecoxib 25 mg (2799); Naproxen 1000 mg (2787)	63	3948(71.0%)	NA	NA	719(12.9%)	12 weeks
Kivitz 2004 ³⁴	USA	Rofecoxib 12.5 mg (424); Nabumetone 1000 mg (410)	63.0	573(68.7%)	NA	NA	124(11.9%)	6 weeks
Schnitzer 2004 (TARGET) ¹⁹	Multinational	Lumiracoxib 400 mg (9117); tNSAIDs 1000 mg (9127)	63.4	13933(76%)	NA	8057(44%)	4326(23.7%)	52 weeks
Singh 2006 (SUCCESS-I) ⁵	Multinational	Celecoxib 200/400 mg (8800); Diclofenac 100 mg or Naproxen 1000 mg (4394)	62.2	10007(75.8%)	535(4%)	NA	937(7.15%)	12 weeks
Laine 2007 (MEDAL) ¹⁸	Multinational	Etoricoxib 60 or 90 mg (17412); Diclofenac 150 mg (17289)	63.2	20305(74%)	2260(6.5%)	NA	12006(35%)	78 weeks
Cheung 2010 ³²	Mainland China, Taiwan	Celecoxib 400 mg (440); Diclofenac 100 mg (440)	51	738(83.9%)	22(2.5%)	NA	18(2%)	12 weeks

H. pylori: *Helicobacter pylori*; tNSAID: traditional nonsteroidal anti-inflammatory drug. NA: Not available.

Table 2. Summary of findings: the gastrointestinal events with coxibs vs. traditional NSAIDs by concomitant aspirin use

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	traditional NSAIDs	coxibs			
Concomitant use of low-dose aspirin - YES					
Complicated GI events	21 per 1000	19 per 1000 (14 to 26)	RR 0.90 (0.66 to 1.24)	18397 (5)	+++O Moderate ¹
Clinical GI events	60 per 1000	46 per 1000 (37 to 57)	RR 0.77 (0.62 to 0.95)	18397 (5)	++++ High
Symptomatic ulcer	39 per 1000	27 per 1000 (20 to 35)	RR 0.68 (0.51 to 0.90)	18340 (4)	++++ High
Endoscopic ulcer	298 per 1000	137 per 1000 (74 to 244)	RR 0.46 (0.25 to 0.82)	164 (2)	++++ High
Concomitant use of low-dose aspirin - NO					
Complicated GI events	13 per 1000	4 per 1000 (2 to 8)	RR 0.33 (0.14, 0.83)	56135 (5)	+++O Moderate ²
Clinical GI events	29 per 1000	15 per 1000 (11 to 19)	RR 0.50 (0.39, 0.64)	56135 (5)	++++ High
Symptomatic ulcer	16 per 1000	9 per 1000 (7 to 11)	RR 0.55 (0.43, 0.69)	55767 (4)	++++ High
Endoscopic ulcer	251 per 1000	50 per 1000 (28 to 90)	RR 0.20 (0.11, 0.36)	983 (2)	++++ High

*The basis for the **assumed risk** is the annualized incidence in the traditional NSAID group from Silverstein 2000. Annualized incidence data were not available for endoscopic ulcer; we used the median control group risk across studies as the assumed risk. The **corresponding risk** (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).

1. Downgrade one level for imprecision.

2. Downgrade one level for inconsistent results (Heterogeneity: $P = 0.002$, $I^2=69\%$)

CI: Confidence interval; RR: Risk ratio; NSAID: nonsteroidal anti-inflammatory drug; GI: Gastrointestinal.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Supporting Information Legends

Table S1. Search strategy (Medline, Ovid)

Table S2. The risk of bias for included studies

Table S3. Sensitivity analysis by sample size and study quality.

Figure S1. Meta-analysis evaluating the interaction of low-dose aspirin use and the gastrointestinal benefit of coxibs over traditional NSAIDs.

PRISMA Checklist

Table 1 | Checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	Title
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, 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	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	NA
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	4-5
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	5
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	5
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	5
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	5
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	5-6
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means)	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	6-7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	6
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	7
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	7-8
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	8
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)	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	Fig 2-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	8-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Table 2
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	11. Appendix
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	11-12
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	13-14
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 (such as supply of data) and role of funders for the systematic review	16