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CLINICAL RESEARCH STUDY

Comparing Rates of Dyspepsia with Coxibs vs NSAID+PPI: A Meta-Analysis

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ABSTRACT

PURPOSE: Because dyspeptic symptoms are far more prevalent than ulcer complications in users of nonsteroidal anti-inflammatory drugs (NSAIDs), economic models indicate that dyspepsia rates (not ulcer complications) are the major determinant of cost-effectiveness in treating arthritis. We performed a meta-analysis to compare rates of dyspepsia for two common therapies in high-risk patients with arthritis: cyclooxygenase-2 inhibitor (Coxib) alone and combination therapy with a nonselective NSAID and a proton pump inhibitor (PPI) (NSAID+PPI).

METHODS: We performed a systematic review to identify trials comparing either a Coxib versus NSAID or NSAID+PPI versus NSAID in chronic arthritis. We selected studies that report incident dyspepsia, defined a priori as “epigastric pain,” “dyspepsia,” and “nausea.” We then performed meta-analysis to compare the relative risk reduction and absolute risk reduction of dyspepsia for Coxib versus NSAID and NSAID+PPI versus NSAID.

RESULTS: Meta-analysis of 26 studies comparing dyspepsia between Coxibs and NSAIDs revealed a 12% relative risk reduction for Coxibs with an absolute risk reduction of 3.7%. Meta-analysis of four studies comparing dyspepsia between the NSAID+PPI combination and NSAIDs alone revealed a 66% relative risk reduction for NSAID+PPI with an absolute risk reduction of 9%. Compared with the NSAID strategy, the number needed to treat to prevent dyspepsia was 27 for Coxibs and 11 for NSAID+PPI.

CONCLUSION: NSAID+PPI affords greater risk reduction for dyspepsia than Coxibs when compared with the common baseline of NSAIDs. Because there are limited head-to-head data comparing Coxibs versus NSAID+PPI, these data provide the best indirect evidence that NSAID+PPI may be superior to Coxibs in minimizing incident dyspepsia. © 2006 Elsevier Inc. All rights reserved.

KEYWORDS: Cox-2 inhibitors; Proton pump inhibitors; Dyspepsia; Meta-analysis

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used medications for chronic arthritis, accounting for 111 million prescriptions annually and 3% of the American prescription drug market.^{1,2} These agents continue to serve as the mainstay of treatment despite their association with clinically significant peptic ulcer complications, including symptomatic ulcers, ulcer hemorrhages, and ulcer perforations.³ The economic impact of these adverse events is significant, resulting in more than 100 000 hospitalizations annually at a cost of \$1.6 billion.^{1,4}

The prevalence of patients at high risk for developing an NSAID complication, including the elderly and patients taking Coumadin, steroids, or aspirin,³ has increased signif-

icantly with the aging of the American population and the increasing use of aspirin for cardiovascular prophylaxis. Management guidelines for the use of anti-inflammatory drugs in arthritis have traditionally recommended two competing therapies in these high-risk patients: a cyclooxygenase-2 inhibitor (Coxib) alone or a nonselective NSAID in combination with a proton pump inhibitor (PPI) (NSAID+PPI).^{5,6}

Although it is well established that both Coxibs and NSAID+PPI therapy reduce ulcer complications by 40% to 60% versus NSAIDs alone,⁷⁻¹¹ it is unclear whether these therapies reduce dyspeptic symptoms versus NSAIDs alone. It is relevant to examine dyspeptic symptoms because the most prevalent and resource-consuming side effects of NSAIDs are not peptic ulcer complications but foregut dyspeptic symptoms such as “epigastric pain,” “dyspepsia,” and “nausea.”¹² Recent data from a meta-analysis indicate that between 8% and 12% of patients receiving chronic high-dose NSAID therapy develop recurrent dyspeptic symptoms.¹² In contrast, only 1% to 2% develop severe complications such as ulcer hemorrhage or perforation.⁷⁻¹¹ Dyspeptic symptoms may result in the extensive use of varied health care resources, including primary care and subspecialty office visits, upper endoscopy, endoscopic biopsy, antisecretory therapy, and *Helicobacter pylori* testing and treatment.¹³ Therefore, although dyspeptic symptoms are often dismissed as a nuisance of less clinical significance than dramatic ulcer bleeds or perforations, they are responsible for a significant portion of the economic and clinical burden of NSAID therapy. We previously demonstrated that the rate of dyspeptic symptoms has important cost-effectiveness implications when selecting between Coxibs and nonselective NSAIDs,^{14,15} a result reflecting the high prevalence and expense of dyspeptic symptoms in NSAID users. Specifically, we previously demonstrated that the incidence of NSAID-induced dyspepsia is one of only five key drivers of overall cost-effectiveness when selecting between Coxibs and nonselective NSAIDs, and plays a larger role in driving outcomes than the incidence of ulcer hemorrhage.¹⁴

It is therefore relevant to examine the rates of dyspeptic symptoms for Coxibs versus the NSAID+PPI combination. Moreover, in light of recent concerns regarding the cardiovascular safety of Coxibs, it is especially relevant to reassess the putative gastrointestinal advantages of Coxibs in comparison with nonselective NSAIDs.

Because there are few head-to-head data comparing Coxibs versus the NSAID+PPI combination, we performed a meta-analysis to indirectly compare Coxibs and NSAID+PPI through the common baseline of NSAIDs alone. We therefore evaluated 2 groups of studies: Coxib

versus NSAID studies and NSAID+PPI versus NSAID studies. We formulated three a priori hypotheses: (1) Coxibs have a lower incidence of dyspeptic symptoms versus NSAIDs, (2) NSAID+PPI therapy has a lower incidence of dyspeptic symptoms versus NSAIDs, and (3) NSAID+PPI therapy affords a greater risk reduction for dyspepsia than Coxibs when compared with the common baseline of NSAIDs.

CLINICAL SIGNIFICANCE

- Using the combination therapy of nonselective non-steroidal anti-inflammatory drug plus proton pump inhibitor to treat chronic arthritis pain may result in fewer cases of dyspepsia than treatment with a cyclooxygenase-2 inhibitor alone.

METHODS

Search Strategy and Inclusion Criteria

We conducted a structured search of MEDLINE, along with a CD-ROM-assisted (DDW Abstracts-on-Disc; American Gastroenterological Association, Bethesda, Md) review of published abstracts from three major subspecialty journals (*American Journal of Gastroenterology*, *Arthritis and Rheumatism*, and *Gastroenterology*), to identify relevant English-language studies from January 1990 to March 2005. In addition, we reviewed the bibliographies of key review articles for references not captured by our search strategy. We targeted randomized, controlled trials that compared Coxib versus NSAID, NSAID+PPI versus NSAID, or Coxib versus NSAID+PPI in the management of chronic arthritis pain.

Table 1 lists the keywords and search strings used to perform the systematic review. Two reviewers (B.S., M.F.) assessed the generated titles for relevancy and only rejected titles that fulfilled the following explicit exclusion criteria: not written in English, not concerning a clinical question regarding human subjects, not related to chronic arthritis, or solely related to acute arthritis or an acute pain syndrome. The reviewers then individually assessed the relevancy of all abstracts corresponding with the remaining titles and excluded abstracts for the following reasons: fulfilled one or more of the title exclusion criteria; was not a randomized clinical trial; and did not compare Coxib versus NSAID, NSAID+PPI versus NSAID, or Coxib versus NSAID+PPI. The reviewers then independently assessed the relevancy of all articles corresponding with the remaining abstracts and included articles if they fulfilled all of the previous criteria and reported data regarding prespecified foregut symptoms of dyspepsia, including “dyspepsia” itself, “epigastric pain,” and “nausea.”¹³ Because the American Gastroenterological Association does not include symptoms of gastroesophageal reflux (eg, “acid reflux,” “heartburn,” and “pyrosis”) within the definition of dyspepsia,¹³ and because there are limited biologic and clinical data to support the hypothesis that NSAIDs cause acid reflux, we did not include reflux symptoms in our analysis. Each study was independently abstracted for data by 2 inves-

Table 1 Systematic Review Search Strategy

Group	Search Terms	Significance of Grouping
1	MEDLINE	Targeted bibliographic database
2	Randomized-controlled-trial or controlled-clinical-trial or randomized-controlled-trials or random-allocation or double-blind-method or single-blind-method or clinical-trial or clinical-trials or (clin* near trial*) or ([singl* or doubl* or trebl* or tripl*) near (blind* or mask*)	Filter to identify randomized controlled trials
3	(Rofecoxib or celecoxib or valdecoxib or etoricoxib or Coxib or Cox-2 or cyclooxygenase-2) OR ([naproxen or diclofenac or ibuprofen or ketorolac or meloxicam or indomethacin or ketoprofen or nabumetone or etodolac or piroxicam or sulindac or aspirin or ASA or salsalate or NSAID] and [lansoprazole or omeprazole or esomeprazole or rabeprazole or pantoprazole or proton pump inhibitor*])	Targeted content keywords
4	(TG = animal or letter [pt] or editorial [pt] or review [pt] or news [pt] or cancer or carcinoma or malignancy or neoplasm)	Excluded study types and content

Coxib = cyclooxygenase-2 inhibitor; ASA = acetyl salicylic acid; NSAID = nonsteroidal anti-inflammatory drug.

*Keyword truncation. The four search groups were combined as follows: (1 AND 2 AND 3 NOT 4).

tigators (B.S., M.F.), and the results were entered onto a standardized electronic abstraction form. In addition, the abstractors assigned a score for methodologic quality by applying the Jadad scale, which is a standardized instrument focusing on features related to internal validity, where a score greater than 3 denotes “high quality.”¹⁶ We measured interrater agreement for each step with a κ statistic and adopted a threshold of 0.7 or greater as the definition for acceptable agreement.¹⁷ Disagreements were settled by discussion and consensus between the 2 primary reviewers and a third-party arbiter (F.K.).

Statistical Analysis

Before conducting statistical analysis, we first constructed evidence tables and performed a qualitative assessment for

homogeneity by comparing key study features, including patient demographic characteristics (age and gender), indication for treatment, concurrent use of aspirin or corticosteroids, *H. pylori* status, and history of complicated ulcer. If the studies were qualitatively homogeneous, we then performed meta-analysis using Stata statistical software v8.0 (Stata Corp, College Station, Tex) to compare the relative risk reduction (RRR) and absolute risk reduction (ARR) for dyspeptic symptoms (combined outcome of patients with “dyspepsia” plus patients with “epigastric pain” plus patients with “nausea”) in the following groups of studies: (1) Coxib versus NSAID studies and (2) NSAID+PPI versus NSAID studies. For dose-ranging studies with more than 2 arms, we collapsed all patients receiving the same class of drug into one arm to fit each study into the 2×2 factorial design required for meta-analysis. We then calculated the number needed to treat with either a Coxib or NSAID+PPI therapy to prevent one additional dyspeptic symptom compared with NSAID alone.

We performed a statistical test for heterogeneity and adopted a *P* value of greater than .05 as evidence for homogeneity.¹⁸ If the data were homogeneous, we then selected a fixed-effects model.¹⁸ If the data were heterogeneous, we then performed both a fixed and random-effects model.¹⁸

Because our comparison between Coxibs and NSAID+PPI was indirect (through the common baseline of NSAIDs), we compared the incidence of dyspepsia in the NSAID arms from both groups of studies (Coxib vs NSAID studies and NSAID+PPI vs NSAID studies). We first calculated the weighted mean incidence of dyspepsia from the NSAID arms of each group of studies and then compared the weighted means using a chi-square test. If the weighted means were not statistically different at the $\alpha = 0.05$ level, we then assumed that the NSAIDs behaved similarly in both groups of studies.

Sensitivity Analyses

We performed a series of 4 sensitivity analyses to test the robustness of our results: (1) meta-analysis confined to studies with high methodologic quality, defined as a Jadad score of 4 or 5;¹⁶ (2) meta-analysis of the symptom “dyspepsia” alone; (3) meta-analysis of the symptom “epigastric pain” alone; and (4) meta-analysis of the symptom “nausea” alone. In addition, because all Coxibs may not be equally comparable, we conducted separate analyses for the following Coxibs: (1) celecoxib, (2) etoricoxib, (3) lumiracoxib, (4) rofecoxib, and (5) valdecoxib.

Assessment for Publication Bias

We performed a qualitative appraisal of publication bias by constructing a funnel plot and observing for evidence of asymmetry,¹⁸ and performed a quantitative appraisal for publication bias by conducting an Egger’s test.¹⁸ We assumed there was evidence for publication bias if there

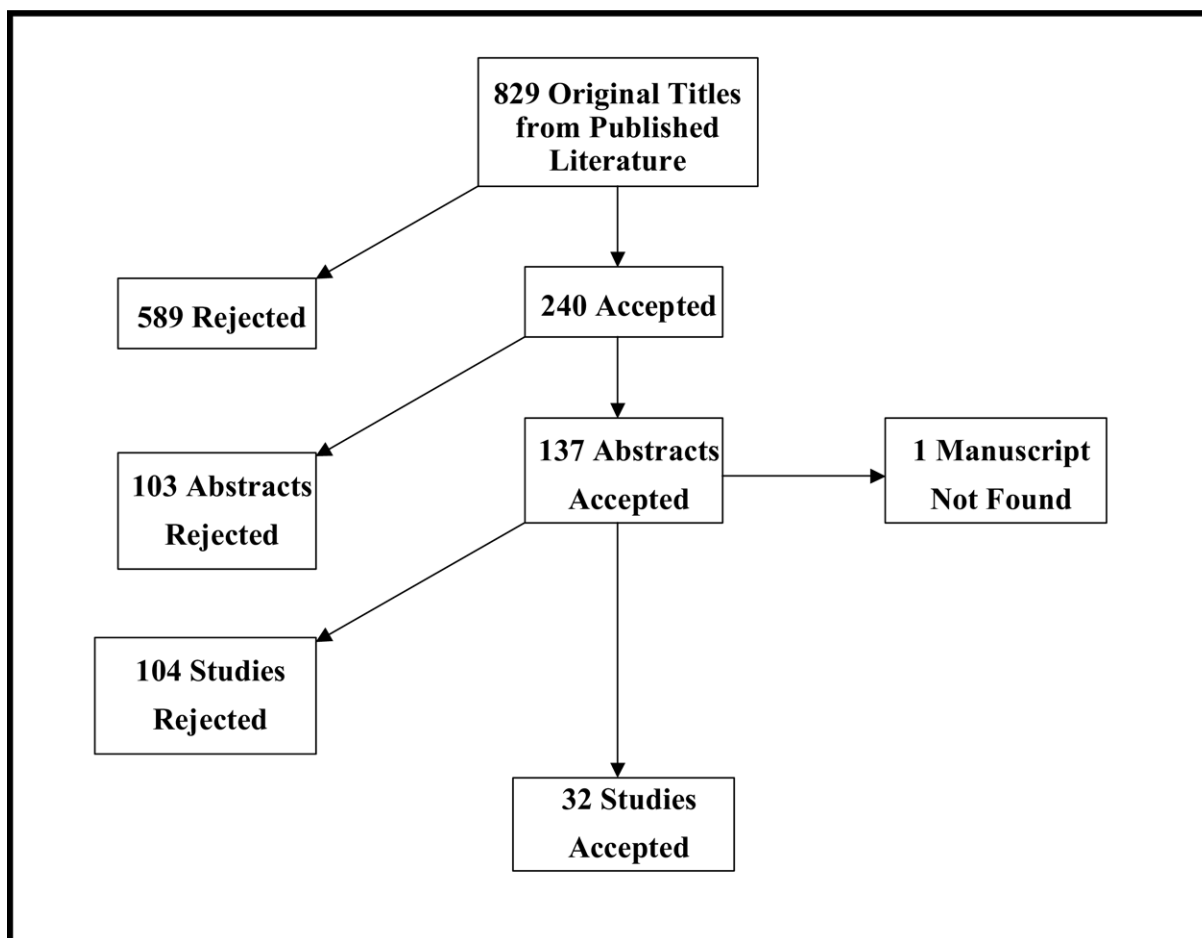


Figure 1 Results of literature search.

was a qualitative lack of small “negative” studies on the funnel plot, or if the P value for the Egger’s test was less than .10.¹⁸

RESULTS

Article Selection

The search strategy identified 829 titles (Figure 1). Of these, we selected 32 studies that met our explicit inclusion criteria and reported one or more of our prespecified outcomes ($\kappa > 0.9$ for each phase of selection).^{9,11,19-48} There were 42 079 participants in the 32 trials. The reported mean age ranged from 39 to 74 years. The follow-up period ranged from 1 to 72 weeks (mean = 18 weeks). Twenty-six studies compared rates of incident dyspeptic symptoms between Coxibs and NSAIDs,^{9,11,19-42} and 4 studies compared rates of incident dyspeptic symptoms between NSAID+PPI and NSAIDs.⁴³⁻⁴⁶ We identified only 2 studies that compared incident dyspeptic symptoms between a Coxib and NSAID+PPI combination therapy.^{47,48}

Article Quality

Tables 2 and 3 provide information regarding the 32 trials included in the meta-analysis, including their Jadad quality

score. The mean Jadad score was 3.5 ± 1.8 . Sixty-nine percent of the trials met criteria for high quality (Jadad score ≥ 3). All of the studies were described as “randomized,” and all studies but one²⁹ were described as “double blind.” Sixty percent of the trials described appropriate concealed allocation, 67% described appropriate blinding techniques, and 98% described withdrawals and dropouts.

Dyspeptic Symptoms Between Coxibs and NSAIDs

Table 2 provides information regarding the 26 randomized trials ($N = 41\,529$ subjects) that compared a Coxib versus a nonselective NSAID.^{9,11,19-48} The studies were qualitatively similar in terms of mean age, gender breakdown, treatment indication, corticosteroid and aspirin use, *H. pylori* status, and history of complicated ulcer. Meta-analysis of the 26 studies revealed a 12% RRR in dyspeptic symptoms for Coxibs versus nonselective NSAIDs (RR = 0.88; 95% confidence interval [CI] = 0.85-0.91) with an ARR of 3.7% (Figure 2). Therefore, 27 patients need to be treated with a Coxib instead of a nonselective NSAID to prevent one additional dyspeptic symptom. Because these results were statistically homogeneous (P value for test of heterogeneity = .12), we did not perform a random effects model.

Table 2 Evidence Table of Randomized Trials Comparing Coxibs versus Nonsteroidal Anti-Inflammatory Drugs

First Author (Citation)	N	Study Duration (wk)	Mean Age (y)	Proportion HP positive	Proportion with Past Ulcer	Proportion on Steroids	Proportion on Aspirin	Jadad Score	NSAID Comparator	Coxib Comparator
Bensen (19)	659	12	55	Not stated	0.08	Not stated	Not stated	1	Naproxen	Valdecoxib
Cannon (20)	784	52	63	Not stated	Not stated	Not stated	Not stated	5	Diclofenac	Rofecoxib
Day (21)	735	6	63	Not stated	Not stated	Not stated	Not stated	5	Ibuprofen	Rofecoxib
Dougados (22)	170	6	39	Not stated	Not stated	Not stated	Not stated	1	Ketoprofen	Celecoxib
Emery (23)	655	24	55	Not stated	0.08	0.42	Not stated	5	Diclofenac	Celecoxib
Geusens (24)	734	12	53	Not stated	Not stated	0.57	Not stated	5	Naproxen	Rofecoxib
Goldstein (25)	537	12	56	0.33	0.21	0.11	Not stated	5	Naproxen	Celecoxib
Hawkey (26)	581	24	62	0.57	Not stated	Not stated	Not stated	3	Ibuprofen	Rofecoxib
Hawkey (27)	439	12	51	0.6	0.12	0.59	Not stated	5	Naproxen	Rofecoxib
Hawkey (28)	784	13	58	0.69	0.33	Not stated	Not stated	5	Ibuprofen	Lumiracoxib
Izhar (29)	28	12	58	Not stated	Not stated	Not stated	Not stated	0	Diclofenac	Celecoxib
Kivitz (30)	613	12	59	Not stated	0.12	Not stated	Not stated	5	Naproxen	Valdecoxib
Kivitz (31)	834	6	63	Not stated	Not stated	Not stated	0.15	5	Nabumetone	Rofecoxib
Kivitz (32)	843	12	62	Not stated	Not stated	Not stated	0.18	4	Naproxen	Celecoxib
Kivitz (33)	893	13	51	0.41	Not stated	Not stated	Not stated	3	Ibuprofen	Lumiracoxib
Leung (34)	445	12	63	Not stated	Not stated	Not stated	Not stated	5	Naproxen	Etoricoxib
Makarowski (35)	249	12	62	Not stated	0.1	Not stated	Not stated	1	Naproxen	Valdecoxib
Matsumoto (36)	833	52	56	Not stated	Not stated	Not stated	0.18	5	Naproxen	Celecoxib
McKenna (37)	400	6	61	Not stated	0.08	Not stated	0.15	0	Diclofenac	Celecoxib
Mylykangas (38)	926	6	62	Not stated	0.04	Not stated	Not stated	5	Naproxen	Rofecoxib
Pavelka (39)	722	26	55	0.37	0.075	Not stated	0.06	5	Diclofenac	Valdecoxib
Saag (40)	693	52	62	Not stated	Not stated	Not stated	Not stated	5	Diclofenac	Rofecoxib
Schnitzer (41)	18,244	52	63	0.44	Not stated	Not stated	0.24	5	Ibuprofen	Lumiracoxib
Sikes (42)	842	12	60	0.4	0.14	Not stated	Not stated	3	Diclofenac/ ibuprofen	Valdecoxib
Silverstein (9)	7968	78	60	0.38	0.08	0.3	0.2	5	Diclofenac/ ibuprofen	Celecoxib
Simon (43)	918	12	54	Not stated	Not stated	0.37	0.08	5	Naproxen	Celecoxib

NSAID = nonsteroidal anti-inflammatory drug; Coxib = cyclooxygenase-2 inhibitor; HP = *Helicobacter pylori*.

There was no qualitative or quantitative evidence of publication bias (*P* value for Egger’s test >.10).

Dyspeptic Symptoms Between NSAID+PPI and NSAID

Table 3 provides information regarding the 4 randomized trials (N = 550 subjects) that compared combination NSAID+PPI

therapy versus a nonselective NSAID.⁴³⁻⁴⁶ These studies were qualitatively similar (Table 3). Meta-analysis of the 4 studies revealed a 66% RRR in dyspeptic symptoms for NSAID+PPI versus nonselective NSAIDs (RR = 0.34; CI = 0.22-0.54) with an ARR of 9% (Figure 3). Therefore, 11 patients need to be treated with NSAID+PPI therapy instead of a nonselective NSAID to prevent one additional dyspeptic symptom. Because

Table 3 Evidence Table of Randomized Trials Comparing NSAID+PPI versus NSAIDs*

First Author (Citation)	N	Duration of Study (wk)	Mean Age (wk)	Proportion HP positive	Proportion with Past Ulcer	Jadad Score	NSAID + PPI Comparator	NSAID Comparator
Bianchi Porro (43)	103	12	52	Not stated	Not stated	1	Omeprazole+indomethacin, ketoprofen or diclofenac	Indomethacin, ketoprofen, or diclofenac
Bianchi Porro (44)	104	12	58	0.4	Not stated	5	Pantoprazole+indomethacin, ketoprofen or diclofenac	Indomethacin, ketoprofen, or diclofenac
Cullen (45)	168	24	56	0.24	0.24	1	Omeprazole+diclofenac, naproxen, indomethacin, nabumetone or piroxicam	Diclofenac, naproxen, indomethacin, nabumetone, or piroxicam
Ekstrom (46)	175	12	59	0.52	0.25	1	Omeprazole+NSAID	NSAID

HP = *Helicobacter pylori*; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.

*Proportion of patients taking aspirin and/or steroids not provided in any studies.

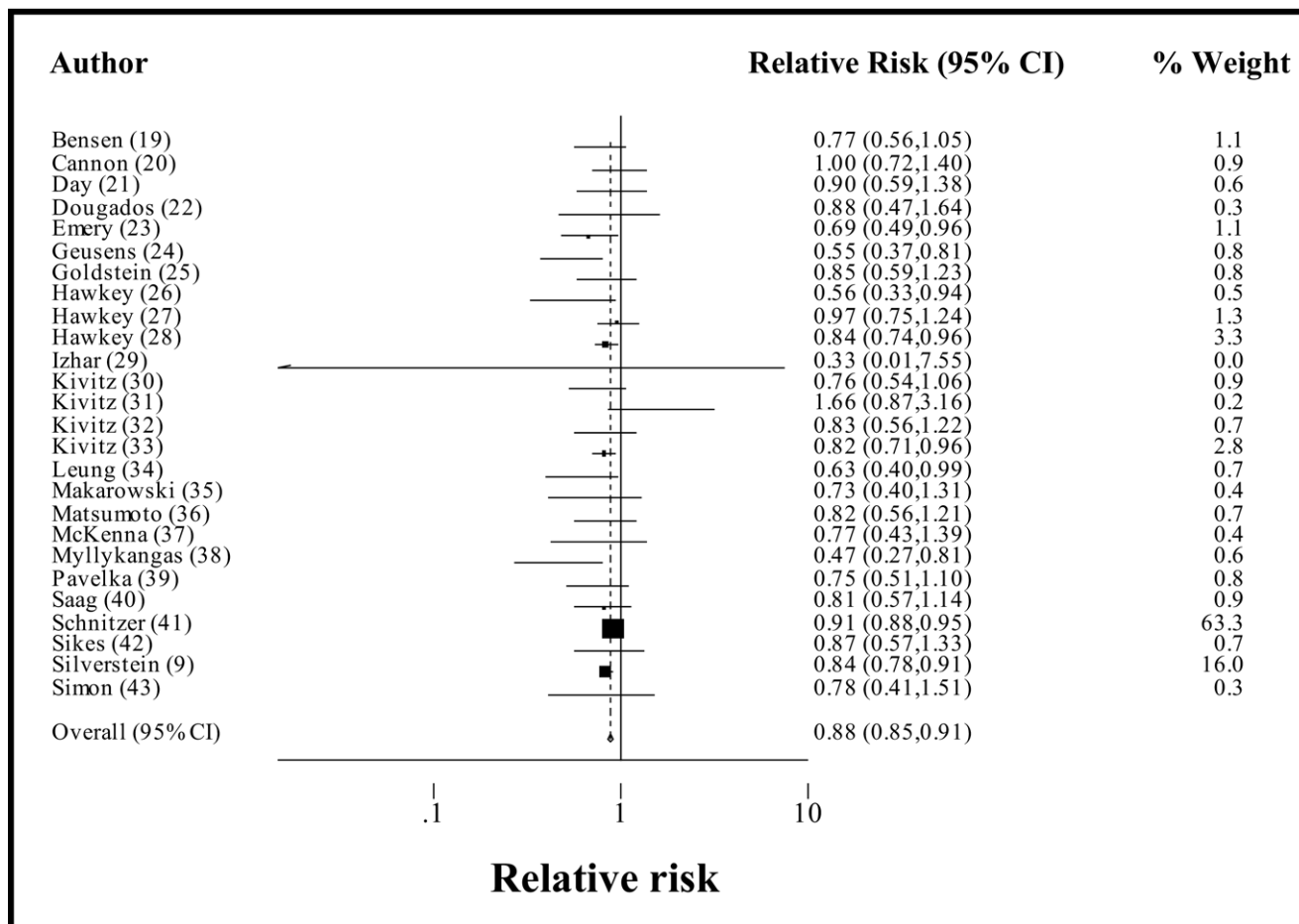


Figure 2 Meta-analysis using the fixed-effects model of randomized controlled trials that report upper gastrointestinal dyspeptic symptoms in patients receiving a cyclooxygenase-2 inhibitor (Coxib) versus a nonselective nonsteroidal anti-inflammatory drug (NSAID). Summary estimate is the relative risk with 95% confidence intervals (CIs).

these results were statistically homogeneous (P value for test of heterogeneity = .08), we did not perform a random effects model. There was no qualitative or quantitative evidence of publication bias (P value for Egger's test >.05). The 2000 study by Bianchi Porro et al⁴⁴ had a lower RR than the three other studies. When this study was removed, the RRR of NSAID+PPI versus NSAID decreased from 66% to 58% (ie, RR moved from 0.34 to 0.42). In both instances (with vs without the 2000 Bianchi Porro study), the RRR afforded by NSAID+PPI versus NSAID surpassed the RRR afforded by Coxibs versus NSAID (12%).

Dyspeptic Symptoms Between Coxib and NSAID+PPI

We identified only 2 studies, both presenting data from the same study population in Hong Kong, that compared a Coxib versus an NSAID+PPI combination.^{47,48} Chan et al^{47,48} reported data that compared the gastrointestinal safety of celecoxib versus combination therapy with diclofenac and omeprazole in patients with a recent NSAID-related ulcer hemorrhage. Although the primary outcome was recurrent hemorrhage, the authors also measured incident dyspeptic

symptoms. The authors reported a 45% relative reduction in dyspeptic symptoms in the NSAID+PPI arm versus the Coxib arm.⁴⁸ Specifically, the authors found 6-month incident dyspepsia rates of 13.7% (16/116) and 7.5% (8/106) for the Coxib and NSAID+PPI arms, respectively (RR = 0.55; P = .13 for chi-square).⁴⁸ Although this difference was not statistically significant at the α = 0.05 level, the trial was not powered to measure differences in dyspepsia. Therefore, these results might reflect a type II error.

Sensitivity Analyses

Table 4 lists the results of the prespecified sensitivity analyses. In all cases, the NSAID+PPI strategy provided a greater degree of risk reduction than Coxibs versus the common baseline of NSAIDs. In addition, none of the individual Coxibs achieved a risk reduction equal to the NSAID+PPI combination. Of the competing Coxibs with at least 2 studies measuring dyspeptic symptoms, valdecoxib achieved the greatest degree of risk reduction versus NSAID (RR = 0.71; 95% CI = 0.59-0.86). Because there was only one study using etoricoxib that met our inclusion criteria,³⁴ we could not perform a separate meta-analysis for etoricoxib.

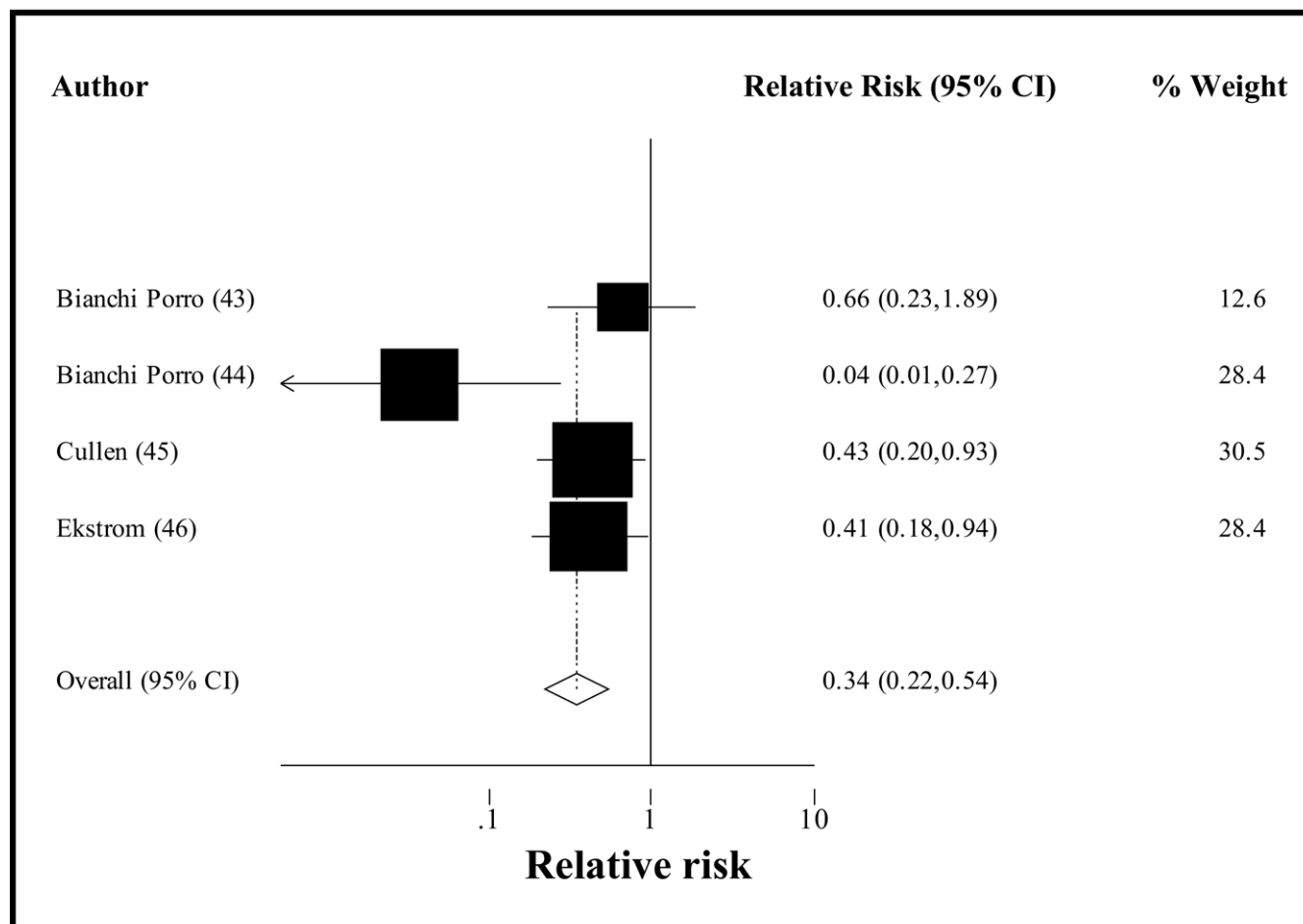


Figure 3 Meta-analysis using the fixed-effects model of randomized controlled trials that report upper gastrointestinal dyspeptic symptoms in patients receiving NSAID and proton pump inhibitor (PPI) (NSAID+PPI) combination therapy versus a nonselective NSAID. Summary estimate is the relative risk with 95% CI.

Comparison of NSAID Arms Between Studies

The weighted mean incidence of dyspepsia from the NSAID arms of the 25 Coxib versus NSAID studies and the four NSAID+PPI versus NSAID studies was 18.1%

and 19.1%, respectively. The difference between these values was not statistically significant ($P = .67$), suggesting that the NSAID arms behaved similarly in both groups of studies.

Table 4 Results of Sensitivity Analyses

Analyses	Coxib vs NSAID Studies (RR; 95% CI)	NSAID+PPI vs NSAID Studies (RR; 95% CI)
Analysis confined to studies with high methodologic quality (Jadad score >4)	0.89 (0.86-0.91)	0.03 (0.005-0.27)*
Analysis of the symptom "dyspepsia" alone	0.95 (0.91-0.99)	0.32 (0.18-0.54)
Analysis of the symptom "epigastric pain" alone	0.78 (0.72-0.84)	---†
Analysis of the symptom "nausea" alone	0.83 (0.77-0.91)	0.66 (0.23-1.89)‡
Analysis confined to studies using celecoxib	0.84 (0.78-0.91)	N/A
Analysis confined to studies using rofecoxib	0.74 (0.64-0.86)	N/A
Analysis confined to studies using valdecoxib	0.71 (0.59-0.86)	N/A
Analysis confined to studies using lumiracoxib	0.91 (0.88-0.94)	N/A

NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor; RR = relative risk; CI = confidence interval; N/A = not available; Coxib = cyclooxygenase-2 inhibitor.

*Only one citation in this cell scored >4 on the Jadad score (citation 44).

†No NSAID+PPI vs NSAID studies reported "epigastric pain" alone.

‡Only one NSAID+PPI vs NSAID citation reported "nausea" alone (citation 43). Therefore, the result in this cell reflects only one study.

DISCUSSION

Our meta-analysis indicates that the NSAID+PPI combination affords greater risk reduction for dyspeptic symptoms than Coxibs when compared with the common baseline of nonselective NSAIDs. Specifically, compared with a nonselective NSAID, the number needed to treat to prevent one person from developing a dyspeptic symptom is 27 for Coxibs and 11 for the NSAID+PPI combination. Because there are limited head-to-head data comparing Coxibs versus NSAID+PPI therapy, these data provide strong indirect evidence that NSAID+PPI therapy may be superior to Coxibs in minimizing incident dyspeptic symptoms for patients with chronic arthritis. Although our data are indirect, they have convergent validity with the only 2 published head-to-head trials to date that directly compare a Coxib with NSAID+PPI therapy; studies in which the combination of diclofenac and omeprazole was associated with 45% fewer dyspeptic symptoms than celecoxib alone.^{47,48}

Because dyspeptic symptoms are far more prevalent than ulcer complications in NSAID users, the rate of dyspepsia has significant cost-effectiveness implications when selecting between competing anti-inflammatory strategies. Specifically, dyspeptic symptoms are up to 12 times more common than ulcer hemorrhage or perforation in NSAID users (8%-12%¹² vs 1%-2%⁷⁻¹¹). Thus, the cost of developing a dyspeptic symptom need only be one-twelfth that of a serious ulcer complication for both types of adverse events to have the same economic impact. Moreover, the outpatient costs of managing a seemingly minor dyspeptic symptom can rival the costs of managing a clinically significant ulcer complication. For example, a typical patient with NSAID-related dyspepsia might require a primary care visit, gastroenterology subspecialist visit, upper endoscopy with biopsy, testing and treatment for *H. pylori*, course of PPI therapy, and subsequent follow-up care. The combined third-party payer costs of these resources may exceed \$3500, a value that approaches the Medicare reimbursement for the inpatient management of an ulcer hemorrhage (~\$4600).⁴⁹ It is therefore not surprising that economic models are careful to include dyspeptic symptoms in determining the relative cost-effectiveness of competing therapies in chronic arthritis and have found that the incidence of dyspepsia has a greater influence on overall cost-effectiveness than the incidence of dramatic yet rare ulcer hemorrhage or perforation.^{12,13} In light of this reality, our data provide a strong clinical and economic rationale for substituting the NSAID+PPI combination in lieu of Coxibs in high-risk patients with arthritis.

Despite the endorsement of Coxibs by at least one professional society as the drug class of choice for the initial management of moderate-to-severe arthritis pain,⁵⁰ our results add to the emerging data that Coxibs may not be the preferred therapy in patients at high-risk for gastrointestinal complications of NSAIDs. In particular, 4 previous findings cast uncertainty regarding the purported gastrointestinal safety advantages of Coxibs

versus NSAID+PPI therapy. Despite the significant RRR in gastrointestinal complications afforded by Coxibs, their ARR compared with NSAIDs is less than 1% for clinically significant ulcer complications,⁷⁻¹¹ an ARR that does not offset its increased costs versus generic NSAIDs.¹⁴ Prospective data in high-risk patients indicate that Coxibs do *not* provide an additional risk reduction for ulcer complications when compared with the NSAID+PPI combination.^{47,48} Cost-effectiveness analysis reveals that Coxibs are more expensive yet less effective than the NSAID+PPI strategy in high-risk patients.¹⁵ Whereas data reveal that the use of concurrent aspirin attenuates the relative gastrointestinal protective effects of Coxibs,⁹ PPIs are highly effective in minimizing aspirin and other NSAID-related gastropathy.^{43-46,51,52} Our results build on these data and further question the position of Coxibs as a gastrointestinal panacea. In light of recent concerns regarding the cardiovascular safety of Coxibs, coupled with the apparent cost-ineffectiveness of Coxibs,^{14,15} these data suggest that the purported gastrointestinal benefits of Coxibs may not offset their additional risks and higher cost compared with the NSAID+PPI combination.

Our analysis has several potential limitations. First, because there are few head-to-head data comparing Coxibs versus NSAID+PPI therapy, we relied on an indirect comparison of these agents through the common baseline of NSAIDs. Nonetheless, there was no significant difference in the incidence of dyspeptic symptoms between the NSAID arms from both groups of included studies (Coxib vs NSAID and NSAID+PPI vs NSAIDs). This similarity between NSAID arms suggests that the NSAIDs behaved similarly in both groups of studies and, therefore, bolsters the argument that NSAIDs could serve as a common baseline to indirectly compare Coxibs and NSAID+PPI combination therapy. Moreover, our indirectly generated results are qualitatively similar to results from published head-to-head data.^{47,48} Second, there are far fewer studies comparing NSAID+PPI versus NSAID than Coxib versus NSAID. Therefore, our estimate of the former comparison is less precise than the latter. Nonetheless, the CIs surrounding the RR derived from the NSAID+PPI versus NSAID studies (RR = 0.34; CI = 0.22-0.54) do not overlap with the intervals surrounding the RR derived from the Coxib versus NSAID studies (RR = 0.88; 95% CI = 0.85-0.91). Moreover, although there are differences in the precision of these estimates, there is no a priori reason to believe that the inclusion of more NSAID+PPI versus NSAID studies would qualitatively alter the results, especially in light of the convergent validity between our retrospective meta-analysis and prospective head-to-head data.^{47,48} Third, our outcome measure (combined outcome of patients with “dyspepsia” plus patients with “epigastric pain” plus patients with “nausea”) relies on patient self-report rather than a validated definition of “dyspepsia.” However, in our judgment, the clinically significant issue is not whether the outcome is a

validated measure, but rather that the outcome is significant enough to be perceived and reported by patients. Because patient self-perception drives subsequent resource use, it is important to rely on self-report in comparing competing therapeutic strategies. Patients experiencing “dyspepsia,” “nausea,” or “epigastric pain” may seek medical care regardless of whether their symptoms meet strict criteria as determined by a validated instrument.

CONCLUSION

Our analysis reveals that the NSAID+PPI strategy may be superior to Coxibs in minimizing incident dyspeptic symptoms during the treatment of chronic arthritis. Given the high prevalence and expense of dyspeptic symptoms, our data further the argument that NSAID+PPI therapy may be preferred over Coxibs in the treatment of patients with arthritis at high risk for adverse gastrointestinal events.

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