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SYSTEMATIC REVIEW

Safety of Cyclooxygenase-2 Inhibitors in Osteoarthritis: Outcomes of a Systematic Review and Meta-Analysis

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Abstract

Objective Our aim was to assess the safety of cyclooxygenase-2 (COX-2) inhibitors in the management of osteoarthritis (OA) in a systematic review and meta-analysis of randomized, placebo-controlled trials.

Methods A comprehensive literature search was undertaken in the databases MEDLINE, Cochrane Central Register of Controlled Trials (Ovid CENTRAL) and Scopus. Randomized, double-blind, placebo-controlled, parallel-group trials that assessed adverse events (AEs) with COX-2 inhibitors in patients with OA were eligible for inclusion. Two authors appraised titles, abstracts and full-text papers for suitability and then assessed the studies for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcomes reporting. The primary outcomes of interest were gastrointestinal disorders, cardiac disorders, vascular disorders, nervous system disorders, skin and subcutaneous tissue disorders, hepatobiliary disorders, renal and urinary disorders, as well as overall severe and serious AEs, drug-related AEs and mortality. Secondary outcomes were withdrawals due to AEs (i.e. the number of participants who stopped the treatment due to an AE) and total number of AEs (i.e. the number of patients who experienced any AE at least once).

Results Database searches identified 2149 records from which, after exclusions, 40 trials were included in the meta-analysis. The use of COX-2 inhibitors in OA was associated with a significant increased risk of drug-related AEs compared with placebo (relative risk (RR) 1.26, 95% CI 1.09–1.46; $I^2 = 24\%$). The risk of upper gastrointestinal complications (including dyspepsia, gastritis and heartburn) was significantly increased with COX-2 inhibitors versus placebo (RR 1.19, 95% CI 1.03–1.38; $I^2 = 0\%$), particularly for abdominal pain, which increased by 40% with COX-2 inhibitors (RR 1.40, 95% CI 1.08–1.80; $I^2 = 0\%$). The risk of hypertension increased by 45% overall (RR 1.45, 95% CI 1.01–2.10; $I^2 = 25\%$); however, when rofecoxib was removed from the analysis the risk of hypertension in the COX-2 inhibitor group was no longer significant (RR 1.21, 95% CI 0.80–1.83; $I^2 = 20\%$). The overall risk of heart failure and edema was increased by nearly 70% with COX-2 inhibitors versus placebo (RR 1.68, 95% CI 1.22–2.31; 0%) and this level of risk did not change appreciably when rofecoxib was excluded (RR 1.67, 95% CI 1.21–2.29; 0%).

Conclusions In our analysis, COX-2 inhibitors were associated with an increased risk of upper gastrointestinal AEs, especially abdominal pain. We also found an increased risk of cardiovascular AEs with COX-2 inhibitors, namely hypertension, heart failure and edema.

1 Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the enzyme cyclooxygenase (COX), which mediates the conversion of arachidonic acid to inflammatory prostaglandins (PGs). COX-1 is constitutively expressed in the gastric epithelium, therefore providing protection to the gastric mucosa as it regulates the production of acid and mucus. COX-2 is

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Key Points

Although specifically designed to avoid the gastrointestinal side effects associated with non-selective NSAIDs, our analysis shows that cyclooxygenase-2 (COX-2) inhibitors are associated with an increased risk of upper gastrointestinal adverse events (AEs), especially abdominal pain, when used to treat pain in osteoarthritis (OA).

As expected, COX-2 inhibitors were associated with an increased risk of cardiovascular AEs; the risk of heart failure and edema remained significant even when rofecoxib was removed from the analysis.

These results confirm that a cautious approach to the use of COX-2 inhibitors (as for other NSAIDs) for the symptomatic management of pain and inflammation in OA is advisable, limiting use to intermittent or cyclical use rather than chronic treatment in order to minimize safety concerns.

involved in inflammation and is a source of the inflammatory mediators prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2) via the arachidonic acid pathway [1]. COX-2 inhibitors are a subclass of NSAIDs that were designed to selectively interrupt the production of inflammatory mediators without compromising gastric epithelial function [2]. COX-2 inhibitors are indicated for anti-inflammatory, anti-pyretic and analgesic effects in disorders such as osteoarthritis (OA), rheumatoid arthritis (RA) and acute pain.

There are few COX-2 inhibitors in current clinical use: celecoxib (200 mg/day, oral), etoricoxib [60 mg/day, oral; although not approved by the US Food and Drug Administration (FDA)] and parecoxib (80 mg/day, intravenous or intramuscular injection for postoperative pain; not approved by the FDA). Further, the FDA and European Medicines Agency (EMA) have withdrawn approval for other COX-2 inhibitors due to an increased risk of cardiovascular adverse events (AEs); rofecoxib was withdrawn in 2004 due to thrombotic cardiovascular events observed in a randomized controlled trial (RCT) [3]; valdecoxib was withdrawn in 2005 due to skin reactions and cardiovascular events post-coronary artery bypass graft surgery in two RCTs [4, 5]; and lumiracoxib was withdrawn by the EMA in 2007 due to liver toxicity and skin reactions [6], and did not gain full FDA approval.

The proposed mechanism for an increase in occurrence of cardiovascular events is an imbalance between prostacyclin and thromboxane A_2 (TXA_2), with prostacyclin production decreased but TXA_2 continuing, leading to platelet activation, vascular proliferation, vascular contraction and cell adhesion, which may occur within the coronary arteries. COX-2 inhibition leads to reduced PGI_2 from the vascular endothelium; thus, the protective effect of PGI_2 is lost, which predisposes to injury, cell adhesion and vessel contraction. TXA_2 production by platelets is not inhibited by COX-2 inhibitors, which leads to platelet activation and a prothrombotic state (Fig. 1) [7].

There are meta-analyses comparing the relative safety of COX-2 inhibitors with non-selective NSAIDs [8–14]. However, the objective of this study was to assess the safety of oral COX-2 inhibitors in the management of OA in a systematic review and meta-analysis of randomized, placebo-controlled trials.

2 Methods

The protocol of this systematic review and meta-analysis was previously registered in the PROSPERO database (registration number: CRD42017068278). The systematic review was performed in accordance with the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions [15]. The findings were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. All the review process (study selection and risk of bias assessment) was undertaken using Covidence, the Cochrane platform for systematic reviews, and was performed by EC, NF, SS and LS.

2.1 Eligibility Criteria

Randomized, double-blind, placebo-controlled, parallel-group trials that have assessed the AEs associated with COX-2 inhibitors (celecoxib, rofecoxib, etoricoxib,

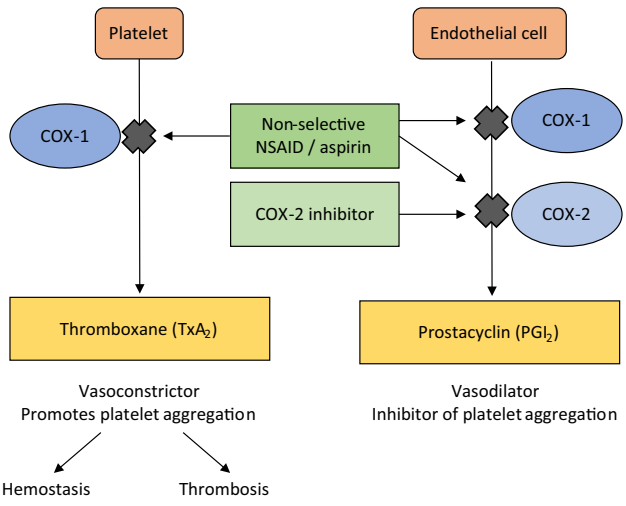

Fig. 1 Effect of cyclooxygenase (*COX*) inhibition on platelets and endothelium. *NSAID* non-steroidal anti-inflammatory drug

valdecoxib but not lumiracoxib as it never gained full FDA approval) in patients with OA were eligible for inclusion in this meta-analysis.

Studies that allowed concomitant anti-osteoarthritis treatments during the trial (other than rescue medication as acetaminophen or aspirin) were also excluded, as were animal trials.

2.2 Data Sources and Search Strategies

A comprehensive literature search was undertaken in the following databases: MEDLINE (via Ovid), Cochrane Central Register of Controlled Trials (Ovid CENTRAL) and Scopus. Each database was searched from inception up to 30 June 2017. We searched for randomized placebo-controlled trials of COX-2 inhibitors in OA, using a combination of study design-, treatment- and disease-specific key words and Medical Subject Heading (MeSH) terms.

While adverse effects were the outcomes of interest for this study, we decided to avoid the outcome-specific key words in the search strategies, because of the possibility that a study on the efficacy of a drug may have not mentioned terms related to adverse events in its title, abstract or in the keyword section. The search was limited to English and French publications and to human subjects. Detailed search strategies for MEDLINE/CENTRAL and Scopus databases are reported as Electronic Supplementary Material (ESM1).

Two clinical trial registries, ClinicalTrials.gov (clinicaltrials.gov/) and the World Health Organization's International Clinical Trials Registry Platform Search portal (apps.who.int/trialsearch/) were also checked for trial results that were unpublished. Finally, recent meta-analyses were also screened for any additional relevant studies.

2.3 Study Selection

Two members of the review team independently evaluated each title and abstract to exclude only obvious irrelevant studies, according to the predefined eligibility criteria. At this step, the criteria related to adverse effects was not considered for selection, as studies focusing on the efficacy of a treatment may not report data about adverse effects in the abstract; this means that all trials mentioning only the efficacy information were retrieved at this step. After this first step, the two investigators independently reviewed the full text of each of the articles not excluded during the initial screening stage to determine whether the studies met all selection criteria. At this stage, studies were excluded due to previously unidentified duplication, conference abstracts alone being available, a non-placebo comparator being used alone against COX-2 medication in the trial, an indication other than OA, safety not being included as an outcome of the trial, a non-COX-2 intervention or incorrect study design. All differences of opinion regarding the selection of articles were resolved through discussion and consensus between the two investigators; any persistent disagreement was solved with the intervention of a third person (another member of the review team).

2.4 Data Extraction

The full texts of the selected studies were screened by independent reviewers for extraction of relevant data, using a standard data extraction form. Outcome results data were independently extracted by two investigators from the review team. For each study, the following data were extracted: characteristics of the manuscript, characteristics of the trial, objective and design of the study, characteristics of the patients, characteristics of the disease, characteristics of the treatments, AEs (outcomes) reported during the trial and the main conclusion of the study. In the case of multiple dosage arms for COX-2 inhibitors being included in a trial, the maximum dose was used to categorize the study. If multiple follow-up times were included, the longest follow-up time was used to categorize the study. The raw data (number of events in each group) were extracted for each outcome. The number of patients who experienced at least once any body-system–related AE (e.g. nervous system, gastrointestinal system), as well as AEs within each body system (e.g. headache, abdominal pain) were extracted. As much as possible, data from the intention-to-treat (ITT) analysis were considered.

2.5 Outcomes of Interest

The main System Organ Classes (SOCs) that are likely to be affected by the use of COX-2 inhibitors in the treatment of OA were explored in this meta-analysis. The primary outcomes of interest were gastrointestinal disorders, cardiac disorders, vascular disorders, nervous system disorders, skin and subcutaneous tissue disorders, hepatobiliary disorders, renal and urinary disorders, as well as overall severe and serious AEs, drug-related AEs and mortality. Secondary outcomes were withdrawals because of AEs (i.e. the number of participants who stopped the treatment because of an AE) and total number of AEs (i.e. the number of patients who experienced any AE at least once).

2.6 Assessment of Risk of Bias in Included Studies

Two authors of the review team independently assessed the risk of bias in each study using the Cochrane Collaboration's tool for risk of bias assessment [15]. The following characteristics were evaluated:

- Random sequence generation: we assessed whether the allocation sequence was adequately generated.
- Allocation concealment: we assessed the method used to conceal the allocation sequence, evaluating whether the intervention allocation could have been foreseen in advance.
- Blinding of participants and personnel: we assessed the method used to blind study participants and personnel from knowledge of which intervention a participant received and whether the intended blinding was effective.
- Blinding of outcome assessment: we assessed the method used to blind outcome assessors from knowledge of which intervention a participant received and whether the intended blinding was effective.
- Incomplete outcome data: we assessed whether participants' exclusions, attrition and incomplete outcome data were adequately addressed in the paper.
- Selective outcomes reporting: we checked whether there was evidence of selective reporting of adverse events.

Each of these items was either categorized as 'low risk of bias', 'high risk of bias', or 'unclear risk of bias'. 'Low risk of bias' or 'high risk of bias' was attributed to an item when there was sufficient information in the manuscript to judge the risk of bias as 'low' or 'high'; otherwise, 'unclear risk of bias' was attributed to the item. Disagreements were solved by discussion between the two reviewers during a consensus meeting and involved, when necessary, another member of the review team for the final decision.

2.7 Data Analysis

Analyses were performed using STATA 14.2 software. The units of analysis were the number of participants experiencing a specific adverse event. We described harms associated with the treatment as risk ratio with 95% confidence interval (95% CI). We computed an overall effect size for each primary or secondary outcome (AE). Anticipating substantial variability among trial results (i.e. the inter-study variability), we assumed heterogeneity in the occurrence of the AEs; thus, we planned to use random-effects models for the meta-analyses. We estimated the overall effects and heterogeneity using the DerSimonian and Laird random-effects model [17]. As this method provides a biased estimate of the between-study variance with sparse events [18, 19], we also performed the meta-analyses using the Restricted Maximum Likelihood (REML) method [20]. As rofecoxib was withdrawn by the FDA and EMA in 2004 due to thrombotic cardiovascular events, we performed a sensitivity analysis for AEs for the COX-2 inhibitor class minus rofecoxib.

We tested heterogeneity using the Cochran's Q test. As we are performing a random-effect meta-analysis, we used the Tau-squared (τ^2) estimate as the measure of the between-study variance. The I-squared (I^2) statistic was used to quantify heterogeneity, measuring the percentage of total variation across studies due to heterogeneity [21]. The quality of each evidence was assessed using the GRADE approach [22] and a summary of findings table was prepared using GRADEpro online software [23].

3 Results

3.1 Study Selection

Database searches initially identified 2149 records. After exclusions, 73 articles were screened in full against the inclusion criteria. A flowchart (Fig. 2) with the number of included studies at each step was established, including the reasons for excluding studies during the full-text reading process. Forty-one of these met the eligibility criteria and included a placebo comparator, but a further five were excluded as the specific outcomes of interest to our strategy were not specified. Thirty-six papers were included, which actually comprised 40 trials as four papers presented results from two studies [24–58].

3.2 Study Characteristics

Table 1 presents the characteristics of the studies included through the systematic review process. The year of publication of the included studies ranged from 1999 to 2017 and the follow-up time ranged from 6 weeks to 24 months. The number of trials including an arm for each specific COX-2 inhibitor (or two arms if two COX-2 inhibitors were included) were as follows: celecoxib 20 (49%), etoricoxib 6 (15%), rofecoxib 10 (24%), celecoxib and etoricoxib 4 (10%), celecoxib and rofecoxib 1 (2%). The anatomic regions included per trial are as follows; knee 24 (59%), hip 2 (5%), knee or hip 13 (32%), any OA 1 (2%), not specified 1 (2%).

3.3 Risk of Bias of Individual Studies

Figures 3 and 4 include a summary of the risk of bias assessed for each study included in the meta-analysis and all our findings were associated with a 'moderate' to 'high' certainty of evidence.

3.4 Primary Outcomes

We reported only the results from the DerSimonian and Laird random-effects model, because we found no difference in the effects computed by the two methods.

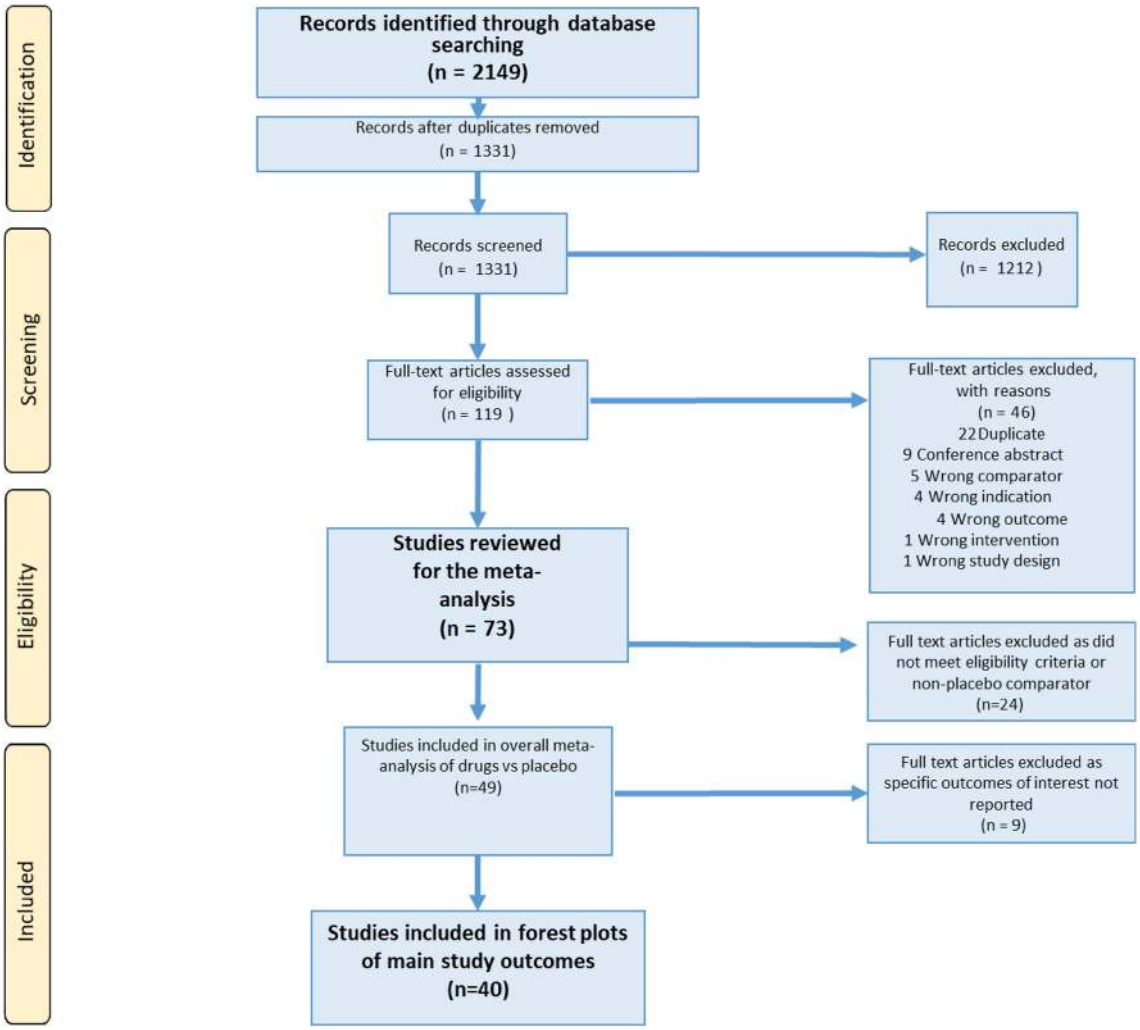

Fig. 2 Flowchart of the study selection process

3.4.1 Gastrointestinal Complications

The relative risk of upper gastrointestinal complications overall, including ulcer-related events, dyspepsia and abdominal pain, was significantly increased with COX-2 inhibitors versus placebo (RR 1.19, 95% CI 1.03–1.38; $I^2 = 0\%$) (Fig. 5). The risk of dyspepsia (RR 1.08, 95% CI 0.90–1.30; $I^2 = 0\%$) and ulcer-related AEs (RR 2.08, 95% CI 0.58–7.46; $I^2 = 0\%$) was not significantly increased in the COX-2 inhibitor group; however, the risk of abdominal pain increased significantly, by 40%, with COX-2 inhibitors (RR 1.40, 95% CI 1.08–1.80; $I^2 = 0\%$).

There was no increase in the relative risk of nausea and vomiting (RR 0.96, 95% CI 0.75–1.22; $I^2 = 0\%$) nor any significant difference in the risk of constipation (RR 1.00, 95% CI 0.58–1.75; $I^2 = 0\%$) between the COX-2 inhibitors and placebo group (ESM2).

3.4.2 Cardiovascular Events

The risk of hypertension increased significantly, by 45% overall across the 15 studies, including celecoxib, rofecoxib and etoricoxib (RR 1.45, 95% CI 1.01–2.10; $I^2 = 25\%$) (Fig. 6). However, when rofecoxib was removed from the analysis, the risk of hypertension in the COX-2 inhibitor group was no longer significant (RR 1.21, 95% CI 0.80–1.83; $I^2 = 20\%$) (ESM2).

The incidence of heart failure (HF)-related events was reported differently across the studies; thus, a grouped analysis was performed. The overall risk of HF and edema was increased with COX-2 inhibitors versus placebo (RR 1.68, 95% CI 1.22–2.31; 0%) (Fig. 7). The overall increase in risk of around 70% was not changed appreciably when rofecoxib studies were excluded (RR 1.67, 95% CI 1.21–2.29; 0% for celecoxib and etoricoxib only) (ESM2).

Table 1 Characteristics of the studies included through the systematic review process

Study	Location of OA	Age of participants (years) by study group [mean ± SD or median (IQR)]	Active treatment(s)	Dose	Trial duration	Data provided in the article (type of AE)
Bensen et al. 1999 [24]	Knee	Placebo 62 (37–85)/active 62 (21–89)—celecoxib 50 mg bd	Celecoxib	50 mg bd	12 weeks	TEAE reported, covering some SOCs, plus discontinuations of treatment (ulcer complications, hypertension, headache, dyspepsia, upper respiratory infection, symptomatic non-bleeding duodenal ulcer, diarrhea, any GI AE, peripheral edema, abdominal pain)
		Placebo 62 (37–85)/active 62 (32–84)—celecoxib 100 mg bd		100 mg bd		
		Placebo 62 (37–85)/active 63 (25–87)—celecoxib 200 mg bd		200 mg bd		
Bingham et al. (Trial 1) 2007 [25]	Knee/hip	Placebo 62.8 (9.7)/active 62.5 (9.3)—celecoxib 200 mg od	Celecoxib	200 mg od	26 weeks	TEAE, not classified by SOC, plus treatment discontinuations (AE of congestive heart failure, pulmonary edema or cardiac failure, exceeding predefined limits of change in BP, SBP within 26 weeks)
		Placebo 62.8 (9.7)/active 62.1 (10.2)—etoricoxib 30 mg od	Etoricoxib	30 mg od		
Bingham et al. (Trial 2) 2007 [25]	Knee/hip	Placebo 60.9 (8.6)/active 62.2 (9.5)—celecoxib 200 mg od	Celecoxib	200 mg od	26 weeks	TEAE, not classified by SOC, plus treatment discontinuations (AE of congestive heart failure, pulmonary edema or cardiac failure, exceeding predefined limits of change in BP, SBP within 26 weeks)
		Placebo 60.9 (8.6)/active 61.9 (9.6)—etoricoxib 30 mg od	Etoricoxib	30 mg od		
Cannon et al. 2008 [26]	Any	Placebo 57.8 (10.1)/active 59.3 (10.6)—celecoxib 200 mg bd	Celecoxib	200 mg bd	12 weeks	TEAE, covering some SOCs, plus treatment discontinuations (lower extremity edema, hypertension, GI system adverse events, congestive heart failure)
		Placebo 57.8 (10.1)/active 59.3 (10.3)—etoricoxib 90 mg od	Etoricoxib	90 mg od		
Conaghan et al. 2013 [27]	Knee	Placebo 61.3 (38–81)/active 62.0 (38–90)	Celecoxib	100 mg bd	12 weeks	TEAE, covering some SOCs, plus treatment discontinuations (abdominal pain, dyspepsia, heartburn, vascular disorders, rash, all GI AE, GI disorders, diarrhea, dry skin, allergic contact dermatitis, allergic rash, gastric pain, flatulence, headache, localized erythema, localized itching, nervous system disorders, bloating, infections and infestations)
Cryer et al. (Trial 1) 2011 [28]	Knee	Placebo 61.6 (50–83)/active 61.5 (49–90)	Celecoxib	200 mg od	12 weeks	TEAE, covering some SOC, plus treatment discontinuations (nasopharyngitis, constipation, Upper GI AE, sinusitis, headache, dyspepsia, dizziness, peripheral edema, arthralgia, upper abdominal pain, diarrhea, nausea, back pain, cough, vomiting)
Cryer et al. (Trial 2) 2011 [28]	Knee	Placebo 61.6 (50–87)/active 62.3 (50–89)	Celecoxib	200 mg od	12 weeks	TEAE, covering some SOC, plus treatment discontinuations (sinusitis, upper abdominal pain, headache, diarrhea, upper GI AEs, arthralgia, nausea, constipation, cough, dyspepsia, back pain, vomiting, dizziness, peripheral edema, nasopharyngitis)
Day et al. 2000 [29]	Knee/hip	Placebo 63.1 (9.7)/active 64.9 (8.4)—rofecoxib 12.5 mg od	Rofecoxib	12.5 mg od	6 weeks	TEAE, not defined by SOC, plus treatment discontinuations (epigastric discomfort, gastric ulcer, diarrhea, nausea)
		Placebo 63.1 (9.7)/active 62.8 (9.3)—rofecoxib 25 mg od;		25 mg od		
DeLemos et al. 2011 [30]	Knee/hip	Placebo 58.9 (11.6)/active 60.0 (11.3)	Celecoxib	200 mg od	12 weeks	TEAE, not defined by SOC (insomnia, dry mouth, nervousness, somnolence, fatigue, dizziness, flushing, anorexia, nausea, constipation, upper respiratory tract infection, headache, pruritus, vomiting, diarrhea)

Table 1 (continued)

Study	Location of OA	Age of participants (years) by study group [mean ± SD or median (IQR)]	Active treatment(s)	Dose	Trial duration	Data provided in the article (type of AE)
Ehrich et al. 1999 [31]	Knee	Placebo 62.6 (38–80)/active 63.9 (35–81)	Rofecoxib	125 mg od	6 weeks	TEAE, not defined by SOC, plus treatment discontinuations (lower extremity edema, upper respiratory infection, sinusitis, weight gain, viral syndrome, GI bleeding, nausea, headache, dizziness, dyspepsia, diarrhea)
Ehrich et al. 1999 [31]	Knee	Placebo 62.6 (38–80)/active 64.0 (46–84)	Rofecoxib	25 mg od	6 weeks	TEAE, not defined by SOC, plus treatment discontinuations (lower extremity edema, diarrhea, dyspepsia, upper respiratory infection, GI bleeding, viral syndrome, headache, nausea, dizziness, weight gain, sinusitis)
Essex et al. 2012 [32]	Knee	Placebo 58.0 (8.8)/active 58.0 (8.8)—celecoxib 200 mg od	Celecoxib	200 mg od	6 weeks	TEAE, not defined by SOC, plus treatment discontinuations (dizziness, diarrhea, depression, abdominal pain, nausea, dyspepsia, gastroesophageal reflux disease, headache)
Essex et al. 2014 [33]	Knee	Placebo 61.7 (11.2)/active 59.6 (10.6)—celecoxib 200 mg od	Celecoxib	200 mg od	6 weeks	TEAE, not defined by SOC, plus treatment discontinuations (depression, abdominal pain, dyspepsia)
Essex et al. 2016 [34]	Knee	Placebo 63.9 (11.1)/active 65.9 (11.1)—celecoxib 200 mg od	Celecoxib	200 mg od	6 weeks	TEAE, not defined by SOC, plus treatment discontinuations (dyspepsia, diarrhea, depression, constipation, abdominal pain, dizziness)
		Placebo 63.9 (11.1)/active 64.1 (11.4)—naproxen 500 mg bd				
Fleischmann et al. 2006 [35]	Knee	Placebo 61.5 (11.68)/active 61.3 (11.14)	Celecoxib	200 mg od	13 weeks	TEAE, covering some SOC, plus treatment discontinuations (GI events (excluding ulcers), GI AE suspected to be drug related, GI AE, edema, chest pain)
Ghosh et al. 2007 [36]	Knee	Male and female means only, male = 56.81 and female = 53.72	Etoricoxib	90 mg od	4 weeks	TEAE, covering some SOC, plus treatment discontinuations (hematemesis, lower limb edema, hypertension, cerebrovascular accident, GI side effects, ankle edema)
Gordo et al. 2017 [37]	Knee	Placebo 64.5 (11.2)/active 62.2 (9.5)—celecoxib 200 mg od	Celecoxib	200 mg od	6 weeks	TEAE, covering some SOC, plus treatment discontinuations (abdominal pain, headache, upper GI event, diarrhea, dyspepsia)
Gottesdiener et al. 2002 [38]	Knee	Placebo 62.52 (41–79)/active 61.74 (41–79)—etoricoxib 5 mg od	Etoricoxib	5 mg od	6 weeks	TEAE, not defined by SOC, plus treatment discontinuations (headache, nausea, diarrhea, lower extremity edema, heartburn, hypertension)
		Placebo 62.52 (41–79)/active 62.47 (42–87)—etoricoxib 10 mg od		10 mg od		
		Placebo 62.52 (41–79)/active 61.25 (40–84)—etoricoxib 30 mg od		30 mg od		
		Placebo 62.52 (41–79)/active 60.03 (40–79)—etoricoxib 60 mg od		60 mg od		
		Placebo 62.52 (41–79)/active 60.10 (41–84)—etoricoxib 90 mg od		90 mg od		

Table 1 (continued)

Study	Location of OA	Age of participants (years) by study group [mean ± SD or median (IQR)]	Active treatment(s)	Dose	Trial duration	Data provided in the article (type of AE)
Karlsson et al. 2009 [39]	Knee/hip	Placebo 61.9 (9.66)/active 62.8 (9.31)	Rofecoxib	25 mg od	6 weeks	TEAE, covering some SOC (abdominal pain [upper], respiratory disorders, reflux, dyspepsia, nervous system disorders, headache, abdominal pain [not specified], GI side effects overall, constipation, loose stools, pharyngolaryngeal pain, back pain, dizziness, arthralgia, infections and infestations, neck pain, diarrhea, nasopharyngitis, pain in extremity, musculoskeletal and connective tissue disease symptoms, nausea, flatulence)
Kivitz et al. 2001 [40]	Hip	Placebo 64 (30–85)/active 62 (28–93)—celecoxib 100 mg od;	Celecoxib	100 mg od	12 weeks	TEAE, covering some SOC, plus treatment discontinuations (central nervous systems AE, nausea, headache, constipation, dyspepsia, pruritus, peripheral edema, rash, flatulence, diarrhea, dizziness, GI AE, abdominal pain)
		Placebo 64 (30–85)/active 62 (30–86)—celecoxib 200 mg od;		200 mg od		
		Placebo 64 (30–85)/active 61 (28–88)—celecoxib 400 mg od		400 mg od		
Laine et al. 1999 [41]	Not specified	Placebo 61 (47–85)/active 62 (49–83)—rofecoxib 25 mg od	Rofecoxib	25 mg od	6 months	TEAE, not defined by SOC, plus treatment discontinuations (ulcer complication, abdominal pain, upper respiratory infection, diarrhea)
		Placebo 61 (47–85)/active 62 (49–86)—rofecoxib 50 mg od		50 mg od		
Lehmann et al. 2005 [42]	Knee	Placebo 61.7 (10.22)/active 62.9 (10.45)	Celecoxib	200 mg od	13 weeks	TEAE, not defined by SOC, plus treatment discontinuations (nausea, arthralgia, urinary tract infection, headache, dyspepsia, nasopharyngitis, hypertension, influenza, diarrhea, upper abdominal pain)
Leung et al. 2002 [43]	Knee/hip	Placebo 64.09 (8.9)/active 62.93 (9.23)—etoricoxib 60 mg od	Etoricoxib	60 mg od	12 weeks	TEAE, covering some SOC, plus treatment discontinuations (all GI nuisance symptoms, nausea, dyspepsia, hypertension, diarrhea, congestive heart failure, peptic ulcer bleed, upper respiratory infection, back pain, lower extremity edema, heartburn, epigastric discomfort, abdominal pain)
McKenna et al. (Trial 1) 2001 [44]	Knee	Placebo 63.2 (10.8)/active 62 (10.0)—celecoxib 200 mg od	Celecoxib	200 mg od	6 weeks	TEAE, covering some SOC, plus treatment discontinuations (pharyngitis, moderate GI AE, severe GI AE, any GI AE, arthralgia, abdominal pain, tooth disorder, headache, diarrhea, upper respiratory infection, sinusitis, dyspepsia)
		Placebo 63.2 (10.8)/active 61.5 (10.0)—rofecoxib 25 mg od	Rofecoxib	25 mg od		
McKenna et al. (Trial 2) 2001 [44]	Knee	Placebo 60.5 (34–88)/active 63.0 (32–85)—celecoxib 100 mg bd	Celecoxib	100 mg bd	6 weeks	TEAE, not defined by SOC, plus treatment discontinuations (ALT increased, headache, flatulence, upper respiratory infection, peripheral edema, constipation, nausea, myalgia, accidental injury, diarrhea, abdominal pain, pain, dizziness, dyspepsia, back pain, anemia)
Puopolo et al. 2007 [45]	Knee/hip	Placebo 64.0 (10.1)/active 62.1 (9.0)—etoricoxib 30 mg od	Etoricoxib	30 mg od	12 weeks	TEAE, not defined by SOC, plus treatment discontinuations (hypertension, nausea, dyspepsia, epigastric discomfort, pulmonary edema, cardiac failure)
Reginster et al. 2007 [46]	Knee/hip	Placebo 63.8 (10.2)/active 62.59 (9.8)—etoricoxib 60 mg od	Etoricoxib	60 mg od	12 weeks	TEAE, covering some SOC, plus treatment discontinuations (urinary tract infection, influenza-like disease, dyspepsia, upper respiratory infection, bronchitis, heartburn, back pain, lower extremity edema, serious thrombotic CV events, abdominal pain, upper GI bleeding, congestive heart failure, GI nuisance AE, nausea, hypertension, sinusitis, epigastric discomfort)

Table 1 (continued)

Study	Location of OA	Age of participants (years) by study group [mean ± SD or median (IQR)]	Active treatment(s)	Dose	Trial duration	Data provided in the article (type of AE)
Rother et al. 2007 [47]	Knee	Placebo 62.8 (9.8)/active 62.4 (9.6)	Celecoxib	100 mg bd	6 weeks	TEAE, covering some SOC (skin and subcutaneous tissue disorders, upper abdominal pain, constipation, respiratory, thoracic and mediastinal disorders, exanthema, gastritis, toothache, back pain, pruritus, joint effusion, musculoskeletal and connective tissue disorder, dyspepsia, erythema, flatulence, sciatica, allergic dermatitis, psychiatric disorders, nausea, arthralgia, skin irritation, depression, GI AE, urticaria, nasopharyngitis, diarrhea)
Saag et al. 2000 [48]	Knee/hip	Placebo 62 (40–87)/active 60 (39–91)—rofecoxib 12.5 mg od	Rofecoxib	12.5 mg od	6 weeks	TEAE, not defined by SOC, plus treatment discontinuations (diarrhea, lower extremity edema)
		Placebo 62 (40–87)/active 62 (39–85)—rofecoxib 25 mg od		25 mg od		
Sawitzke et al. 2010 [49]	Knee	Placebo 56.9 (9.8)/active 57.6 (10.6)—celecoxib 200 mg od	Celecoxib	200 mg od	24 months	TEAE, not defined by SOC (cerebrovascular accident, coronary angioplasty, abdominal wall abscess)
Schnitzer et al. 2005 [50]	Knee	Placebo 61 (10.2)/active 60 (8.4)—rofecoxib 25 mg od	Rofecoxib	25 mg od	6 weeks	TEAE, covering some SOC plus treatment discontinuations (arthralgia, pain in limb, myalgia, dyspepsia, GI adverse events, stomatitis, back pain, abdominal distension, nasopharyngitis, diarrhea, dizziness, pain (not otherwise specified), insomnia, sinus headache, GI hemorrhage, pharyngitis, neck pain, urinary tract infection, bleeding-related adverse events, headache, nausea, constipation)
Schnitzer et al. 2011 [51]	Hip	Placebo 61.7 (10.27)/active 61.7 (9.72)	Celecoxib	200 mg od	13 weeks	TEAE, covering some SOC, and deaths, plus treatment discontinuations (arthralgia, CV events excluding chest pain, diarrhea, chest pain, peripheral edema, upper respiratory infection, nasopharyngitis, GI events excluding ulcers, nausea, pain in extremity, back pain, dyspepsia, edema, headache)
Sheldon et al. 2005 [52]	Knee	Placebo 60.2 (11.09)/active 60.2 (10.54)	Celecoxib	200 mg od	13 weeks	TEAE, not defined by SOC (back pain, urinary tract infection, bronchitis, upper respiratory tract infection, nasopharyngitis, arthralgia, headache, sinusitis, diarrhea, influenza)
Smugar et al. (Trial 1) 2006 [53]	Knee/hip	Placebo 61.8 (41–85)/active 61.8 (39–88)—rofecoxib 12.5 mg od	Rofecoxib	12.5 mg od	6 weeks	TEAE, covering some SOC plus treatment discontinuations (patients exceeding SBP limit, hypertension, edema, GI AEs, congestive heart failure)
		Placebo 61.8 (41–85)/active 60.9 (39–90)—rofecoxib 25 mg od;	Celecoxib	25 mg od		
		Placebo 61.8 (41–85)/active 61.8 (40–92)—celecoxib 200 mg od		200 mg od		
Smugar et al. (Trial 2) 2006 [53]	Knee/hip	Placebo 61.8 (40–87)/active 61.8 (40–87)	Rofecoxib	25 mg od	6 weeks	TEAE, covering some SOC plus treatment discontinuations (patients exceeding SBP limit, hypertension, edema, GI AEs, congestive heart failure)
Tannenbaum et al. 2004 [54]	Knee	Placebo 64.6 (9.9)/active 64.1 (10.4)	Celecoxib	200 mg od	13 weeks	TEAE, covering some SOC plus treatment discontinuations (arthralgia, influenza, chest pain, hypertension, peripheral edema, headache, dyspepsia, upper abdominal pain, GI events, diarrhea, nasopharyngitis)

Table 1 (continued)

Study	Location of OA	Age of participants (years) by study group [mean ± SD or median (IQR)]	Active treatment(s)	Dose	Trial duration	Data provided in the article (type of AE)
Truitt et al. 2001 [55]	Knee/hip	Placebo 83.0 (80–93)/active 83.3 (80–95)—rofecoxib 12.5 mg od	Rofecoxib	12.5 mg od	6 weeks	TEAE, not defined by SOC, plus treatment discontinuations (lower extremity edema, headache, edema, nausea, urinary tract infection, diarrhea, upper respiratory infection, fluid retention, peripheral edema, rash, congestive heart failure, constipation)
		Placebo 83.0 (80–93)/active 83.8 (80–93)—rofecoxib 25 mg od		25 mg od		
Weaver et al. 2006 [56]	Knee	Placebo 62.3 (10.1)/active 62.3 (10.2)	Rofecoxib	12.5 mg od	6 weeks	TEAE, covering some SOC, plus treatment discontinuations (appendicitis, vomiting, gastric disorder, nausea, laboratory measures AE, digestive gas symptoms, oral ulcer, epigastric discomfort, dyspepsia, constipation, any cardiovascular AE, thrombotic event, acid reflux, heartburn, diarrhea, myocardial infarction, flatulence)
Wiesenhutter et al. 2005 [57]	Knee/hip	Placebo 59.5 (8.4)/active 61.3 (9.6)	Etoricoxib	30 mg od	12 weeks	TEAE, covering some SOC, plus treatment discontinuations (headache, edema, lower extremity edema, edema-related AE, heartburn, congestive heart failure, pulmonary edema or cardiac failure, nausea, hypertension-related AE)
Williams et al. (Trial 1) 2000 [58]	Knee	Placebo 62.6 (11.3)/active 63.0 (10.4)—celecoxib 100 mg bd	Celecoxib	100 mg bd	6 weeks	TEAE, covering some SOC, plus treatment discontinuations (any GI AE, peripheral edema, arthralgia, abdominal pain, myalgia, nausea, back pain, diarrhea, urinary tract infection, dyspepsia, headache)
		Placebo 62.6 (11.3)/active 62.7 (10.9)—celecoxib 200 mg od		200 mg od		
Williams et al. (Trial 2) 2000 [58]	Knee	Placebo 61.3 (11.6)/active 62.0 (11.8)—celecoxib 100 mg bd	Celecoxib	100 mg bd	6 weeks	TEAE, covering some SOC, plus treatment discontinuations (diarrhea, headache, upper respiratory infection, dyspepsia, sinusitis, Any GI AE)
		Placebo 61.3 (11.6)/active 61.3 (12.2)—celecoxib 200 mg od		200 mg od		

AE adverse event, *ALT* alanine aminotransferase, *bd* twice daily, *BP* blood pressure, *CV* cardiovascular, *GI* gastrointestinal, *IQR* interquartile range, *OA* osteoarthritis, *od* once daily, *SBP* systolic blood pressure, *SD* standard deviation, *SOC* system organ class, *TEAEs* treatment-emergent adverse events

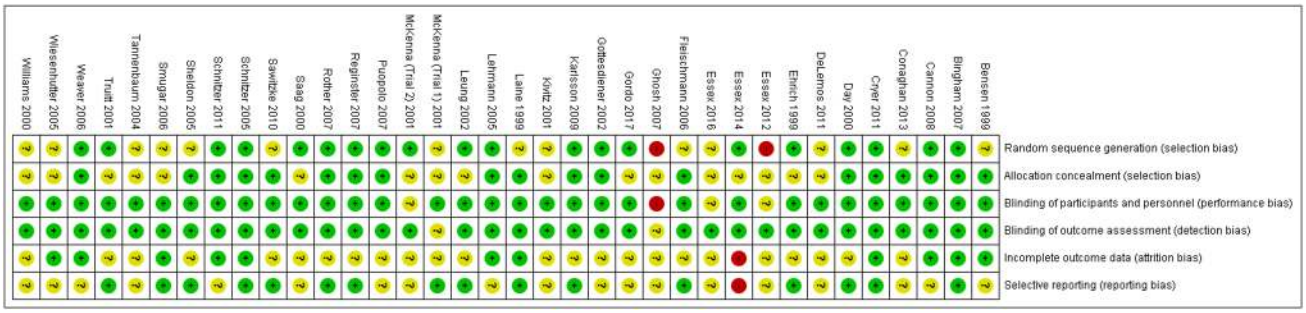

Fig. 3 Risk of bias summary: review of authors' judgements about each risk of bias item for each included study

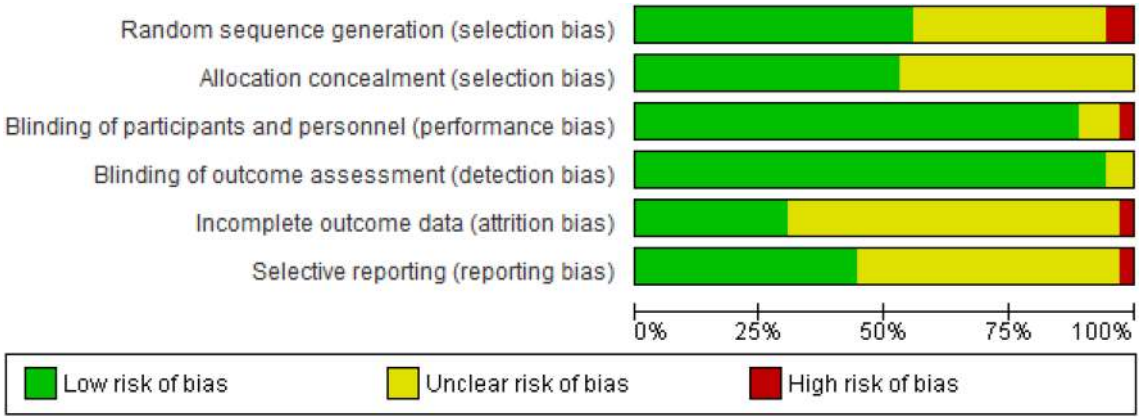

Fig. 4 Risk of bias graph: review of authors' judgements about each risk of bias item presented as percentages across all included studies

The risk of congestive HF (CHF) was not significantly increased (RR 1.18, 95% CI 0.24–5.71; $p = 0.944$; $I^2 = 0\%$). The risk of peripheral edema was increased by 61% (RR 1.61, 95% CI 1.09–2.40; $I^2 = 0\%$) and the risk of generalized edema increased by 91% (RR 1.91, 95% CI 1.08–3.39; $I^2 = 0\%$).

3.4.3 Other Primary Outcomes

Central nervous system (CNS) AEs were grouped into dizziness, headache and other (incorporating insomnia, depression and psychiatric disorders). No appreciable difference in the risk of CNS AEs was observed between the placebo and COX-2 inhibitor groups (RR 0.94, 95% CI 0.84–1.04; 0%) (ESM2). Neither was there any increase in the risk of dermatological AEs (rash or pruritis) (RR 1.02, 95% CI 0.76–1.37; 0%) (ESM2). Too few studies reported on renal and hepatic AEs and mortality for these to be included in the meta-analysis.

The risk of drug-related AEs was significantly increased with COX-2 inhibitors versus placebo (RR = 1.26, 95% CI 1.09–1.46; $I^2 = 24\%$) (Fig. 8). There was no significant difference in risk of serious AEs (SAEs) with COX-2 inhibitors versus placebo, although a lower rate of SAEs was recorded (RR 0.76, 95% CI 0.48–1.19; $I^2 = 21\%$) (ESM2).

3.5 Secondary Outcomes

Overall, there was no increase in total risk of AEs between the COX-2 inhibitor group and the placebo group, even with the highest dose of COX-2 inhibitor included in the analysis (RR 1.03, 95% CI 0.97–1.10; $I^2 = 66\%$) (ESM2). Too few studies reported on withdrawals due to AEs for this to be included in the meta-analysis.

3.6 GRADE Assessment of Findings

We assessed the certainty of evidence for each primary or secondary outcome for COX-2 inhibitors compared with placebo, using the GRADE approach [22]. Our findings were associated with 'moderate' to 'high' certainty of evidence. Table 2 summarizes the significant findings while Table 3 summarizes the non-significant findings for the safety outcomes assessed in this meta-analysis.

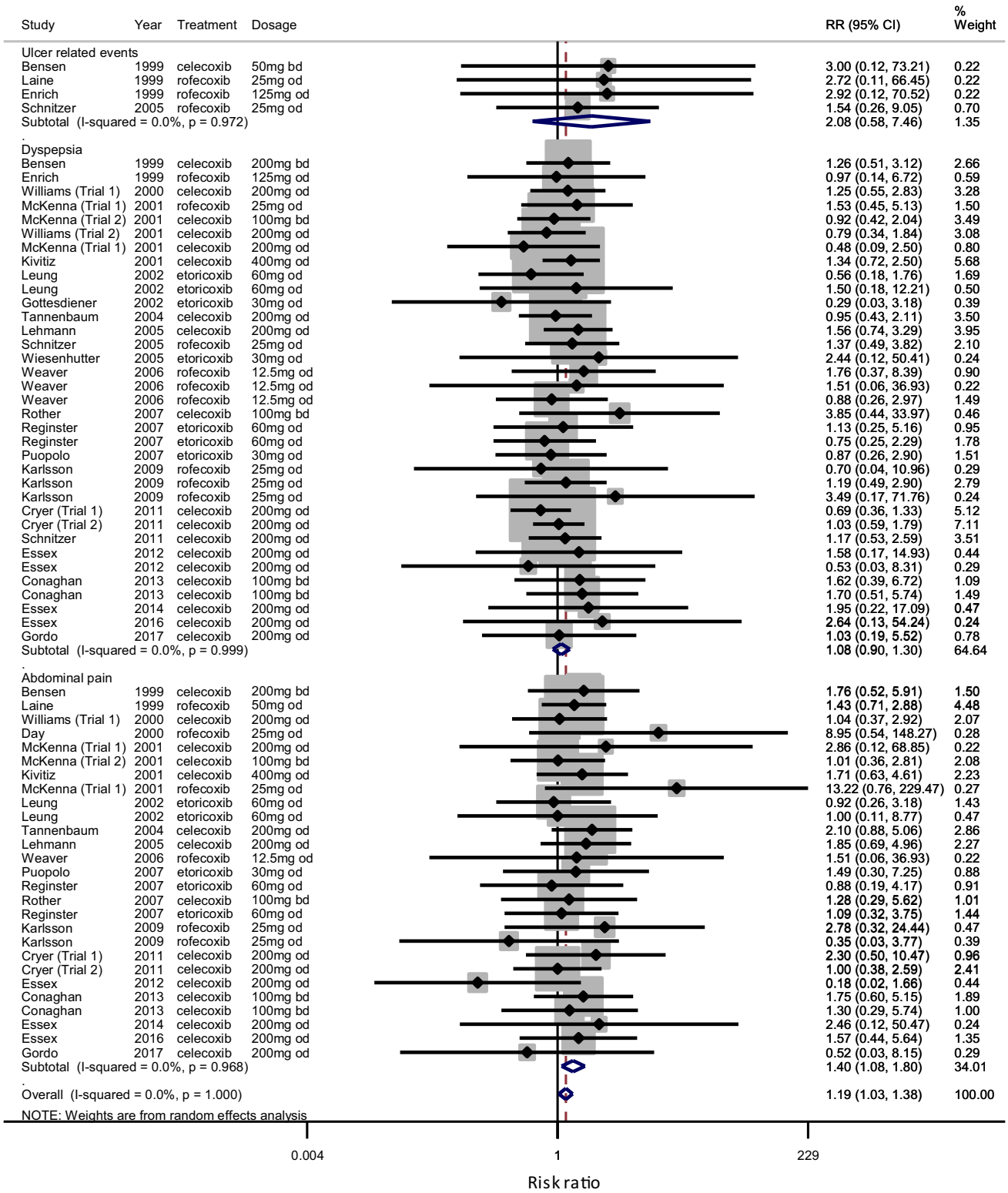

Fig. 5 Relative risk of upper gastrointestinal adverse events (ulcer-related events, dyspepsia, abdominal pain) for COX-2 inhibitors versus placebo. *CI* confidence interval, *COX-2* cyclooxygenase-2, *RR* relative risk

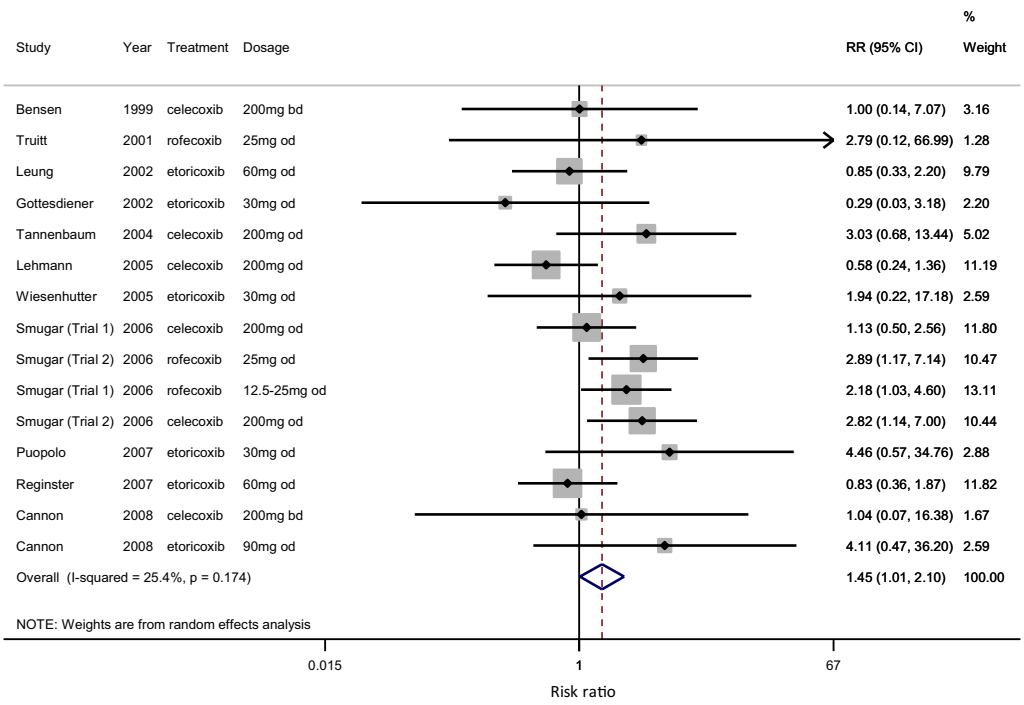

Fig. 6 Relative risk of hypertension adverse events for COX-2 inhibitors versus placebo. *CI* confidence interval, *COX-2* cyclooxygenase-2, *RR* relative risk

4 Discussion

Overall, our analysis found a significant increased risk of drug-related AEs with COX-2 inhibitors compared with placebo. While it is widely accepted that NSAIDs with COX-2 selectivity are associated with less gastrointestinal toxicity compared with non-selective NSAIDs, nonetheless, our study found a 19% increase in upper gastrointestinal AEs overall with COX-2 inhibitors compared with placebo, and a 40% increase in risk of abdominal pain. This finding is in line with another recent meta-analysis from Bhala et al., that found an increase in upper gastrointestinal complications with COX-2 inhibitors, albeit a lower risk than that with the non-selective NSAIDs ibuprofen and naproxen, but similar to the risk with diclofenac [11]. A retrospective pooled analysis of 21 RCTs of 9461 patients aged ≥ 65 years with OA, rheumatoid arthritis or ankylosing spondylitis that examined the incidence of gastrointestinal AEs (abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea) with celecoxib versus non-selective NSAIDs found a significantly lower incidence of gastrointestinal intolerability reported with celecoxib than naproxen, ibuprofen or diclofenac ($p < 0.001$) [59].

As may be expected with COX-2 inhibitors, we found a significant increase in cardiovascular AEs; specifically, a 45% increased risk of hypertension that decreased to 21% when rofecoxib was excluded from the analysis. Nonselective NSAIDs and COX-2 selective inhibitors increase blood pressure in both normotensive subjects as well as in patients with hypertension. The mechanism for the increase in blood pressure is most likely due to their impact on vasoactive endothelium-derived factors, particularly via the inhibition of prostaglandin synthesis, important for the regulation of vascular tone and sodium excretion [60]. The comparative effect of rofecoxib, celecoxib and naproxen on ambulatory blood pressure has been studied in 400 patients with arterial hypertension, diabetes mellitus and OA. Rofecoxib, but not celecoxib and naproxen, significantly increased 24-hour systolic blood pressure after 6 weeks of therapy [61].

Elevated arterial hypertension is a major risk factor for stroke, ischemic heart disease and HF [62]. We found a 68% overall increase in risk of CHF and edema (peripheral and generalized) with COX-2 inhibitors, which was not reduced when rofecoxib was excluded from the analysis. A systematic review and meta-analysis assessed the risk of developing incident HF with the use of NSAIDs for any indication, finding a higher risk of developing HF with NSAIDs, which was significantly elevated with non-selective NSAIDs, but not with COX-2 inhibitors [63]. The rates of hospital admission for CHF with rofecoxib, celecoxib and NSAIDs have been compared in 150,000 individuals aged ≥ 65 years. Users of rofecoxib and NSAIDs, but not celecoxib, were associated with a higher incidence of admission than non-NSAIDs users [64].

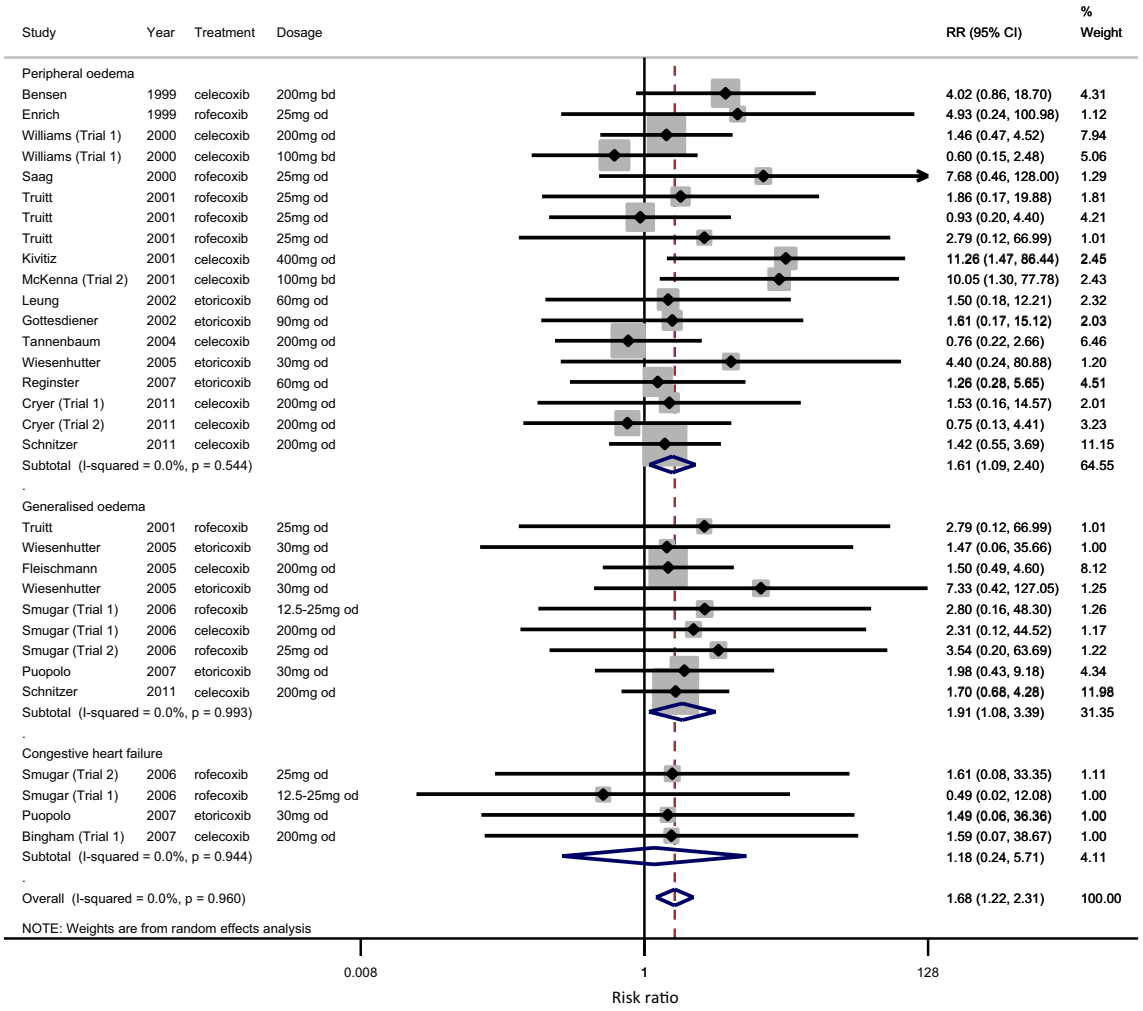

Fig. 7 Relative risk of edema (peripheral and generalized) and heart failure adverse events for COX-2 inhibitors versus placebo. *CI* confidence interval, *COX-2* cyclooxygenase-2, *RR* relative risk

In the Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen Or Naproxen (PRECISION) trial, celecoxib was found to be non-inferior to naproxen or ibuprofen for the primary composite outcome of cardiovascular death (including hemorrhagic death), nonfatal myocardial infarction or nonfatal stroke [65]. In a subgroup analysis of OA patients, fewer major cardiovascular AEs were observed in patients treated with celecoxib compared with ibuprofen [66]. This confirms the findings of a Japanese prospective observational study of 10,529 patients with OA or RA prescribed celecoxib or an NSAID, in which celecoxib was not shown to be associated with increased cardiovascular risk in comparison with NSAIDs [67].

We found no significant increase in the risk of total AEs or serious AEs with the use of COX-2 inhibitors (Table 3). Neither was there an increase in the rate of constipation, nausea and vomiting, CNS AEs or dermatological AEs with COX-2 inhibitors versus placebo. Insufficient data on renal and hepatic events or death, or withdrawals due to AEs were reported to include in this meta-analysis.

4.1 Limitations

Around half of the studies identified from the literature search that met the inclusion criteria did not provide AE data suitable for inclusion in the meta-analysis. Included studies were of short duration, that is, 75% of studies were between 2 and 26 weeks' duration. Many studies lacked detail on how AEs were collected, with many relying on patient self-reporting. The grouping of AEs could have led to lack of resolution, and possible double counting. In combining different drugs and doses into one meta-analysis, we chose the highest dose when multiple doses were presented in a trial, which could have led to an exaggeration of AEs. Sensitivity analysis of the two approaches (highest dose vs multiple dose) revealed only marginal differences in the magnitude

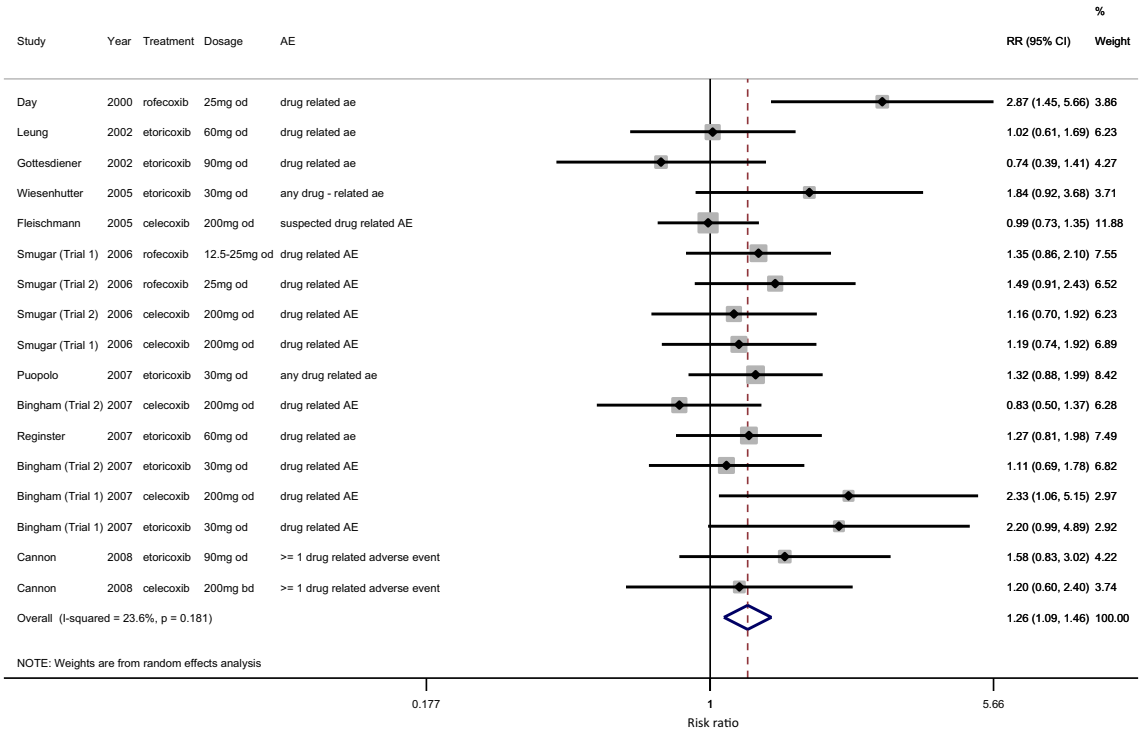

Fig. 8 Relative risk of drug-related adverse events for COX-2 inhibitors versus placebo. AE adverse event, *CI* confidence interval, *COX-2* cyclooxygenase-2, *RR* relative risk

Table 2 Summary of significant safety findings for COX-2 inhibitors versus placebo in patients with osteoarthritis

Outcomes	No. of participants Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI) Risk ratio	Anticipated absolute effects	
				Risk with placebo	Risk difference with COX-2 inhibitors
Treatment-related adverse events	7463	⊕⊕⊕⊕ HIGH	1.26 (1.09–1.46)	144 per 1000	37 more per 1000 (13 more to 66 more)
Upper gastrointestinal adverse events overall	23,974	⊕⊕⊕⊕ HIGH	1.19 (1.03–1.38)	29 per 1000	5 more per 1000 (1 more to 11 more)
Abdominal pain	9907	⊕⊕⊕⊕ HIGH	1.40 (1.08–1.80)	23 per 1000	9 more per 1000 (2 more to 19 more)
Hypertension	7360	⊕⊕⊕⊕ HIGH	1.45 (1.01–2.10)	27 per 1000	12 more per 1000 (0 fewer to 30 more)
Heart failure and edema	14,111	⊕⊕⊕⊕ HIGH	1.68 (1.22–2.31)	10 per 1000	7 more per 1000 (2 more to 14 more)

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

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

CI confidence interval, *COX-2* cyclooxygenase-2

Table 3 Summary of non-significant safety findings for COX-2 inhibitors versus placebo in patients with osteoarthritis

Outcomes[a]	No. of participants Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI) Risk Ratio	Anticipated absolute effects	
				Risk with placebo	Risk difference with COX-2 inhibitors
Total adverse events	14,908	⊕⊕⊕◯ MODERATE[b]	1.03 (0.97–1.10)	471 per 1000	14 more per 1000 (14 fewer to 47 more)
Serious adverse events	10,393	⊕⊕⊕⊕ HIGH	0.76 (0.48–1.19)	18 per 1000	4 fewer per 1000 (9 fewer to 3 more)
Constipation	3066	⊕⊕⊕⊕ HIGH	1.00 (0.58–1.75)	16 per 1000	0 fewer per 1000 (7 fewer to 12 more)
Nausea or vomiting	9956	⊕⊕⊕⊕ HIGH	0.96 (0.75–1.22)	31 per 1000	1 fewer per 1000 (8 fewer to 7 more)
Hypertension (celecoxib and etoricoxib only)	5280	⊕⊕⊕⊕ HIGH	1.21 (0.80–1.83)	28 per 1000	6 more per 1000 (6 fewer to 23 more)
Central nervous system adverse events	14,649	⊕⊕⊕⊕ HIGH	0.94 (0.84–1.04)	87 per 1000	5 fewer per 1000 (14 fewer to 3 more)
Rash or pruritus	4248	⊕⊕⊕⊕ HIGH	1.02 (0.76–1.37)	36 per 1000	1 more per 1000 (9 fewer to 13 more)

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

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

CI confidence interval, *COX-2* cyclooxygenase-2

[a]Renal and hepatic events and death were not reported as outcomes in sufficient studies to analyze

[b]I^2 between 50 and 75% ($p < 0.001$)

of the outcome. Our analysis was limited to studies in OA patients only; thus, safety issues could be missed in relevant subgroups such as in patients after coronary artery bypass graft surgery, or in patients with rheumatoid arthritis.

5 Conclusions

Along with non-selective NSAIDs, the use of COX-2 inhibitors in OA is associated with a significant increased risk of drug-related AEs compared with placebo. Specifically, we found an increased risk of upper-gastrointestinal AEs with COX-2 inhibitors, especially abdominal pain. We also found an increased risk of cardiovascular AEs with COX-2 inhibitors, namely hypertension, heart failure and edema. Our results confirm that a cautious approach to the use of NSAIDs and COX-2 inhibitors for the management of pain and inflammation in OA is advisable, with selection of treatment tailored to the individual patient characteristics. In OA patients at increased risk of gastrointestinal AEs, COX-2 inhibitors with the addition of a proton pump inhibitor may be used in preference to a non-selective NSAID; while for patients at increased risk of cardiovascular AEs, the use of COX-2 inhibitors should be avoided. Low-dose celecoxib (200 mg/day) may be the preferred NSAID due to its lower propensity for gastrointestinal and cardiovascular toxicity. To maximize the risk : benefit of NSAIDs, including COX-2 inhibitors, the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO) recommends intermittent or longer cycles of NSAID use rather than chronic treatment in order to minimize safety concerns [68].

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Compliance with Ethical Standards

All authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

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Conflict of interest O. Bruyère reports grants from Biophytis, IBSA, MEDA, Servier, SMB and Theramex outside the submitted work. C. Cooper reports personal fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GlaxoSmithKline, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB outside of the submitted work. J-Y. Reginster reports grants from IBSA-Genevrier, Mylan, CNIEL, Radius Health (through institution); consulting fees from IBSA-Genevrier, Mylan, CNIEL, Radius Health, Pierre Fabre; fees for participation in review activities from IBSA-Genevrier, MYLAN, CNIEL, Radius Health, Teva; payment for lectures from AgNovos, CERIN, CNIEL, Dairy Research Council (DRC), Echolight, IBSA-Genevrier, Mylan, Pfizer Consumer Health, Teva, Theramex outside of the submitted work. E. Curtis reports lecture fees and travel support from Eli Lilly, Pfizer and UCB outside of the submitted work. N. Fuggle reports travel support from Eli Lilly and Pfizer outside of the submitted work. E. Dennison reports personal fees for lectures or advisory boards from UCB and Pfizer outside of the submitted work. N. Corp reports partial funding of employment at Keele University from Versus Arthritis (registered charity), and travel support from Versus Arthritis outside of the submitted work. S. Maggi reports research grants from Takeda, MSD, Pfizer, GSK and consulting fees or honorarium from MSD and Pfizer outside of the submitted work and outside of the research topic. G. Honvo, S. Shaw, L. Spooner, G. Ntani, C. Parsons and J. Baird report nothing to disclose.

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