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Rofecoxib for osteoarthritis (Review)

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[Intervention Review]

Rofecoxib for osteoarthritis

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ABSTRACT

Background

Editor's note: The anti-inflammatory drug rofecoxib (Vioxx) was withdrawn from the market at the end of September 2004 after it was shown that long-term use (greater than 18 months) could increase the risk of heart attack and stroke. Further information is available at www.vioxx.com.

Osteoarthritis is a chronic disease of the joints, characterised by joint pain, stiffness and loss of physical function. Its onset is age-related and occurs usually between the ages of 50 and 60. It is the commonest cause of disability in those aged over 65, with OA of the knee and/or hip affecting over 20 per cent of the elderly population.

Objectives

To establish the efficacy and safety of rofecoxib in the management of OA by systematic review of available evidence.

Search methods

We searched the following databases up to August 2004: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, National Research Register, NHS Economic Evaluation Database, Health Technology Assessment Database. The bibliographies of retrieved papers and content experts were consulted for additional references.

Selection criteria

All eligible randomised controlled trials (RCTs) were included. No unpublished RCTs were included in this edition of the review.

Data collection and analysis

Data were abstracted independently by two reviewers. A validated checklist was used to score the quality of the RCTs. Comparable trials were pooled using fixed effects model.

Main results

Twenty-six RCTs were included. The comparators were placebo, diclofenac, ibuprofen, naproxen, nimesulide, nabumetone, paracetamol, celecoxib and Arthrotec. The evidence reviewed indicated that rofecoxib was more effective than placebo (patient global response RR 1.75 95% CI: 1.35, 2.26) but was associated with more adverse events (RR 1.32 95% CI 1.11, 1.56). There were no consistent differences in efficacy between rofecoxib and any of the active comparators at equivalent doses. Endoscopic studies indicated that compared to ibuprofen 800mg three times a day, rofecoxib caused fewer erosions and gastric ulcers at doses of 25mg and 50mg; the difference in duodenal ulcers was evident only at a dose of 25mg. Rofecoxib 50mg also caused more endoscopically observed ulcers greater than rofecoxib 25mg (RR 2.48 CI: 1.21, 5.11). Very few of the trials reported overall rates of GI adverse events although rofecoxib was found to cause fewer GI events

than naproxen. Only one of the nine trials comparing rofecoxib to celecoxib reported on the overall rates of GI events and this was a comparison of the higher recommended dose of rofecoxib with the lower recommended dose of celecoxib. Similarly, the three trials in older hypertensive patients that examined the cardiovascular safety of rofecoxib and celecoxib used non-comparable doses; the results of these studies indicated that rofecoxib caused more patients to have oedema and a clinically significant increase in systolic blood pressure. This difference between rofecoxib and celecoxib was not evident in studies conducted in more general populations.

Authors' conclusions

Rofecoxib was voluntarily withdrawn from global markets in October 2004 therefore there are no implications for practice concerning its use. There remains a number of questions over both the benefits and risks associated with Cox II selective agents and further work is ongoing.

PLAIN LANGUAGE SUMMARY

Rofecoxib for osteoarthritis

Editor's note: The anti-inflammatory drug rofecoxib (Vioxx) was withdrawn from the market at the end of September 2004 after it was shown that long-term use (greater than 18 months) could increase the risk of heart attack and stroke. Further information is available at www.vioxx.com.

Does Rofecoxib work for treating osteoarthritis and how safe is it?
To answer this question, scientists found and analyzed 26 studies. These studies included over 20 000 people with osteoarthritis and lasted up to 1 year. Studies compared people taking rofecoxib at 12.5, 25 or 50 mg once a day to people taking a placebo (sugar pill) or other NSAIDs such as diclofenac, ibuprofen, naproxen, nimesulide, nabumetone, paracetamol (Tylenol), celecoxib or Arthrotec. These studies provide the best evidence we have today.

What is osteoarthritis and how could rofecoxib help?
Osteoarthritis (OA) is the most common form of arthritis that can affect the hands, hips, shoulders and knees. In OA, the cartilage that protects the ends of the bones breaks down and causes pain and swelling. Rofecoxib is often referred to as a 'COX II inhibitor' and is one of the new non-steroidal anti-inflammatory drugs (NSAIDs) prescribed to decrease pain and inflammation. Other NSAIDS, such as naproxen (Naprosyn) are also prescribed but they come with warnings that they may cause stomach problems such as ulcers, bleeds and sores that can be serious. Rofecoxib is thought to be safer on the stomach than other NSAIDS.

Rofecoxib was taken off the market in October 2004. A study had shown that people taking rofecoxib to prevent colon cancer had more heart attacks and strokes than people taking a sugar pill.

What did studies testing rofecoxib in OA show?
Studies showed people taking rofecoxib improved more than people taking a sugar pill.

Three studies showed that
• 29 out of 100 people felt better overall with a sugar pill
• 53 out of 100 people felt better overall with rofecoxib at 12.5 mg per day.

Studies also showed that improvements were about the same whether people took rofecoxib or a different NSAID.

How safe was it in the studies?
Very few studies recorded and reported stomach problems. When rofecoxib was compared to a sugar pill, more people taking rofecoxib had kidney problems, water retention and high blood pressure but the number of people with stomach problems was about the same.

When compared to other NSAIDs, less people taking 25 or 50 mg rofecoxib had stomach problems than when taking ibuprofen (800 mg three times a day) or naproxen. Rofecoxib also caused less diarrhea than arthrotec.

What is the bottom line?
Rofecoxib was withdrawn from the world wide market in October 2004 and is no longer available.

When considering which non-steroidal anti-inflammatory drug (NSAID) to use, it must be remembered that the effects and safety of a drug is different among people and depends on the drug. The effect and safety also depends on the dose and how it acts in the body.

There are still questions about the effects and safety of other Cox-II inhibitors and more research is being done.

BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis and is caused by degeneration of the joint cartilage and growth of new bone, cartilage and connective tissue. OA is a chronic disease and causes pain, stiffness and loss of physical function. It is often associated with significant disability and impaired quality of life, particularly when the knee and hip joints are affected. The onset of OA is age-related and occurs usually between the ages of 50 and 60.

OA is not curable therefore management relies on pain control, strategies to reduce stiffness and maintain physical function, and drugs to modify the disease process. Non-drug management (physiotherapy, occupational therapy, weight loss and exercise) can control some symptoms but invariably drugs are required. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to reduce pain and inflammation. These are a diverse group of compounds that share many pharmacological properties and side-effects, including a propensity to cause damage to the gastro-intestinal tract. These gastro-intestinal (GI) effects commonly present as symptoms such as nausea, dyspepsia and gastritis. NSAIDs can however cause more serious GI complications (ulcers, perforations, obstructions and bleeding). Studies have indicated that ulcers that are visible on endoscopy are present in up to 40% of chronic NSAID users (Stalnikowicz 1993) but 85% of them never become clinically apparent. Perforations, obstructions and bleeds can be fatal but are less common with an estimated incidence of approximately 1.5% per year (Silverstein 1995). NSAIDs are weak acids and rapidly penetrate the superficial gastric mucosal lining cells, which can lead to erosion of the cells and cause symptoms. Whilst these local effects are important, they do not automatically result in ulcers; research indicates this is in part due to systemic inhibition of prostaglandins.

NSAIDs primarily act on the cyclo-oxygenase (Cox) enzyme that converts arachidonic acid into prostaglandins. Prostaglandins are a group of hormone-like chemicals that are normally present in the body and, amongst other functions, mediate inflammation and pain. Two principal forms of the Cox enzyme have been described; Cox I and Cox II (Vane 1998). Cox I is responsible for the production of prostaglandins that are essential for maintenance of normal endocrine and kidney function, gastric mucosal integrity and the processes that stop bleeding (haemostasis). Cox I is normally present in high concentrations in platelets, vascular endothelial cells, the stomach and kidney collecting tubules. Platelet Cox-1 mediates the production of thromboxane A2, a prostaglandin that promotes constriction of the blood vessels and activates the platelets causing them to aggregate.

In contrast, Cox II is normally virtually undetectable in most tissues but it is produced in response to inflammatory and mitogenic stimuli; this suggests that it has an important role in the mediation of inflammation (Vane 1998). It has been shown that Cox II is induced in rheumatoid synoviocytes, macrophages and polymorphonuclear leukocytes (Vane 1998). Cox II also is involved in production of prostacylin, a prostaglandin that dilates blood vessels, and inhibits aggregation of the platelets.

Research indicated that the GI adverse events associated with NSAIDs are due, at least in part, to inhibition of Cox I. It was therefore hypothesised that if an NSAID inhibited Cox II alone, whilst having a minimal effect on Cox I, the gastrointestinal adverse effects could be reduced with no impact on effectiveness. This led to the development of the group of NSAIDs known as the coxibs, which currently includes celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, and valdecoxib. This review examines the safety and efficacy of rofecoxib, which is licensed for OA at a dose of 12.5mg to 25mg/day.

OBJECTIVES

To assess the clinical efficacy and safety of rofecoxib in OA by systematic review of available evidence.

METHODS

Criteria for considering studies for this review

Types of studies

Published prospective randomised controlled trials (RCTs) of parallel design. Studies published in any language were considered. No unpublished studies were sought for this edition of the review.

Types of participants

Patients with OA of any age and either sex.

Types of interventions

Rofecoxib versus placebo or another active comparator.

Types of outcome measures

Studies were included if any accepted method to assess disease severity or progression was used.

The outcome measures sought were those agreed to at OMERACT III (Bellamy 1997), where the assessment includes at least one validated measure of pain, physical function or global assessment of the patient.

EFFICACY MEASURES:
OMERACT outcomes
1) partial or total reduction of pain
2) improvement on the degree of the studied joint movements
3) global assessment by the patient
4) joint imaging for studies of 1 yr or more

In addition to these outcomes: validated outcome measures of physical function were sought, for example the WOMAC, HAQ, and LEQUESNE INDEX, physician global assessment and quality of life.

SAFETY MEASURES:
Data were also collected on the number of (incidence and severity of):
1) total withdrawals
2) withdrawals due to adverse events (AEs)
3) withdrawals due to gastro-intestinal AEs (GI AEs)
4) withdrawals due to lack of efficacy
5) total adverse events (AEs) associated with therapy
6) number of patients with cardiovascular event(s)
7) number of patients with ulcer(s) and/or perforation and/or obstruction and/or GI bleed (PUBs).
8) number of patients with perforation and/or obstruction and/or GI bleed (POBs)
9) deaths

Search methods for identification of studies

We searched MEDLINE (1966 to week 36 2004), EMBASE (1980 to week 36 2004) and the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 3: 2004) to identify trials of rofecoxib in OA patients. The Cochrane Collaboration trial filter was used for the MEDLINE search. The bibliographies of retrieved reviews were scanned for additional references.

MEDLINE search
1. (cyclooxygenase-2 or cyclooxygenase 2 or cyclooxygenase-II or cyclooxygenaseII).ti,ab.
2. (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).ti,ab.
3. (cox-2 or cox2 or cox-II or coxII).ti,ab.
4. (rofecoxib or vioxx or MK-0966).af
5. Cyclooxygenase inhibitors/
6. or/1-5
7. exp *arthritis/
8. (arthrit$ or osteoarthrit$).ti,ab.
9. 7 or 8
10.6 and 9

EMBASE search
1. (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).ti,ab.
2. (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).ti,ab.
3. (cox-2 or cox2 or cox-II or coxII).ti,ab.
4. (rofecoxib or vioxx or MK-0966).af.
5. Cyclooxygenase 2 inhibitor/
6. Cyclooxygenase 2/
7. Rofecoxib/
8. or/1-7
9. (arthrit$ or osteoarthrit$).ti,ab.
10. exp Arthritis/
11. 9 or 10
12. 8 and 11

Cochrane Library/CENTRAL
1. (CYCLOOXYGENASE* near INHIBITOR*
2. (CYCLO next OXYGENASE*) near INHIBITOR*
3. COX* near INHIBITOR*
4. ROFECOXIB or VIOXX
5. CYCLOOXYGENASE-INHIBITORS:ME
6. #1 or #2 or #3 or #4 or #5
7. ARTHRITIS or OSTEOARTHRITIS
8. ARTHRITIS*:ME
9. (#7 or #8)
10.(#6 and #9)

The titles and abstracts identified by the searches were assessed by two reviewers (RF, SG) for inclusion.

Data collection and analysis

STUDY SELECTION AND DATA EXTRACTION
Two reviewers (SG and DF or RF) independently ascertained whether each study met the inclusion criteria for the review and a double abstraction process was undertaken. Any discrepancies were resolved by discussion and where this was not possible the authors of the study were contacted for clarification. Abstracts were considered in tandem with the full publication.

QUALITY ASSESSMENT
The methodological quality of the included studies was assessed by two independent reviewers (SG,LM) on the basis of randomisation, adequate concealment of randomisation, degree of blinding, use of intention to treat analysis and description of dropouts and withdrawals. The Jadad and Schultz assessment tools (Jadad 1996, Schulz 1995) were used to assign the quality scores to each study.

DATA ANALYSIS
Where possible data from intention to treat (ITT) analysis were abstracted. Results are presented in both absolute and relative terms and are presented as relative risks (RR) or mean differences (MD) with their 95% confidence intervals (95% CI). A fixed effects model was used throughout. Data on the incidence of ulcers detected on endoscopy were considered separately from those that presented clinically.

RESULTS

Description of studies

A total of 26 RCTs met the inclusion criteria for this review. Five have been published in abstract form only: Moskowitz 2003; CRESCENT (Sowers); Geba (MSD 090); Schnitzer 2001; VACT 2. All but three of the publications acknowledged sponsorship from either Pfizer or MSD Herrera 2003; Bianchi 2003; Niccoli 2002.

The following comparators were used: naproxen (3 RCTs (NAPROXEN 901 OC/OF and Advantage 2000); placebo (12 RCTs Ehrich 2001(MSD 029); Ehrich 1999 (pilot); Schnitzer 2001; Day 2000 (MSD 040); Geba (MSD 090); Kivitz 2004(MSD 085); Hawkey 2000(MSD 045); Laine 1999 (MSD 044); Saag 2000 (MSD 034); Truitt 2001(MSD 058); Gibofsky 2003; McKenna 2000; diclofenac (3 RCTs: Cannon 2000(MSD 035); Saag 2000 (MSD 034); Niccoli 2002); ibuprofen (4 RCTs: Day 2000 (MSD 040); Hawkey 2000(MSD 045); Laine 1999 (MSD 044); Saag 1998 (MSD 033)); nabumetone (3 RCTs: Kivitz 2004(MSD 085); Truitt 2001(MSD 058) Geba (MSD 090)); diclofenac/misoprostol (1 RCT Acevedo 2001(MSD902)) nimesulide: (2 RCTs: Bianchi 2003; Herrera 2003) ; celecoxib/ paracetamol VACT. VACT 2; AMG Niccoli 2002; celecoxib Geba (MSD 090); McKenna 2000; SUCCESS VI; SUCCESS VII; Bianchi 2003; VACT; VACT 2; Gibofsky 2003; Schnitzer 2001; CRESCENT (Sowers) and valdecoxib Moskowitz 2003.

Of these studies two evaluated GI safety by endoscopic examination of patients Hawkey 2000(MSD 045); Laine 1999 (MSD 044) and the results have therefore been considered separately.

Risk of bias in included studies

The methodological quality of the included studies was assessed using a validated checklist (Jadad 1996) that rates the appropriateness of randomisation (2 points), appropriateness of double blinding (2 points) and description of dropouts and withdrawals (1 point), the total possible score is five. In addition, concealment allocation was assessed and rated as A (blind randomisation), B (unclear methods of randomisation), or C (quasi-randomisation) (Schulz 1995). Quality was assessed independently by two reviewers (SG, LM). Differences were resolved by consensus.

Quality was not assessed on those trials published in abstract form only. All but one trial were randomised, double blinded trials; Niccoli 2002 was single-blinded. All trials except for Hawkey

2000(MSD 045) and Laine 1999 (MSD 044) included a description of the reasons for dropouts. The Herrera 2003 and Ehrich 2001(MSD 029) papers received a quality score of three because neither the method of randomisation nor the method of double-blinding was described. Niccoli 2002 received a quality score of three because it was singled blinded and the method of randomization was not described. Hawkey 2000(MSD 045) did not give the reason for withdrawal, nor the method of randomization and so also scored a three. McKenna 2000 and Bianchi 2003 both had a quality score of four because they did not describe the method of blinding. Laine 1999 (MSD 044) also scored a four because the reason for dropout was not described. The remaining papers all included a description of appropriate randomisation and double blinding so received two additional points and an overall quality score of five out of five. Clear methods of concealment of allocation was stated in five trials (Day 2000 (MSD 040), Ehrich 1999 (pilot), Kivitz 2004(MSD 085), Laine 1999 (MSD 044), SUCCESS VI) and therefore received a concealment rating of A. The remaining trials did not clearly indicate clear methods of concealment of allocation and thus received a concealment rating of B.

Effects of interventions

1. ROFECOXIB versus PLACEBO

13 RCTs were identified that had a rofecoxib arm and a placebo arm; two included only a rofecoxib and a placebo arm Ehrich 2001(MSD 029); Ehrich 1999 (pilot), whilst the other 11 had additional active comparators. The comparators were: ibuprofen (4 RCTs: Day 2000 (MSD 040); Hawkey 2000(MSD 045); Laine 1999 (MSD 044); Saag 1998 (MSD 033)); nabumetone (3 RCTs: Geba (MSD 090); Kivitz 2004(MSD 085); Truitt 2001(MSD 058)) celecoxib (3 RCTs: Gibofsky 2003; McKenna 2000; Schnitzer 2001) and valdecoxib (1 RCT: Moskowitz 2003).

1.1 EFFICACY

Meta-analysis was possible for a number of efficacy outcomes; rofecoxib was consistently found to be superior to placebo across the WOMAC subscales although some heterogeneity was seen in the results due to the findings of Gibofsky 2003. Similarly, all patient/investigator ratings, measured on both continuous and dichotomous scales in both individual trials and the pooled results, indicated rofecoxib to be superior apart from one trial's investigator improved/ not improved 25mg 6 weeks Gibofsky 2003 and another's patient measures of disease status Truitt 2001(MSD 058). The number needed to treat (NNT) with rofecoxib versus placebo to achieve an improvement in patient global assessment was 5 (95% CI: 4, 6)(see Additional tables, Table 1; Table 2) Two studies (Truitt 2001(MSD 058); Day 2000 (MSD 040)) reported on joint tenderness at 6 weeks, which was less in both the 12.5mg and 25mg groups. One study reported SF36 physical component and mental components at 6 weeks; all rofecoxib doses were superior to placebo Ehrich 2001(MSD 029). Four trials reported on paracetamol rescue, which was less in the rofecoxib group apart from in Gibofsky 2003. Rofecoxib also caused statistically significantly fewer withdrawals due to lack of efficacy across all doses and timepoints.

1.2 SAFETY

Meta-analysis was possible for a number of safety outcomes. Many of the trials did not report total numbers of adverse events. Rofecoxib was found to have a statistically significant greater overall rate of adverse events at the following dose/duration: 12.5mg 6 weeks; 25mg 6 weeks and 50mg 18 weeks. The number of serious adverse events was greater at a dose of 12.5mg at 6 weeks (RR: 3.95 CI: 1.05, 14.63). The event rates were too low in the 25mg trials to allow meaningful comparison. The rates of total GI events were statistically significant over 6 weeks with the 25mg dose (RR: 3.39 CI: 1.47; 7.84). One study showed a statistically significant increase in systolic BP using 25mg at 6 weeks (RR: 2.89 CI: 1.17, 7.84) and rofecoxib 12.5mg caused a greater incidence of lower extremity oedema at 6 weeks (RR: 2.40 CI: 1.05, 5.48). No other differences were observed. Withdrawals due to adverse events were significantly greater in the rofecoxib 12.5mg group over 6/8 weeks (RR: 2.18 CI: 1.34, 3.55) and 50mg at 12 weeks (RR: 2.04 CI: 1.24, 3.36) but not 25mg at 6 weeks (RR: 1.56 CI: 0.94, 2.59). Two trials reported withdrawals due to GI adverse and CV adverse events and found no statistically significant differences McKenna 2000; Saag 1998 (MSD 033). The one trial that reported withdrawals due to CV adverse events found no difference Saag 1998 (MSD 033). Pooled analysis of the two 18 week endoscopy studies indicated that there were no statistically significant differences in the rates of ulcers or erosions apart from rofecoxib causing fewer ulcers greater than or equal to 5mm in diameter (RR: 0.42 CI: 0.20, 0.86).

2. ROFECOXIB versus DICLOFENAC

Three published RCTs were identified that compared rofecoxib (12.5mg or 25mg per day) to diclofenac 50mg three times a day. Other than the rates of withdrawals there were no poolable data therefore the results of individual studies are presented below.

The first RCT was an Italian two-week, single-blind study that compared the renal tolerability of rofecoxib 25mg per day with that of diclofenac 150 mg per day and amtolmetin guacyl (AMG) in 90 individuals between 60 and 80 years of age Niccoli 2002. The publication was however ambiguous about the methodology used in this study and states that dropouts were replaced by the next eligible patient, who was assigned to the same treatment arm. Six patients were "discounted" (1 AMG; 1 diclofenac; 4 rofecoxib) because they withdrew from the study during the first week of treatment due to intolerance or adverse events. Patients were also withdrawn if any adverse event related to the study drug occurred. The paper does however state that all adverse events statistics (excluding those for renal function) were based on the 96 patients originally enrolled.

The other two RCTs enrolled 693 Saag 2000 (MSD 034) and 784 patients Cannon 2000(MSD 035) over 40 years of age with OA of the knee or hip. Over a one-year period rofecoxib 12.5mg and 25mg per day was compared under double-blind conditions to 50mg diclofenac three times per day. Neither of the primary publications states that the trials were of identical design, but data from the two 'replicate' trials have been pooled in a post-hoc analysis of data collected from liver-function tests Cannon 2003 and two-year follow up data have also been published in abstract form Cannon 2003.

There are however a number of ambiguities in the report of MSD 034 which makes it difficult to validate the results (see notes Table of Included Studies). Although it is described as a one-year study, the publication states that "primary efficacy analyses were based on the average change from baseline over the first 12-week treatment period. Analyses were also performed at 26 and 52 weeks". No 12-week data are reported and no measures of dispersion given for the 52 week data. After 26 weeks of treatment topical or systemic analgesics and corticosteroids were permitted for breakthrough OA pain. Figure 4 in the publication indicates

"p<0.001 vs. placebo for all active treatments" despite no placebo group being reported in the methods section. There are also some conflicts in the text with regard to the designation of the primary endpoints with Figure 4 and the results section indicating that they were the WOMAC subscales and the methods section which indicates only the WOMAC pain. The methods section states that for clinical comparability two conditions had to be met: in any two of the primary endpoints, the 95% confidence intervals (CIs) of mean differences between treatment groups were to be within predefined comparability bounds (+/- 10mm on a 100-mm VAS and +/- 0.5 on a Likert); and all 3 of the posterior probabilities (with noninformative prior distributions) that the true mean differences are within the predefined clinical comparability bounds were p<.05.

2.1 EFFICACY

Other than for withdrawals due to lack of efficacy, no pooling of efficacy data was possible and therefore results for individual studies are presented below. Pooled data indicated that over one year fewer individuals taking rofecoxib 25mg per day withdrew due to lack of efficacy compared to those taking diclofenac 50mg three times a day (RR: 1.43 CI 1.05, 1.94). There were no statistically significant differences in the 12.5mg comparison (RR: 1.11 CI: 0.80, 1.54).

After two weeks, the Italian study stated that rofecoxib and diclofenac significantly improved the measures of pain, and according to the patients' and physicians' global assessment of disease activity, the reduction in the diclofenac group was significantly greater (p<0.001) Niccoli 2002. Patient global assessment of pain (WMD -6.26 95% CI: -10.78, -1.74); patient global disease activity (WMD -6.39; 95% CI: -10.87, -1.91); physician disease activity (WMD -5.08; 95% CI: -9.66, -0.50). The results however may be compromised due to the unusual methodology.

In the first of the one year studies, all three groups experienced significant improvement in disease status from baseline, which met the author's pre-specified criteria for comparable efficacy; comparability stated if for all three primary endpoints, the 95% confidence intervals of the difference in the mean treatment response between two treatments were within + or - 10mm on a 100mm VAS scale or 0.5 on a Likert scale Cannon 2000(MSD 035). There were statistically significant differences in favour of diclofenac for the patients' assessment of response to therapy and the physicians' assessment of disease status, although the paper states that this was only measured up to 26 weeks. The authors report that treatment by factor analysis for the 3 primary endpoints showed that there was no statistically significant interaction with treatment for various subgroups, including location of the study joint (knee or hip), previous OA medication (NSAID/paracetamol), age and gender.

In the second year-long RCT, only the mean changes were available without any measures of dispersion Saag 2000 (MSD 034). In addition, no 12-week data were reported, despite this being stated as the primary endpoint. At 52 weeks there were no statistically significant differences between rofecoxib 12.5mg and rofecoxib 25mg, but the 12.5mg dose showed statistically significant less efficacy compared to diclofenac on pain on walking on a flat surface, investigator global assessment of response to therapy, patient global assessment of disease status and increased rescue paracetamol use. None of these endpoints were designated as primary. There is additionally ambiguity concerning the results of rofecoxib 25mg versus diclofenac with the table not indicating any statistically significant differences but the text stating " Efficacy results were consistent for each dose of rofecoxib compared with diclofenac for the endpoints: patient global assessment of response to therapy and investigator global assessment of disease status (p=0.03 vs. 25mg, and p=0.01 vs. 12.5mg respectively). For patient global assessment of disease status rofecoxib was different [less improvement] from diclofenac (p=0.01)." Although the methods section states the grounds for clinical comparability the results state that the 95% confidence intervals for the difference between 12.5mg and 25mg rofecoxib vs. diclofenac were contained within the prespecified comparability grounds for the WOMAC scales, indicating clinical comparability.

2.2 SAFETY

The two-week renal tolerability study stated that both diclofenac and rofecoxib impaired renal function (unlike AMG). The validity of the results may however be compromised by the unusual methodology Niccoli 2002. The authors concluded that rofecoxib caused increased water and salt retention as indicated by a significant increase in body weight, systolic and diastolic blood pressure and serum sodium and uric acid. A significant reduction in diuresis and creatinine clearance also occurred; 6 patients experienced oliguria and mild malleolar oedema and weight gain, 4 patients developed hypertension and an additional 4 patients withdrew from the study due to acute development of marked peripheral oedema and rapid weight gain. In the diclofenac group there was an increase in BUN and serum creatinine, potassium and uric acid, with a decrease in 24-hour urine volume and creatinine clearance. One patient withdrew due to gastric intolerance and a further 8 experienced gastric pain. AMG treated patients did not show any significant impairment of renal function. The only between group comparison reported was a significant reduction in creatinine clearance in the diclofenac group compared to both the AMG and the rofecoxib group.

The first one-year RCT, reported no differences in GI events, CV events, oedema or PUBs Cannon 2000(MSD 035). The diclofenac group experienced greater increases in mean alanin and aspartate aminotransferase levels. No episodes of GI bleeding were reported.

The second one-year RCT only presented data for drug related adverse experiences occurring in >= 5% of patients Saag 2000 (MSD 034). The authors report that the rates of individual adverse experiences were generally similar between the groups for all events occurring at >=5% of individuals except for abdominal pain which occurred at a significantly higher rate in the diclofenac group compared to both the rofecoxib groups 13/230 vs. 2/231 and 2/232(p=0.01). Four deaths were reported in the diclofenac group with none in the rofecoxib group; no death was considered to be drug related by the investigator with all having previous medical history of related disorders. More patients discontinued due to adverse experiences and due to GI adverse experiences in the diclofenac group. No rates of overall GI adverse events are reported as the publication only reports those occurring with an incidence of >= 5%. Discontinuations due to cardiovascular events, including hypertension, palpitation, and Transient Ischaemic Attack (TIA) occurred in 3/231, 4/232 and 3/230 (RR: 1.00; 95% CI: 0.2, 4.9) and (RR: 1.3; 95% CI: 0.3; 5.8) respectively. Diclofenac again was shown to raise transaminase levels 10/230 compared to 1/232 receiving 25 mg rofecoxib.

The ambiguities in the reports not withstanding, the withdrawal data from the two trials one-year could be pooled: There were fewer

withdrawals due to AE in both the 12.5mg rofecoxib (RR: 0.71 CI: 0.52, 0.97) and 25mg (RR: 0.70 CI: 0.51, 0.95) groups respectively. There were no statistically significant differences in the withdrawals due to GI adverse events, total withdrawals and CV adverse events.

The post-hoc analysis of liver-function tests indicates that there were statistically significantly less disturbances of liver function in the rofecoxib groups compared to the diclofenac. The number of patients reported is not consistent with the primary papers however and only percentage results are reported with no indication of the numbers in each group Cannon 2003.

3. ROFECOXIB VERSUS IBUPROFEN

Four double-blind RCTs were identified that compared rofecoxib to ibuprofen in patients with OA; Saag 1998 (MSD 033); Day 2000 (MSD 040); Laine 1999 (MSD 044); Hawkey 2000(MSD 045). Two of these RCTs were of identical design and used endoscopy to compare the gastro-duodenal impact of 16 to 24 weeks treatment with either 25mg or 50 mg rofecoxib once daily, ibuprofen 800mg three times a day or placebo in 775 Hawkey 2000(MSD 045) and 742 Laine 1999 (MSD 044) patients. Neither trial enrolled aspirin users. At 16 weeks "because of an anticipated lack of efficacy in the placebo group, 95% of placebo patients and 5% of patients in the other groups (in a blinded fashion) were randomly discontinued, via a separate set of individually sealed envelopes". Investigations were performed at baseline, 6, 12 and 24 weeks. Only 12-week endoscopy data are included in this review due to the random discontinuations. The Hawkey paper also states that 89 patients did not undergo treatment-phase endoscopy. The discussion in the publication also states "the ulcer incidence rates for the rofecoxib groups did not change significantly in the second three months compared to the first three months. This suggests no change in the risk of GI injury with COX-2 specific inhibition with rofecoxib over 6 months. However without a placebo group for comparison in the second 3 months of the study, this inference cannot be confirmed". Neither publication makes it clear at what time point the trial profiles and the analysis of adverse events and withdrawals relate to. Therefore it is assumed to be 16 weeks. The incidence of events in many cases is given in percentages and, because the denominators are uncertain, the numerators may be incorrect.

The other two RCTs compared rofecoxib (12.5mg or 25mg once daily) to ibuprofen (800mg three times a day) or placebo over a six week period in 1156 Saag 1998 (MSD 033) and 809 adults with OA Day 2000 (MSD 040).

3.1 EFFICACY

The endoscopy study patients completed a 5-point Likert 'Patient Global Assessment of Disease Efficacy' at each visit. Both trials reported that the mean change from baseline was significantly greater in the active treatment groups compared to placebo ($p<0.001$). Insufficient data were presented to permit statistical combination of the results and rofecoxib and ibuprofen were not statistically compared. There was no statistically significant difference in the pooled estimates of withdrawals due to lack of efficacy Hawkey 2000(MSD 045); Laine 1999 (MSD 044).

Although the two 6-week trials were of similar design, lack of appropriate data in the publication prevented pooling of the trials for all outcomes apart from withdrawals due to lack of efficacy.
The Saag publication states that the treatments had comparable efficacy over the six-week period, but only presents mean values with no measures of dispersion Saag 1998 (MSD 033). The number of patients reporting a good or excellent global assessment of response to therapy was 126/221 in the ibuprofen group compared to 120/219 in the 12.5mg rofecoxib group (RR: 0.96 95%CI: 0.81, 1.13) and 138/227 in the rofecoxib 25mg group (RR: 1.07 95% CI: 0.91, 1.25). The publication also reports that overall rates of withdrawals due to lack of efficacy (LOE) indicated comparable efficacy with 12.5mg rofecoxib, but that 25 mg was superior i.e. had fewer withdrawals (RR: 0.46 95% CI: 0.21, 1.00). However when the results were pooled with the second RCT Day 2000 (MSD 040), the results did not reach significance: 12.5mg (RR: 0.9; 95% CI: 0.54, 1.52) and 25mg (RR: 0.57; 95% CI: 0.31, 1.03).

The Day publication states that the clinical efficacy of both rofecoxib groups was comparable with that of ibuprofen, using pre-specified comparability criteria Day 2000 (MSD 040). The effect of 25mg rofecoxib was however statistically significant superior to that of ibuprofen in two of the primary measures; patient global response to therapy (RR: 0.22 CI: 0.06, 0.38) and investigator global disease status (RR: 0.19 CI: 0.06, 0.32). The secondary criterion of patient measured disease status also indicated statistical superiority of 25mg dose (RR: 3.77 CI: 0.09, 7.45). Joint tenderness results were also significantly in favour of rofecoxib 25mg but WOMAC scores did not indicate any significant difference.

3.2 SAFETY

Data at 12 weeks from the two identical endoscopy studies Hawkey 2000(MSD 045); Laine 1999 (MSD 044) were pooled; rofecoxib at doses of 25mg and 50mg was associated with fewer gastric ulcers than ibuprofen 800mg three times a day (RR: 0.15 CI: 0.09, 0.25) and (RR: 0.23 CI: 0.14, 0.36). However, although the results indicated that rofecoxib also caused fewer duodenal ulcers at a dose of 25mg (RR: 0.24 CI: 0.09, 0.63), at the 50mg dose, the reduction did not reach significance (RR: 0.55 CI: 0.27, 1.12). Information on the number of erosions on endoscopy was also reported in broad terms but data from the two RCTs could not be combined because Laine and the pooled analysis reported results in graphical form only Hawkey 2001. Results from the Hawkey trial indicated both doses of rofecoxib were associated with fewer erosions (25mg WMD -2.98 CI: -3.71, -2.25) and 50mg WMD -2.74 CI: -3.48, -2.00) Hawkey 2000(MSD 045).

With respect to the number of complicated upper GI events, there is some ambiguity about the number of bleeds experienced. The Laine publication states that three ulcer complications occurred (2 upper GI bleeding episodes in the ibuprofen group and 1 in the 25mg rofecoxib group) and the Hawkey publication that one patient receiving placebo developed an upper GI bleed and 1 receiving ibuprofen. However the publication of the combined analysis states that "sixteen of the clinical presentations with a bleed that were reported during the 12- week placebo controlled parts of the studies were confirmed by the adjudication committee" Hawkey 2000(MSD 045) Hawkey 2001. No breakdown by allocated group was presented.
Data on the rates of withdrawals due to adverse events could be pooled and the only statistically significant difference was that there were fewer in the 25mg rofecoxib group in the endoscope studies at 16 weeks.

Pooling of data on adverse events was hampered due to poor reporting. The Saag publication only reports on adverse events that occurred with an incidence of >=5%; lower extremity oedema and diarrhoea Saag 1998 (MSD 033). No overall rates of adverse events or GI adverse events were presented. The Day publication also

does not report the overall rates of GI events Day 2000 (MSD 040). Pooling of the available data indicated no significant differences at any dose or time-point. For the 25mg dose of rofecoxib there was some indication that there was more lower-extremity oedema (RR: 2.34 CI: 0.84, 6.52) in the Saag trial Saag 1998 (MSD 033). The Day publication reports that the incidence of any laboratory adverse events, body weight change, blood pressure change, oedema and hypertension were not significantly different in the active groups, but no data are presented Day 2000 (MSD 040).

4. ROFECOXIB VERSUS NAPROXEN

Three RCTs were identified that enrolled a total of 6501 patients. Two of the RCTs had identical protocols and were therefore combined into a single publication NAPROXEN 901 OC/OF. Rofecoxib 12.5mg once daily was compared to naproxen 500mg twice daily for six weeks in a total of 944 patients aged 40 years or over with OA of the knee or hip. Matching placebos were used to maintain blinding.

The 12-week double-blind ADVANTAGE study enrolled 5557 patients and compared rofecoxib 25mg daily with naproxen 500mg twice daily Advantage 2000. Again, matching placebos were used to maintain blinding. Six-week data were not reported therefore no meta-analysis could be undertaken. Patients were permitted to take concomitant GI protective medication (PPI, antacids or H2blockers); which were taken in 253/2785 vs 310/2772 individuals (RR: 0.81 CI: 0.69, 0.95).

A fourth study, the Pharmacia sponsored CRESCENT study, examined 24 ambulatory blood pressure in patients with Type II diabetes who were taking ACE inhibitors for hypertension CRESCENT (Sowers). Patients received 25mg rofecoxib (once daily), 200mg celecoxib (once daily) or naproxen 500mg (twice daily) over 12 weeks. Very limited data were available for evaluation as the methods and results have only been published in abstract form.

4.1 EFFICACY

No pooling of data could be undertaken and therefore the results of individual studies are discussed.

The publication for the 901 OC/OF studies presents results graphically with tabulated differences in mean changes with no measures of dispersion. The authors however report that one of the studies in the combined analysis found a statistically significant difference in favour of naproxen for the patient global assessment of response to therapy (one of the designated primary endpoints) NAPROXEN 901 OC/OF. This finding was not duplicated in the second study. There were also some significant differences in favour of naproxen in some of the secondary endpoints and in the combined analysis. However the authors reported that all 95% CI's were well within the pre-stated equivalence boundaries indicating comparable treatment effects. The authors therefore concluded that 12.5mg of rofecoxib once daily was comparable to 500mg naproxen twice daily. However, additional 'rescue' medication was taken by 56% of rofecoxib patients and 53.5% of naproxen patients (RR 1.05 CI: 0.93, 1.18). There were no differences reported in the onset of pain relief (RR 1.11; 95% CI: 0.96, 1.28). Treatment by subgroup interaction tests indicated that the effect was consistent across subgroups.

The ADVANTAGE study permitted rescue medication but no results were reported Advantage 2000. Onset of pain relief was reported to be similar in the two groups and after 12 weeks of therapy there were no statistically significant differences in any of the endpoints between 25mg rofecoxib and 500mg naproxen. Withdrawals due to lack of efficacy were similar 177/2785 vs. 176/2772 (RR: 1.00 CI: 0.82, 1.22).

The abstract for the CRESCENT (Sowers) study reported that the "arthritis assessments demonstrated that changes in total WOMAC were similar for all 3 treatments at week 6 (p=0.4) and week 12 (p=0.39)". No data were provided.

4.2 SAFETY

The Naproxen 901 studies indicated that although there was no statistically significant difference in the overall rates of adverse events, fewer patients in the rofecoxib group experienced GI adverse events 63/471 vs. 114/473 (RR: 0.55 CI: 0.42, 0.73) which led to fewer discontinuations (RR: 0.28 CI: 0.10, 0.75) NAPROXEN 901 OC/OF. Seventeen patients in the study had a serious adverse event (RR: 0.70 CI: 0.27, 1.83), of which six were considered by the investigator to be possibly or probably drug related; 1 case of CHF in the rofecoxib group and 5 in the naproxen group (duodenal ulcer, drug overdose, CHF, gastric ulcer and bleeding gastric ulcer). There were no PUBs in the rofecoxib group and 3 in the naproxen (RR: 0.14 CI: 0.01, 2.77). There were similar rates of reno-vascular events, although numerically more patients discontinued due to hypertension (2/471 vs 0/473 RR: 5.02 CI: 0.24, 104.31) and peripheral/lower extremity oedema (3/471 vs 0/473 RR: 7.03 CI: 0.36, 135.72).

The ADVANTAGE study publication does not present any rates of adverse events other than CV Advantage 2000. There were 5 patients in the rofecoxib group who experienced an MI compared to 1 in the naproxen group (RR: 4.98 CI: 0.58, 42.57). The overall rates of thrombotic events were similar 10/2785 vs. 7/2772 (RR: 1.42 CI: 0.54, 3.73) but more patients experienced a stroke in the naproxen group 0/2785 vs. 6/2772 (RR: 0.08 CI 0.00, 1.36). Numerically more patients in the rofecoxib group experienced hypertension (RR: 1.22 CI: 0.89, 1.68). Subgroup analyses of patients with pre-existing hypertension indicated that the incidence of CV adverse events was higher in these patients but the difference was not statistically significant.

The overall withdrawals due to adverse events were similar 757/2785 vs. 788/2772 (RR: 0.96 CI: 0.86, 1.10), as were the number of patients withdrawing due to laboratory test adverse events 11/2799 vs 5/2787 (RR: 2.19 CI: 0.76, 6.29). The rofecoxib group experienced fewer discontinuations due to GI adverse events; the survival curve separated at 3 weeks and there were statistically significant differences over whole course of study (RR: 0.74; 95% CI: 0.60, 0.92). The cumulative incidence of concomitant GI medication use was statistically significantly lower in the rofecoxib group both at six weeks (RR: 0.80 CI: 0.66, 0.97) and twelve weeks (RR: 0.81 CI: 0.69, 0.95). There were 2 PUBs reported in the rofecoxib group compared to 9 in the naproxen group (RR: 0.22 CI 0.05, 1.02), although it must be borne in mind that patients could take concomitant GI protective medications (PPI, antacids or H2blockers). An abstract presented at the ACR conference (New Orleans 2002) stated that there were 6 PUBs in the rofecoxib group compared to 12 in the naproxen and that respectively 2 and 9 were confirmed by an independent adjudication committee (Geba 2002). In the 15% of patients who had previously stopped NSAID therapy because of GI intolerance, the results of discontinuation due to GI adverse events also favoured rofecoxib (reported RR: 0.53; 95% CI: 0.34, 0.84).

Sub-group analyses were conducted for ADVANTAGE patients receiving low dose aspirin Advantage 2000. The authors however state that it was not powered to be conclusive. As with the entire study population, there were fewer withdrawals due to GI events in patients taking rofecoxib but the difference was not statistically significant 17/352 vs. 31/367 (RR: 0.57 CI: 0.32, 1.01). An analysis of interaction by treatment with low-dose aspirin was also undertaken that indicated no statistically significant modification of effect (p=0.378), which the authors state indicated a consistent risk reduction regardless of aspirin use. Again, there is no analysis of whether these patients were also taking concomitant GI medication but the authors report that there was no statistically significant difference in the reduction in concomitant use of GI medication in the aspirin patients (RR: 0.82 CI: 0.57, 1.18).

The CRESCENT study reported that "at week 6, rofecoxib induced a significant increase in 24-hour systolic blood pressure (+4.2 mm Hg), whereas celecoxib and naproxen did not (-0.1 and -0.8 mmHg respectively; p=0.005). Week 12 results were comparable to week 6." No further data were presented CRESCENT (Sowers).

5. ROFECOXIB VERSUS NABUMETONE

Three 6-week double-blind, placebo-controlled RCTs were identified that compared rofecoxib to nabumetone. Two of the RCTs were identical in design; whilst one has only been published in abstract form Geba (MSD 090), the second has recently been published in full Kivitz 2004(MSD 085). The two RCTs compared rofecoxib 12.5mg daily to nabumetone 1000mg daily and enrolled 978 and 1042 patients with OA of the knee aged 40 or over.

The third RCT was conducted in 341 patients aged 80 years or older (mean age 83) and over six weeks compared rofecoxib 12.5mg and 25mg to nabumetone 1500mg and placebo Truitt 2001(MSD 058). Although the publication does not state that it was double-blind, double dummies were used and safety evaluations were undertaken by a blinded assessor.

5.1 EFFICACY

The RCT conducted in elderly patients indicated similar responses across the patient groups, with no statistically significant differences reported between the active treatment groups in any of the outcome measures. A time-course analysis of changes indicated that the treatment effects were generally at a constant level Truitt 2001(MSD 058).

With respect to the two six-week RCTs, the only efficacy results that could be pooled were the number of patients reporting good or excellent response, which was greater in the rofecoxib 12.5mg group (RR: 1.17 CI: 1.05, 1.29).

MSD 085 indicated that patients receiving rofecoxib were more likely to have a good or excellent response over the 6 weeks as assessed by the patient global response to therapy Kivitz 2004(MSD 085). Sensitivity analysis examining the numbers of individuals completing the study rather than using the modified ITT analysis indicated the same. Sub-group analysis conducted in patients over the age of 65 indicated this was also the case, and the results were compatible with the overall cohort (treatment by age interaction p=0.893). Results were however presented as an average over the whole treatment period with no endpoint results given. Both active groups had mean increases from baseline in each QoL domain on the SF36, which were significant, compared to placebo, for six of the eight domains (not physical function and mental health). Fewer patients taking rofecoxib withdrew due to lack of efficacy (RR: 0.64 CI: 0.41, 0.98).

The publication also presents results on onset of efficacy although both actives were reported to be quicker than placebo, no statistical comparison between rofecoxib and nabumetone was presented. The results also should be treated with caution as this assessment was initiated after the trial had started and was only used in 55.1% of patients. The publication also reported median time to first report of good or excellent PGART response, which was 2 days in the rofecoxib group compared to 4 in the nabumetone (comparison p=0.02) and greater than 5 in the placebo. Overall similar number of patients used paracetamol and the average number of tablets taken was also comparable. The interpretation of the secondary endpoints is uncertain as although there was a statistically significant difference in the walking pain score in favour of rofecoxib, it was based on average of week 2, 4 and 6 scores rather than the endpoint. Again onset of efficacy results were presented, but were only collected in 55.1% of the total cohort. The average onset over the 6 days was statistically significantly greater in the rofecoxib compared to the nabumetone.

The abstract of MSD 090 does not provide sufficient data for analysis of the results Geba (MSD 090). The authors report that rofecoxib was superior to nabumetone in the treatment of OA over six weeks as determined by the PGART and 'relief of pain walking on a flat surface'. They also note that rofecoxib had a more rapid onset of efficacy over the first six days compared to nabumetone. A pooled analysis of the results of the two studies has been presented as posters at conferences.

5.2 SAFETY

Pooled analysis of the results from the 6-week studies, indicated no difference in the rates of withdrawals due to adverse events (RR: 1.24 CI: 0.84, 1.84), total adverse events (RR: 1.09 CI: 0.99, 1.20), serious adverse events (RR: 1.28 CI: 0.57, 2.89), lower extremity oedema (RR: 1.41 CI: 0.72, 2.77) and hypertension (RR: 1.46 CI: 0.53, 4.12). The Kivitz report also states that no patient experienced a gastrointestinal perforation or ulceration Kivitz 2004(MSD 085). Two lower GI bleeds (anorectal haemorrhage and lower GI haemorrhage) occurred but neither was attributed to a study drug. The authors also report that concomitant aspirin use did not appear to increase the rates of adverse events but no sub-group data were presented.

The Truitt report states that there were no gastro-duodenal perforations, ulcers or haemorrhages in the study Truitt 2001(MSD 058). There were no data given for either total number of adverse events or total GI adverse events. Conflicting statements state that one or two cases of congestive heart failure occurred in patients taking nabumetone. There were no significant differences in the rates of lower extremity oedema (both overall, and those attributed to drug treatment).

6. ROFECOXIB VERSUS DICLOFENAC/ MISOPROSTOL

One RCT was identified that compared the 6-week tolerability profile of rofecoxib 12.5mg once daily with twice daily diclofenac 50mg/misoprostol 200mcg. The trial enrolled 483 patients aged 40 years or over with OA. Double-dummy placebo was used to maintain blinding Acevedo 2001(MSD902).

5.1 EFFICACY

There were no significant differences in the 6-week change from baseline of the global disease status as measured by the patient or the investigator Acevedo 2001(MSD902). One patient in each group withdrew due to lack of efficacy.

5.2 SAFETY

At 6 weeks in the rofecoxib group there were significantly fewer GI adverse events (70/242 vs. 117/241 RR: 0.60 CI: 0.47, 0.75) and significantly fewer patients with one or more episodes of diarrhoea (15/242 vs. 48/241 RR: 0.31 CI: 0.18, 0.54) Acevedo 2001(MSD902). The cumulative incidence of diarrhoea over the whole study was greater in the Arthrotec group (RR 0.29 CI: 0.16, 0.51). Rates of abdominal pain were numerically lower in the rofecoxib group (21/242 vs. 32/241) RR: 0.65 CI 0.39, 1.10). The overall rates of adverse events were rofecoxib 128/242 vs. Arthrotec 176/241 (RR: 0.72 CI: 0.63, 0.83) and significantly more people in the Arthrotec group withdrew due to adverse events 10/242 v 22/241 (RR: 0.45 95% CI: 0.2, 0.9). The proportion of people experiencing serious adverse events was similar across the two groups; 3/242 vs. 4/241 (RR: 0.75 CI 0.17, 3.30). Five individuals in each group experienced lower extremity oedema and the rates of cardiovascular events were 14/242 in the rofecoxib group and 10/241 in the Arthrotec group (RR: 1.39 CI: 0.63, 3.08). The authors reported that for all safety outcomes, patients with and without a positive GI history (previous GI ulcer or bleed) responded similarly to treatment, as indicated by a non-significant treatment by stratum interactions. The paper did not report any PUBs.

7. ROFECOXIB VERSUS NIMESULIDE

Two double-blind RCTs were identified that compared rofecoxib to nimesulide in OA of the knee. A Venezuelan RCT compared 30 days treatment with 25mg rofecoxib daily to 300mg nimesulide (slow release formulation) in 114 patients aged over 50 years Herrera 2003. The number of patients in each assessment is not however clear. The second Italian study enrolled 30 patients and had a cross-over design with patients sequentially receiving 7 days treatment with 25mg rofecoxib, 200mg celecoxib and 100mg nimesulide Bianchi 2003. The order in which they received the drugs was determined by randomisation. However, the paper does not report any wash-out period between the study arms, which may have compromised the results; although no differences were observed in any of the baseline measurements in each period. For additional pain relief, patients were also allowed 500mg paracetamol 12 hours after the test drug.

Due to the differences in the dose of nimesulide used, the methodology and the timings of data collection, no meta-analysis of efficacy or safety data could be performed. The results of individual studies are therefore discussed below.

7.1 EFFICACY

The Venezuelan study indicated that there was no statistically significant difference between the groups after 15 days, although the nimesulide group had a more favourable response after 30 days of treatment (p=0.009) using the WOMAC scale Herrera 2003. Similar differences were found with the VAS pain score and the evaluation of response by the investigator (RR: 0.77 CI: 0.61, 0.97) and patients (RR: 0.83 CI: 0.67, 1.03). Analgesic rescue medication was similar in both groups. The nimesulide had a faster onset of action (15 minutes versus 45 minutes), which could be attributed to the formulation. Two patients in each group withdrew due to LOE (RR: 1.00 CI: 0.15, 6.86).

The Italian cross-over study presented data in graphical form only, but reported that as measured by the patient on a 100mm VAS, nimesulide 100mg showed a significantly greater analgesic effect over the first 3 hours of treatment (p<0.001) and at the end of the first and seventh day of treatment (p<0.001) than either rofecoxib 25mg or celecoxib 200mg Bianchi 2003. Nimesulide also had a significantly faster onset of action than either rofecoxib or celecoxib on day 1 and 7, with the reduction in pain from baseline reaching significance after 15 minutes compared to 60 minutes. The pain associated with walking 12 hours after each dose was taken was significantly less in the nimesulide group on day 1 but not on day 7. However, more patients reported paracetamol use at least once during the study when taking nimesulide; 6 patients versus 4 taking paracetamol when taking rofecoxib and celecoxib. Most data were presented in graphical form only apart from the percentage of patients reporting good or very good analgesic efficacy, which was 16/30 in the nimesulide group and 15/30 in the rofecoxib group (RR: 0.94 CI: 0.57, 1.53).

The pooled relative risk for the number of patients taking additional paracetamol was not significantly different between rofecoxib and nimesulide (RR: 0.95 CI: 0.54,1.68).

7.2 SAFETY

The Venezuelan study reported that only three adverse events occurred, none of which required withdrawal from treatment; one patient experienced heartburn and dizziness in the nimesulide group and two patients developed pyresis in the rofecoxib group Herrera 2003. Only the patient global assessment of tolerability was reported in the Italian study; when the patients were receiving rofecoxib or nimesulide, 23/30 reported tolerability as being good or excellent compared to 23/30 when they were receiving nimesulide Bianchi 2003. One patient reported poor tolerability when taking nimesulide. The report states that no patients withdrew due to serious adverse events.

8. ROFECOXIB versus CELECOXIB

A total of nine double-blind RCTs were identified that compared rofecoxib 25mg daily to celecoxib 200mg daily (i.e. higher recommended therapeutic dose rofecoxib vs. lower recommended therapeutic dose celecoxib). Seven of the nine RCTs were 6-week studies (not Bianchi 2003; CRESCENT (Sowers)), which facilitated meta-analysis. Other comparators included in the trials were rofecoxib 12.5mg (VACT; VACT 2) nimesulide (Bianchi 2003)naproxen (CRESCENT (Sowers)), placebo (Gibofsky 2003; McKenna 2000; Schnitzer 2001) and paracetamol (VACT and VACT 2).

Five of the nine were sponsored by the manufacturers of celecoxib (Pharmacia/Pfizer); four have been published in full Gibofsky 2003; McKenna 2000; SUCCESS VI; SUCCESS VII and one in abstract form CRESCENT (Sowers). Three RCTs; VACT; VACT 2; Schnitzer 2001 were sponsored by the manufacturers of rofecoxib (MSD) and only one has been published in full (VACT). One of the RCTs did not acknowledge any pharmaceutical company sponsorship Bianchi 2003. It had a cross-over design and compared three seven day periods of treatment with rofecoxib, celecoxib and nimesulide.

Three of the Pharmacia/Pfizer studies were specifically designed to examine cardio-renal effects and therefore did not collect efficacy data; two have been published in full SUCCESS VI, SUCCESS VII and one only in abstract form CRESCENT (Sowers).

8.1 EFFICACY

Pooled analysis of withdrawals due to lack of efficacy found no statistically significant difference between rofecoxib 25mg and celecoxib 200mg after 6 weeks (RR: 0.76 CI: 0.47, 1.24). The VACT trial also found no statistically significant differences between rofecoxib 12.5mg and celecoxib 200mg. Due to lack of reported similar outcome data, no pooling of WOMAC data was possible other than the function subscale results reported in Gibofsky and VACT (RR: 0.12 CI: -2.41, 2.66). The VACT trial found rofecoxib to be statistically significant superior on the pain and stiffness subscales and the rest-pain and night-pain at the 25mg dose, but not at the 12.5mg dose.

Data on the patient global response to therapy could be pooled, which indicated more patients on 25mg rofecoxib had a good or excellent improvement (RR: 1.14 CI: 1.05, 1.24), but again this difference can be attributed to the higher therapeutic dose used. Pooled data from three trials indicated no difference in the use of paracetamol rescue (RR: 1.07 CI: 0.65, 1.75).

The abstract for the CRESCENT (Sowers) study reported that the "arthritis assessments demonstrated that changes in total WOMAC were similar for all 3 treatments at week 6 (p=0.4) and week 12 (p=0.39)". No data were provided.

8.2 SAFETY

Meta-analysis of safety data could be performed on the number of withdrawals and the incidence of adverse events.

There were no differences in the either the total number of withdrawals (RR: 0.93 CI: 0.76, 1.14) or the number of withdrawals due to adverse events (RR: 1.03 CI: 0.77, 1.39) between 25mg rofecoxib and 200mg celecoxib. Data from two trials on withdrawals due to cardio-renal adverse effects did not indicate any difference (RR: 1.33, CI: 0.58, 3.07) and neither the SUCCESS VI or Schnitzer 2001 reported any significant difference in the rates of individual withdrawals due to specific cardiovascular events. Only McKenna 2000 reported the number of withdrawals due to GI events (RR: 4.27 CI: 0.49, 37.12).

The total incidence of adverse effects was similar in the rofecoxib 25mg group and the celecoxib 200mg group (RR:1.04 CI: 0.95, 1.14). There were no statistically significant differences in the rates of serious adverse events (RR: 3.51, CI: 0.73, 16.84)

Very few studies reported on the rates of GI events; there were more GI events in the rofecoxib 25mg group in McKenna 2000 (RR: 3.05 CI: 1.39, 6.68). Pooling was possible for the incidence of diarrhoea (RR: 0.79, CI: 0.40, 1.57) and dyspepsia (RR: 1.24 CI: 0.82, 1.89).

The pooled data indicated more cardio-renal effects in the rofecoxib 25mg group: oedema (RR: 1.77 CI: 1.27, 2.47), systolic blood pressure increase (RR: 1.54 CI:1.24, 1.90) [NB heterogeneous]. The results were non-significant for diastolic blood pressure increase (RR: 1.55, CI: 0.91, 2.63), CHF (RR: 3.06 CI: 0.73, 12.72), and hypertension (RR: 3.51 CI: 0.73, 16.84). SUCCESS VI also reported a significantly greater increase in systolic blood pressure from baseline (WMD 3.30 CI: 1.89, 4.71). Similarly, CRESCENT (Sowers) reported "at week 6, rofecoxib induced a significant increase in 24-hour systolic blood pressure (+4.2 mm Hg), whereas celecoxib did not (-0.1 mmHg p=0.005). Week 12 results were comparable to week 6. " No further data were presented.

The difference between rofecoxib and celecoxib in the numbers of patients experiencing clinically significant systolic blood pressure and oedema was not evident in studies conducted in standard populations Gibofsky 2003; VACT; Schnitzer 2001.

9. ROFECOXIB versus PARACETAMOL

Two RCTs (VACT 1 and VACT 2) were identified that compared rofecoxib 12.5mg or 25mg per day to paracetamol 4g/day in a total of 1960 patients. VACT 1 (382 patients) was the pilot study and to date VACT 2 (1579 patients) has only been published in abstract form.

No meta-analysis was possible therefore the results of the two trials are discussed individually.

9.1 EFFICACY

In VACT 1 after 6 weeks treatment, there were no statistically significant differences between rofecoxib 12.5mg and paracetamol. However rofecoxib 25mg showed greater efficacy than paracetamol as measured by all WOMAC scales and composite subscales. The Patient Global Response to therapy also indicated that more patients taking rofecoxib (both 12.5 and 25mg per day) had a good or excellent response (RR: 1.44; CI: 1.06, 1.97) and (RR: 1.54; CI: 1.14, 2.08) respectively. More patients in the paracetamol group withdrew than either the rofecoxib groups, which was primarily driven by withdrawals due to lack of efficacy 12.5 mg (RR 0.49 CI: 0.22, 1.09) and 25mg (RR 0.49 CI: 0.22, 1.10). The publication also reported results in the first 6 days; both rofecoxib doses achieved statistically significant differences compared to paracetamol on WOMAC scales (night pain, pain on walking, rest pain and morning stiffness).

As VACT 2 has only been published in abstract form, very few data are available. It reported that "improvements in WOMAC subscales over 6 weeks were significantly greater with all coxibs versus ACET (paracetamol) p-values < or =0.01)". Geba (MSD 090)

9.2 SAFETY

No safety data for VACT 2 are available.

No patient enrolled in VACT 1 experienced either a PUB or a MI during the trial. However, 2 patients withdrew due to oedema; 1 in the rofecoxib 25mg group and 1 receiving celecoxib. Similar numbers of patients withdrew due to adverse events and there were no statistically significant differences in the rates of individual adverse events. Overall rates of GI adverse events were not reported. Similarly the overall rates of serious adverse events were not reported in the main publication, but the abstract presented at EULAR indicated that 2 patients in each rofecoxib group (12.5 mg and 25mg) experienced a serious adverse event compared to none in the paracetamol group (RR 4.90 CI: 0.24, 100.66).

10. ROFECOXIB DOSE RESPONSE

Twelve RCTs included comparisons from different doses of rofecoxib, therefore some meta-analysis could be undertaken Cannon 2000(MSD 035); Day 2000 (MSD 040); Ehrich 1999 (pilot); Ehrich 2001(MSD 029); Hawkey 2000(MSD 045); Laine 1999 (MSD 044); Moskowitz 2003; Saag 1998 (MSD 033); Saag 2000 (MSD 034); Truitt 2001(MSD 058); VACT; VACT 2.

10.1 EFFICACY

Pooled data from six trials indicated that there were fewer withdrawals due to lack of efficacy (LOE) in the 25mg group but the result was not significant (RR 0.66 CI: 0.42, 1.03).

10.2 SAFETY

Rates of adverse events and withdrawals due to adverse events appeared similar across the doses examined. The only statistically significant result was that after one year more patients in the 25mg group had experienced diarrhoea compared to those in the 12.5mg group (RR: 1.74; CI: 1.00, 3.02).

Examination of the two endoscopic studies Hawkey 2000(MSD 045); Laine 1999 (MSD 044) indicated that more people receiving the 50mg dose experienced ulcers compared to those receiving 25mg, although the result was significant only for ulcers of diameter 5mm or more; 3mm (RR 1.67 CI: 0.94, 2.95); 5mm (RR 2.48 CI: 1.21, 5.11); gastric (RR 1.55 CI: 0.80, 3.01) and duodenal (RR 2.27 CI: 0.80, 6.48).

DISCUSSION

In October 2004, Merck voluntarily withdrew rofecoxib after analysis of an ongoing trial of the use of rofecoxib in 2600 patients for the prevention of adenomatous colon polyps indicated that 3.5% of the patients in the rofecoxib group experienced a myocardial infarction or stroke compared to 1.9% of the patients assigned to placebo (p<0.001).

The worldwide withdrawal of rofecoxib was the culmination of growing concern over the adverse renovascular effects of rofecoxib that began after the 1999 publication of the 'Vioxx Gastrointestinal Outcomes Research (VIGOR) trial Bombardier 2000. VIGOR enrolled 658 patients with rheumatoid arthritis and the results indicated that patients receiving rofecoxib were more at risk of experiencing a myocardial infarction than those receiving naproxen. There was much debate as to whether this was a result of detrimental effects of rofecoxib or an aspirin-like cardio-protective effect of naproxen Garner 2004 . The ensuing controversy prompted a number of pooled analyses and epidemiological studies that came to various conclusions Gertz 2002; Konstam 2001; Reicin 2002; Mamdani 2002; Mamdani 2004; Weir 2003; Ray 2002; Solomon 2004; Layton 2003.

The FDA Arthritis Advisory Committee met to discuss the cardiovascular risks of rofecoxib in February 2001 and requested that a warning be included in the information for patients. A subsequent large epidemiological study was sponsored Mamdani 2002 Mamdani 2004. In July 2002, the European regulatory authority (EMEA), undertook a review of the safety of the five then available coxibs (celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib), which was completed in late 2003. It broadly concluded that the "the benefit/risk balance of medicinal products containing celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib remains favourable" and that "available data indicated that a significant and consistent gastrointestinal benefit of Cox-2 inhibitors compared with conventional NSAIDs had not been demonstrated". It was also recommended that each Summary of Product characteristics should be updated with warnings relating to the GI safety, the risk of myocardial infarction and the observed or potential serious skin effects and hypersensitivity. A further review of the safety, prompted by the withdrawal of rofecoxib, is ongoing at the time this Cochrane review was written.

Although rofecoxib has been withdrawn, there is much ongoing debate as to whether the adverse cardio-vascular effects are specific to rofecoxib or whether it is a class effect. This requires an understanding of the pharmacology of the individual drugs and the causes of the adverse events associated with all NSAIDs. In broad terms, the toxicity of NSAIDs is variable amongst patients and drugs and it tends to be dose related and associated with variation in the mode of action, absorption, distribution and metabolism.

It is accepted that NSAID inhibition of the prostaglandin pathway causes alterations in renal function. A number of mechanisms have been suggested including salt and water retention, increased total peripheral vascular resistance due to inhibition of PGE2 and PGI2, and increased endothelin-1 secretion. The most commonly reported renal effect is fluid retention and it is estimated that overall approximately 5% of individuals taking NSAIDs will have clinically detectable fluid retention Whelton 1991. A number of studies have also examined the effect of NSAIDs on blood pressure and blood pressure control in hypertensives. It has been estimated that NSAID treatment increases blood pressure by 3-5mmHg, but there are variations amongst individual NSAIDs, with drugs with an increased half-life presenting an increased risk .

Although the mechanism by which renal function is affected is not fully understood, research has indicated that Cox plays a role. Although it was thought initially that Cox II was produced only as a result of inflammation, further research indicated that under normal circumstances it is found in the kidney and plays and important role in maintaining renal haemodynamics and the regulation of sodium and water excretion. Inhibition of Cox II has been shown to cause sodium retention, hyperkaliemia and water intoxication. Therefore whilst selective Cox II inhibition reduces the incidence of GI events (which would be caused by Cox I inhibition) because it plays a role in reducing aggregation of platelets, there is a theoretical possibility that the resultant suppression of prostacylin production and unopposed thromboxane production, leads to an increases the risk of cardiovascular thrombotic events. Therefore the risk-benefit profile of individual NSAIDs will depend on both the relative Cox I to Cox II inhibition and the absolute inhibition of Cox I.

A number of studies have examined the Cox inhibitory profiles of individual NSAIDs using surrogate markers Van Hecken 2000; Simon 1996; Glaser 1995; Kawai 1998; Reindeau 1997; Warner 1999; Brooks 1999. The findings of individual studies vary, which can be attributed to differences in the experimental methodology; this makes comparisons and the resultant 'rankings' difficult to interpret. Whilst most studies concentrated on the relative inhibitory activity against Cox I and II, some examined absolute levels of inhibition. Warner et al separated rofecoxib into the category of drug that strongly inhibited Cox II with weak activity against Cox I (>50-fold Cox II selective), whilst other Cox II selective agents (celecoxib, etodolac, meloxicam and nimesulide) were classed as compounds that were capable of producing full inhibition of Cox I and Cox II with preference toward Cox II (5 to 50 fold Cox II selective) Warner 1999. The authors also stressed that because all of the drugs in this latter group are capable of inhibition of Cox I, therefore increasing dose could increase GI toxicity Warner 1999.

With respect to the discussion of the findings of this systematic review, it is worthwhile noting that meta-analysis was hampered by the inadequate reporting of outcomes in some trials. Of particular concern, in drugs that are purported to have GI benefits, is the absence of GI event data. Across the studies, a wide range of efficacy outcome measures were used, and the lack of standardisation of outcome assessment reporting (i.e. pre- and post-treatment scores, change with treatment and percentage change with treatment) and inadequacy of reporting of outcomes (i.e. measure of variance

was often not provided), meant that in many instances, it was not possible to statistically pool efficacy results. The focus of the discussions in the publications also tended to be on the statistical significance of the results rather than on the clinical significance. When interpreting the results it must be borne in mind that it has been estimated that moderate improvement in OA is defined as a 10-20 point reduction on a 0-100 interval scale Ehrich 2000.

In this review the data for different doses of drugs and for different types of NSAID in the comparator arm have been separated, as there is evidence to suggest that individual NSAIDs have different toxicity profiles. Meta-analyses of NSAID associated toxicity have demonstrated that low dose ibuprofen carries the lowest risk of GI complications with comparative relative risks of 2 for fenoprofen, aspirin and diclofenac and 2-3 for sulindac, diflusinal, naproxen, indomethacin and tolmetin and above 3 by piroxicam, ketoprofen and azopropazone Henry 1996. Another study conducted using the GPRD database found that ibuprofen again was associated with the lowest relative risk of upper GI bleeding 2.9 (95% CI: 1.7, 5.0) with naproxen 3.1 (95% CI:1.7, 5.9) and diclofenac 3.9 (95% CI: 2.3, 6.5) Lanes 2000.

The use of different doses may similarly affect the outcomes of comparisons and they have therefore been considered separately. Epidemiological studies have shown that GI toxicity varies by a factor of 3 to 10 over the ranges of recommended doses, depending on the NSAID under investigation Lanes 2000; Langman 1994. High doses are more toxic than lower doses with the odds ratio for NSAID associated ulcer complications ranging from 2.5 on low to 8.5 on high Langman 1994 ibuprofen and indomethacin, independent of duration of exposure Lanes 2000.

As expected, in the placebo-controlled trials, rofecoxib showed consistently superior efficacy to placebo and higher doses were effective in more people than lower doses. Rofecoxib in general caused more adverse events than placebo, although there was a lot of variability in the results of individual trials and some of the results were not statistically significant. The rates of overall GI events were not well recorded, but in general the risk of symptoms was not statistically different, although one trial reported rofecoxib 25mg to cause more GI events Kivitz 2004(MSD 085) (RR 3.39 CI: 1.47, 7.84). Only two PUBs were reported in the trials; one in a rofecoxib group and one in a placebo group. The reporting of serious events varied considerably between the trials; meta-analysis of data from four trials using a 12.5mg dose indicated an increased risk of serious adverse events (RR 3.95 CI: 1.05, 14.63). The reno-vascular events were evident, but as previously mentioned are common to all NSAIDs; few trials reported such data. Rofecoxib (25mg) caused statistically significantly more patients with an increase in systolic blood pressure after 6 weeks (RR 2.89 CI: 1.17, 7.14) and the 12.5 mg dose patients experienced more lower- extremity oedema (RR 2.40 CI: 1.05, 5.48). There was heterogeneity in the results of the endoscopic studies; with one study consistently showing more ulcers in the placebo group Laine 1999 (MSD 044) and one in the rofecoxib group Hawkey 2000(MSD 045). Dose comparisons indicated that rofecoxib 50mg caused more endoscopic ulcers than rofecoxib 25mg and additional analyses indicated that there was an increased risk of gastric ulcers compared to duodenal. Very few PUBs were reported.

There were no consistent differences in efficacy between rofecoxib and any of the comparators, including celecoxib. Although there were some statistically significant results, in general these could be attributed to the dosages of the drugs that were compared. For example rofecoxib 25mg was found to be more effective than paracetamol 4g/day, but 12.5mg rofecoxib was not.

With respect to GI symptoms, considering this is the key benefit of these drugs, it was surprising that very few of the trials reported event data to allow adequate consideration of the results. The only statistically significant results were that rofecoxib caused less GI pain than diclofenac in two RCTs. Naproxen, the most GI toxic of the NSAID comparators, caused more withdrawals due to GI events, total GI events and fewer PUBS, and fewer patients used concomitant GI medication. There was insufficient data presented in the publications of the trials that compared rofecoxib to nimesulide or nabumetone to enable any discussion. Rofecoxib 25mg caused more withdrawals due to GI events (RR 4.27 CI: 0.49, 37.12) and GI events (RR 3.05 CI 1.39, 6.68) than 200mg celecoxib after 6 weeks, but this comparison was based on high dose rofecoxib versus low dose celecoxib. Rofecoxib caused less diarrhoea than misoprostol/diclofenac, but again this is to be expected as diarrhoea is a common side-effect of misoprostol Acevedo 2001(MSD902). The two endoscopic trials indicated that rofecoxib 25mg and 50 mg was associated with statistically significant fewer gastric ulcers than ibuprofen, and 25mg rofecoxib caused fewer duodenal ulcers Hawkey 2000(MSD 045); Laine 1999 (MSD 044). Similarly rofecoxib was found to cause fewer erosions. In interpreting the data from these endoscopic studies, consideration must be given to the fact that the link between endoscopically detected ulcers and clinical symptoms has not been fully described and gastrointestinal symptoms are often poorly correlated with endoscopic findings Singh 1996; Larkai 1989.

Analysis of other adverse event data found that there was no statistically significant difference in the number of patients experiencing an adverse event between rofecoxib and any other active comparator, other than Arthrotec, which as previously mentioned is associated with diarrhoea. Again only a few of the trials reported this outcome. There were more withdrawals due to adverse events compared to placebo and 50mg rofecoxib caused more than 25mg. Rofecoxib patients had fewer adverse events than diclofenac after one year and fewer than ibuprofen at 16 weeks. Fewer trials reported on the number of serious adverse events, and this outcome was not reported in any of the diclofenac, ibuprofen or nimesulide comparisons. As expected there were more in the placebo trials, although it was only significant at 12.5mg dose. There were no difference in the reported rates of serious adverse events of rofecoxib compared to naproxen, nabumetone, paracetamol and celecoxib.

Four studies were identified that specifically examined the cardiorenal safety of rofecoxib; three were comparisons of high dose rofecoxib (25mg) and low dose celecoxib (200mg) and were sponsored by Pharmacia/Pfizer. The fourth study did not acknowledge any sponsorship and examined rofecoxib vs. diclofenac or AMG in elderly patients Niccoli 2002. The CRESCENT (Sowers) study examined 24-hour ambulatory blood pressure in treated hypertensive patients with OA and type II diabetes. Results are only available in abstract form; "at week 6, rofecoxib induced a significant increase in 24-hour systolic blood pressure (+4.2 mm Hg), whereas celecoxib and naproxen did not (-0.1 mmHg and -0.8mmHg p=0.005). Week 12 results were comparable to week 6". No further data were presented. The two SUCCESS trials were also conducted in older hypertensive OA patients; clinically significant

systolic blood pressure increase (more than 20mmHg) occurred in 83/960 of patients taking celecoxib and 147/942 patients taking rofecoxib (RR 1.81 CI: 1.40, 2.33); this difference was statistically significant SUCCESS VI; SUCCESS VII. Increased rates of oedema also occurred and it was more common in women. There was no statistically significant difference in the numbers of patients experiencing diastolic BP change. Sub-group analysis indicated these changes occurred in patients taking angiotensin converting enzyme inhibitors and beta-blocker therapy (with or without diuretics), but not those taking calcium channel antagonists or diuretic monotherapy. The difference between rofecoxib and celecoxib in the numbers of patients experiencing clinically significant systolic blood pressure and oedema was not evident in studies conducted in standard populations (Gibofsky 2003; VACT; Schnitzer 2001). There is some question of the treatment of dropouts in the independent study Niccoli 2002, but again indicated that after 2 weeks treatment, compared to diclofenac rofecoxib 25mg daily caused an increase in systolic blood pressure (mean 10mm Hg (SD 11.81) vs 2mmHg (SD 7.45) (WMD 8.00 CI 3.00, 13.00) and diastolic blood pressure mean 9.00 mmHg (SD 7.66 vs 2.00 mmHg (SD6.23) (WMD 8.00 CI: 4.47, 11.53). More patients also experienced oedema (10/34 vs 0/31 (RR 19.20 CI: 1.17, 314.55), hypertension 8/34 vs 0/31(RR 15.54 CI: 0.93, 258. 58) and weight gain 10/34 vs 0/31(RR 19.20 CI: 1.17, 314.55). In the other RCTs that reported cardiorenal adverse events, whilst in some cases there was a trend towards more cardio-renal adverse events, there were no significant differences between rofecoxib and an active comparator in any of the individual studies or pooled analyses. This held true for both the smaller studies and those that included up to 5000 patients.

A key question mark remains over the risk-benefit ratio of the coxibs. Whilst this review provides important information on the relative risks of adverse events, it must be acknowledged that RCTs are not sufficient on their own to provide information on the risk of rare adverse events. The likelihood of detecting an adverse drug reaction (ADR) is dependent on its severity, frequency and occurrence relative to exposure. Although the RCT is the gold-standard of clinical trial designs, the numbers of patients used and the short duration mean that they will only identify the most common and acutely occurring ADRs within the specified subgroup of included patients. Many RCTs will not powered sufficiently to detect differences in rare events such PUBs, POBs and myocardial infarctions. Moreover, trial protocols exclude patients from 'at risk' groups which are not generalisable to the population who will inevitably be exposed to the drug (i.e. people with co-morbidities). Although an exhaustive investigation of all adverse event data is outside the remit of this Cochrane review, a number of additional sources could be used to collate information on ADRs.

A number of such studies of rofecoxib have been conducted and the results have been conflicting and difficult to interpret because drug exposure and confounding factors will vary over the length of a long-term observational study. The usefulness of the information derived from computerised databases is also highly dependent on the accuracy and completeness of data collection and entry, which needs to be rigorously controlled and monitored. The effect of 'channelling bias' must also be taken into account, whereby physicians are more likely to have prescribed Cox II selective drugs to higher risk patients, who are by definition at greater risk. Spontaneous reporting systems such as the Yellow Card system and the MedWatch system in the United States suffer from similar disadvantages in that the number of adverse events that are recorded are a function of the length of time that a drug has been on the market, the amount it is prescribed, the seriousness of the event and the attending publicity. Neither method can be used to calculate incidences or relative safety, as the size of exposed population is generally not known and must be estimated from prescription data.

AUTHORS' CONCLUSIONS

Implications for practice

Rofecoxib was voluntarily withdrawn from global markets in October 2004 and therefore there are no implications for practice concerning its use.
None the less when considering which NSAID to use, it must be borne in mind that the toxicity of NSAIDs is variable amongst patients and drugs, and it tends to be dose related and associated with variation in the mode of action, absorption, distribution and metabolism.

Implications for research

There remains a number of questions over both the benefits and risks associated with Cox II selective agents and further work is ongoing. It is likely that this issue will not be resolved until research has enabled a fuller understanding of the complex mechanism by which the Cox system operates.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Acevedo 2001(MSD902)

Methods	6 weeks double-blind, multicentre international (21 sites) No CCX, aspirin, H2 blockers, antacids, sucralfate, warfarin, ticlopidine or PPIs permitted paracetamol rescue (max 8 tablets) Randomisation: computer generated schedule stratified for history of ulcer and/or upper GI bleeding double dummy ITT analysis Sample size: 220 per group assuming 16% incidence diarrhoea in Arthrotec and 6% rofecoxib. 90% power to detect 10% difference between the treatment groups in the incidence of diarrhoea.
Participants	OA N=483 >=40 yoa (Mean age 62.1 years; range 39-85) requiring regular NSAID therapy Patients stratified according to previous history of gastroduodenal ulcer or GI bleed Exclusion: inflammatory/post traumatic arthritis; infectious disease; malabsorption; uncontolled diabetes; GI disease associated with diarrhoea; renal, cardiovascular or hepatic disease; bleeding disorder; allergic to NSAIDs/paracetamol; positive for faecal occult blood; previous misoprostol use; regular aspirin users; CCX in previous month; history of sustained GI medication. Equivalent baseline characteristics 7.2% prior history of upper GI ulceration/bleeding 13% receiving low dose aspirin; 49% antihypertensive medication
Interventions	rofecoxib 12.5mg/day diclofenac 50mg/misoprostol 200mcg b.d (Arthrotec)
Outcomes	TOLERABILITY: Primary: incidence of spontaneously reported diarrhoea; Secondary: spontaneously reported abdominal pain; discontinuation due to AEs; incidence of all AE, incidence of drug related AEs, proportion with serious AEs, incidence of GI AEs, and NSAID-type GI AEs (acid reflux, dyspepsia, epigastric discomfort, heartburn, nausea and vomiting); EFFICACY: patient global assessment (100mm VAS) and investigator global disease (Likert 0-4)
Notes	WITHDRAWALS: 43 (8.9%) EFFICACY: No SS difference in efficacy. SAFETY: Rofecoxib fewer GI events (28.9% vs. 48.5 %) p<0.001, fewer NSAID type events (18.6% vs. 29.9%) p=0.004, fewer episodes of diarrhoea (6.2 % vs. 19.9%) p>0.001. Lower extremity oedema 2.1% v 2.1%; cardiovascular events 5.8% vs. 4.1% (NS). QA: R=2 B=2 W=1

Risk of bias

Bias	Authors' judgement	Support for judgement

Acevedo 2001(MSD902) *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Advantage 2000

Methods	12 weeks double-blind, multicentre (600 sites) US and Sweden predominantly primary care low dose aspirin permitted GI protective medication permitted to treat GI symptoms (PPI, antacids, H2 blockers) paracetamol rescue Randomisation: computer generated schedule double dummy 'modified' ITT analysis: all who took at least 1 dose Sample size: 2780 per group. 90% power to detect 2% difference between treatments for primary safety variable.
Participants	OA knee, hip, hand or spine N=5557 >=40 yoa (Mean age 63.0 years) ARC functional class I, II, III symptomatic > 6 months requiring regular NSAID or paracetamol therapy Permitted: history of dyspepsia, ulcer, GI bleeding, or other GI symptoms Exclusion: potentially confounding concurrent disease, malabsorption, > 4 days history of GI protective medication during month prior to entry. Equivalent baseline characteristics including CV and GI. 49% taking antihypertensive medication and 13% low dose aspirin. 29% prior history of GI events associated with NSAID use
Interventions	rofecoxib 25 mg od naproxen 500mg bd
Outcomes	Primary: 12 week GI tolerability (discontinuation due to GI adverse events or abdominal pain); Secondary: concomitant GI medication use, discontinuation due to AEs; incidence of all AE, incidence of drug related AEs, incidence of serious AEs, incidence of GI AEs (PUBs), incidence of cardiovascular AEs ; EFFICACY: patient global assessment of disease status(100mm VAS); Medical Outcomes Study 36-item Short Form Health Survey; AUSCAN OA Hand Index. Independent blind adjudication of PUBs and CV events. SUBGROUP: low-dose aspirin users;individuals previously dicontinuing arthritis medication due to GI symptoms; patients with hypertension at baseline (those taking antihypertensive mediation).
Notes	WITHDRAWALS: 1545 (27.8%) EFFICACY: No SS difference in efficacy or discontinuation due to lack of efficacy. SAFETY: Rofecoxib associated with a significantly lower incidence of discontinuation due to GI events (5.9% vs 8.1% RR 0.75, CI: 0.59, 0.96). This difference was evident at 3 weeks and continued over the course of the study. Analysis of interaction of treatment by low-dose aspirin showed no statistically significant modification of effect (p>0.2), indicating a consistent risk reduction regardless of aspirin use. No SS differences in the incidence of hypertension, pre-defined limits of change for systolic or diastolic blood pressure, or lower extremity oedema. Higher incidence of these events in hypertensive patients but not SS. No SS difference in the number of thrombotic cardiovascular events. Five MI in rofecoxib group and 1 in naproxen group (p=0.015). Funded by Merck & Co QA: R=2 B=2

Advantage 2000 *(Continued)*

W=1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Bianchi 2003

Methods	3 weeks 7-day cross over double-blind. single centre Italy. 3 day washout prior to study. No pain treatment 24 hours prior to study RANDOMISATION: latin square design; computer generated random numbers NOT PERMITTED: other analgesia paracetamol rescue: 500mg per day only No washout reported between cross-over phases drugs POWER: Assuming an alpha error of 0.05 and beta of 0.20
Participants	OA knee N=31 >= 18 yoa (Mean age 69.0; range 53-80) INCLUSION: met ACR criteria; OA at least 3 months; minimum VAS of 40mm pain associated with walking. EXCLUSION: concurrent arthritis disease or laboratory test result outside normal reference range; history of allergy to study drugs or hypersensitivity to other NSAIDs; GI ulceration within 30 days; bleeding disorders. Equivalent at baseline
Interventions	rofecoxib 25mg od celexcoxib 200mg od nimesulide 100mg od
Outcomes	Pain intensity (100mm VAS) Total pain relief over 3 hours: addition of time-weighted pain relief scores (expressed as difference between the value recorded at baseline and that recorded at each time point). Analgesic efficacy (0-4 Likert) Total number of paracetamol tablets Global tolerability (0-4 Likert)
Notes	WITHDRAWAL:1 (3%) No wash-out period reported between cross-over phases. EFFICACY: Days 1 and 7 overall analgesic effect over the first 3 hours was significantly more marked for single dose of nimesulide that for rofecoxib or celecoxib. QA: R=2 B=1 W=1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Cannon 2000(MSD 035)

Methods	52 weeks double-blind, randomised, US multicentre no aspirin or CCX rescue paracetamol randomisation : computer generated randomisation scheme double dummy POWER: comparability stated if for all 3 primary endpoints, the 95% confidence intervals of the difference in the mean treatment response between 2 treatments were within + or - 10mm on a 100mm VAS scale or 0.5 on a Likert scale. >99% power to demonstrate comparable efficacy (according to the criteria stated between 25mg rofecoxib and diclofenac if the true difference is 0. ITT analysis Voluntary extension period post study
Participants	OA hip and knee N=784 clinical and radiographic evidence study joint primary source of pain > = 40 yoa (Mean age 63.6) Steinbrocker I-III functional 2 groups: prior NSAID or paracetamol use. Prior NSAID use: post wash-out moderate pain when walking, increase in pain and worse physician assessment of disease status. Prior paracetamol use: post wash-out moderate pain when walking and patient assessment of disease status fair, poor or very poor. stratified depending on whether prior NSAID or paracetamol exclusion: renal impairment, clinically significant abnormalities on physical or laboratory examination at screening; positive faecal occult blood; class III/IV angina, uncontrolled CHF, uncontrolled hypertension, previous stroke or TIA within 2 years, active hepatic disease, recent neoplastic disease, allergy to NSAID/paracetamol, required aspirin at any dose, CCX, warfarin or ticlopidine. Patients with history of gastroduodenal ulcer or GI bleeding were allowed to participate No baseline differences reported women: post menopausal or demonstrably non-gravid.
Interventions	rofecoxib 12.5 mg od rofecoxib 25mg od diclofenac 50mg tds
Outcomes	PRIMARY: WOMAC index: pain when walking*; investigator global disease status (0-4) 26 weeks only*;patient global response to therapy (0-4)*; SECONDARY: WOMAC pain (100mm VAS), stiffness (100mm VAS), functional ability (100mm VAS); joint tenderness (0-3); patient global disease status (100mm VAS) ; investigator global response to therapy(0-4); rescue paracetamol; LOE withdrawals; laboratory tests. For the determination of comparability, the three primary end points were analysed as the averaged response over the 52 week treatment period (first 26 weeks only for the patient's assessment of response to therapy).
Notes	WITHDRAWALS: 336 (42.9%) EFFICACY: LOE: no SS difference.SS improvement from baseline all groups, all OMs. No SS effect for location of joint i.e. hip or knee, previous medication, age or sex.All primary: treatment response within 2 weeks and maintained throughout study. Although differences between therapies within a priori defined limits, diclofenac SS superior for patient response to therapy and investigator disease status. SAFETY: No SS differences between comparators GI ADRs R=2 B=2 W=1

Cannon 2000(MSD 035) *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

CRESCENT (Sowers)

Methods	12 weeks double-blind randomised US multicentre
Participants	OA Type 2 diabetes mellitus also taking ACE inhibitors N= 404 Mean age 63
Interventions	rofecoxib 25mg od celecoxib 200mg od naproxen 500mg bd
Outcomes	PRIMARY: mean change from baseline to week 6 of the average 24-hour systolic blood pressure SECONDARY: 'arthritis efficacy measurements' 24 ambulatory blood pressure measurements
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Day 2000 (MSD 040)

Methods	6 weeks double-blind, multicentre (49 sites) rescue paracetamol (2.6g) stratified into previous NSAID and previous paracetamol no aspirin or CCX double-dummy randomisation: computer generated schedule 1:4:4:4 allocation schedule independently maintained compliance assessed by returned tablet counts ITT analysis but only patients with baseline plus 1 treatment measurement included comparability stated if for 2 out of 3 primary endpoints, the 95% confidence intervals of the difference in the mean treatment response between 2 treatments were within + or - 10mm on a 100mm VAS scale or 0.5 on a Likert scale

Day 2000 (MSD 040) *(Continued)*

	POWER: greater than 99% power to demonstrate comparable efficacy (according to criteria cited) between rofecoxib and ibuprofen if their true difference is 0.
Participants	OA knee or hip N=809 >= 40 years of age (Mean age 63.7; range not given) clinical and radiological diagnosis ARA functional class I-III symptomatic for minimum of 6 months knee and hip primary source of pain increased pain and worse physician global disease status following NSAID /paracetamol withdrawal plus worse patient global for paracetamol women; post menopausal or demonstrably non-gravid Exclusion: CCX, any dose aspirin, warfarin or ticlopidine significant renal impairment; clinically significant abnormal physical or laboratory screening; positive faecal blood test; malabsorption; class III/IV angina or congestive heart failure; uncontrolled hypertension; stroke or TIA within 2 years; active hepatic disease; recent neoplastic disease; allergy to NSAID or paracetamol No baseline differences
Interventions	rofecoxib 12.5mg od rofecoxib 25mg od ibuprofen 800mg tds placebo
Outcomes	PRIMARY: WOMAC index: pain when walking*; patient global response to therapy (0-4 Likert)*; investigator global disease status (0-4 Likert)*; analysed as mean response (change from baseline) over all observation times in the 6-week treatment period. SECONDARY: WOMAC index: pain, stiffness, functional disability; joint tenderness (0-3 Likert); patient global disease status(10cm VAS) ; investigator global response to therapy(0-4 Likert); study joint tenderness (0-3 Likert); rescue paracetamol; LOE withdrawals.
Notes	WITHDRAWALS: 100 (12.4%) Difficult to ascertain whether ITT. Denominators infer that it was, but text states that " only 14 of the 809 randomised patients were excluded from the analysis for one or more of the primary endpoints because of missing baseline or on-treatment data. PLACEBO EFFICACY: rofecoxib SS reduction all OMs and SS superior to placebo.LOE : SS fewer withdrawals in active compared to placebo (p= 0.009).Maximum effects within 2 weeks. IBUPROFEN EFFICACY: All responses SS and no SS differences between groups although some separation evident from graphs.Maximum responses within 2 weeks and sustainedRofecoxib 25mg superior to ibuprofen (p=0.005) for pt response and investigator global disease status.Treatment effects consistent for knee v hip, paracetamol v NSAID. QA: R=2 B=2 W=1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ehrich 1999 (pilot)

Methods	6 weeks randomised Phase II double-blind multicentre US (27 sites) paracetamol rescue (max 8 x 325mg per 24 hours) no data on concomitant randomisation: computer generated allocation schedule matching placebo ITT analysis SUBGROUPS: age, ARA functional class; baseline values for primary endpoints POWER: difference in VAS of 12mm between patient groups at least 80% power (a=0.05, 2 tailed) with a sample size of 60 per treatment group. WOMAC scales: 80% power to detect a difference of 47 mm.
Participants	OA knee N=219 No baseline differences >40 yoa (Mean age 63.5, range 35-84) <= 125 kg in weight ARA I to III knee pain, especially in motion of at least 6 months duration radiographic evidence previous positive NSAID response and to be taking NSAIDs prior to entry randomised if increased pain on prior NSAID withdrawal EXCLUSION: previous gastro-duodenal ulceration; history of GI bleeding; history of GI surgery; renal impairment; diabetes; history of cardiovascular disease, stroke or neurological disorder; hepatic or neoplastic disease; coagulation disorder
Interventions	rofecoxib 25 mg od rofecoxib 125mg od placebo
Outcomes	PRIMARY: WOMAC pain*; patient assessed pain (10cm VAS)*; SECONDARY: WOMAC physical function/stiffness; investigator and patient global response (0-4); investigator global disease status (0-4); patient global disease status (10cm VAS); LOE withdrawals
Notes	WITHDRAWAL: 57 (26.0%) LOE: rofecoxib SS to placebo p<0.001 EFFICACY: all endpoints rofecoxib SS superior to placebo (p<0.001). Although some separation in response curves no SS differences between doses (any endpoint) (p<0.05).improvement occurring at week 1 (SS WOMAC pain) and SS at week 2 other outcomes. SAFETY: similar AE withdrawal rates, 1 PUB in 125mg rofecoxib arm. QA: R=2 B=2 W=1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ehrich 2001(MSD 029)

Methods	6 weeks double-blind, randomised,multicentre US hip patients not randomised to 50mg ANALYSIS: average change from baseline accross the entire six weeks of treatment. ITT. Abstract states that following the 6 week treatment period 472 patients continued in a six month double-blidn extension study. Patients allcoated to placebo or 5mg during the intial 6 weeks were re-allocated to either 12.5mg; 25mg or diclofenac 150mg. The results from this study don't appear to have been published.
Participants	OA knee and hip N=672 >=40 yoa (mean age 61.7; range 38-93) pain in affected joint on majority of days each month characteristic radiographic changes ARC I-III; worsening of pain following discontinuation of NSAID therapy* EXCLUSION: significant renal impairment; evidence of active GI tract bleeding; clinical malabsorption; class III/IV angina or CHF; uncontrolled hypertension; stroke within previous 2 years; active hepatic disease; recent neoplastic disease;allergy to paracetamol or NSAIDs. BASELINE: no SS differences
Interventions	rofecoxib 5 or 12.5 or 25 or 50mg/day Placebo
Outcomes	WOMAC: pain on walking, stiffness, disability; patient global assessment response(0-4); investigator global assessment disease status (0-4); SF-36
Notes	Publication states that " The efficacy results of rofecoxib in the management of OA from this study have been reported elsewhere (refence given for Ehrich 1999)"; numbers presented in Ehrich 1999 don't however match those reported in this publication and it also involves a dose of 125mg, which was not included in the Ehrich 2001 publication. Very little information presented in the publication other than QOL analysis. WITHDRAWAL= 107/672 (15.9%) Justification for analysis " in a previous study, full clincal efficacy response was realised at the first point of measurement and maintained at a generally constant lvel across the entire 6 weeks of treatment. Therefore average response across the treatment period was predefined as the primary calculation of response fore each patient to minimise variability and yeild the most precise estimate of treatment effects. SF-26 mental scores adjust to take into account regression to the mean and by adjusting for physical efficacy as measure by an average primary clincal efficacy endpoints (after adjusting the walking pain VAS response by dividing by 25 to scale it to the categorical scale. No overall rates of adverse events available. EFFICACY: all rofecoxib groups SS superior to placebo (p<0.001) all OMs.Dose response higher doses superior to 5mg ?SSImprovements for all doses rofecoxib SS to placebo in all SF 36 domains except general health. Evidence of dose response : 5mg smaller mean changes than other doses for all endpoints. SAFETY: Incidence of discontinuation due to ADRs equivalent between rofecoxib and placebo- no details. QA: R=1 B=1 W=1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Geba (MSD 090)

Methods	6 weeks double-blind, randomised, multicentre US (115 sites) pre-trial NSAID washout RANDOMISATION: computer generated blinded allocation schedule double dummy rescue paracetamol up to 2600mg except during first 6 days or 24 hours pre efficacy assessment modified ITT analysis: baseline flare, took at least one dose of study drug and had a postbaseline efficacy assessment. low dose aspirin permitted up to 81mg/day for CV prophylaxis (10-14%) POWER: detection of clinically relevant difference between treatment groups in terms of the primary endpoint PGART; 380 patients per active group; 180 placebo estimated that the study would have 99% power to detect a difference of at least 15% between rofecoxib and nabumetone in terms of the percentage of patients with good/excellent PGART response. Statistical significance on PGART endpoint implied consistent with difference of 15 percentage points.
Participants	N=978 OA knee >= 40 years of age (mean 63) OA of greater than 6 months duration history of NSAID response ARC I, II or III flare with NSAID withdrawl pre-trial EXCLUSION: pregnancy; imminent joing replacement; concurrent medical/arthritic disease that could alter study outcome; significant systemic disease that contra-indicated NSAIDs; CCX within one month; misoprostol; sucralfate; histamine blockers; antacids; PPIs; analgesics; wafarin; ticlopidine; high-dose aspirin; appetite suppresants; other medications for chronic diseases; BASELINE: no differences ASPIRIN USE: rofecoixb 46/424; nabumetone 57/410; placebo 21/208
Interventions	rofecoxib 12.5mg/day nabumetone 1000mg/day placebo
Outcomes	PRIMARY: patient global response to therapy (0-4) later stated as the number of patients with good or excellent response. SECONDARY: WOMAC pain walking on a flat surface (100mm VAS); investigator global response to therapy (0-4); LOE withdrawals; SF-36 quality of life;
Notes	WITHDRAWAL: not given Abstract presents brief details of methodology only. Also states that methodology identical to Kivtiz therefore methods copied from this entry in table of characteristics of included studies. There are however slight variations in the methodology described- Kivitz states corticosteroid use per se, whilst Geba abstract states "corticosteroid use within one month". Similarly Geba states " sustained use of antacids, H2 blockers or PPIs", whilst Kivitz states use per se.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Gibofsky 2003

Methods	6 weeks double-blind multicentre US & Canada (61 sites) Double dummy RANDOMISATION: computer generated schedule POWER: 188 patients in each active treatment group and 94 in placebo. Sample sizes sufficient to reject, using a 5% one sided t-test with 80% power, the null hypothesis that celecoxib is inferior to rofecoxib, with noninferiority limits of 10 on the 100 mm VAS and 5.5 points on the WOMAC total domain score. ITT analysis
Participants	OA knee N= 475 >= 40 yoa (Mean age 62.9) INCLUSION: ACR criteria; functional capactiy class rating of I, II or III; OA flare at baseline; negative pregnancy test. EXCLUSION: inflammatory arthritis or acute joint trauma; recent CCX (previous 8 weeks) or hyaluronic acid (6 months) injection; NSAID use within 2 days or 5 half-lives; history of or active malignancy; upper GI ulceration within 30 days; active GI disease, chronic or acute renal or hepatic disease, significant coagulation defect; known NSAID or Cox II hypersensitivity; abnormal laboratory test results at screening. PERMITTED: aspirin <=325mg/day for cardiovascular prevention; acetaminophen; antacids. NOT PERMITTED: NSAIDS; analgesics; oral or injectable CCX or hyaluronic acid; anticoagulants; DMARDs; anti-ulcer medication; daily or almost daily use of antacids; anti-platelet agents. BASELINE: no SS differences FLARE: 3 out of 4 of following: VAS score >= 40mm for patient's assessment of OA pain; OA severity index of >= 7; patient's global assessment of arthritis as poor or very poor; physician's global assessment as poor or very poor.
Interventions	rofecoxib 25mg od celecoxib 200mg od placebo To be taken with evening meal
Outcomes	PRIMARY: Patient assessment of OA pain (100mm VAS); WOMAC total domain score at week 6. SECONDARY: Patient global assessment (1-5 Likert); Physician global assessment (1-5 Likert); OA severity index (composite scale 0-24); WOMAC subscales pain, stiffness and physical function; Patient satisfaction (1-10 Likert).Patient assessment of pain on walking (100mm VAS). IMPROVED defined as a reduction of at least 2 grades from baseline or a change to 'very good'on patient and physician global assessments.
Notes	WITHDRAWAL: 94 (19.7%) QA: R=2 B=2 W=1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hawkey 2000(MSD 045)

Methods	16-24 week double-blind multicentre, international (36 sites) Paracetamol, non-NSAID pain medication and supplied antacids were permitted. No concomitant NSAIDs, aspirin, CCX, anticoagulants, ticlopidine, H2 antagonists, prostaglandin analogues, sucralfate, unapproved antacids, PPIs.All withdrawn 2 weeks prior to baseline. Endoscopy and biopsy at baseline for H pylori status testing. matching placebos randomisation stratified by prescence/absence of history of PUB. In order to allow for an anticipated lack of efficacy in the placebo group, 95% of patients taking placebo and 5% in the other groups were randomly selected and discontinued from the trial in a blinded manner at week 16. Study designed to provide 95% power to detect a difference in the 12 week cumulative ulcer incidence between the rofecoxib or placebo groups and the ibuprofen groups assuming an incidence of 2.5% for the placebo and rofecoxib groups and 15% for the ibuprofen group. no baseline differences ITT analysis
Participants	OA N= 775 >=50 yoa (Mean age 61.5, range 49-89) prior NSAID use 49.4% required treatment for at least 6 months PERMITTED:Patients with history of ulcer, perforation or GI haemmorrhage, endoscopically detected gastroduodenal erosion and active H pylori infection. EXCLUSION : patients with endoscopical evidence at baseline of erosive esophagitis, UGI ulcer or pyloric obstruction. Also previous upper GI surgery, inflammatory bowel disease, reduced renal function, faecal occult blood, unstable medical disease, malignancy within previous 5 years, pregnancy, cerebrovascular events in previous 2 years, anticoagulant therapy, CCX, ticlopidine, aspirin.
Interventions	rofecoxib 25 mg od rofecoxib 50 mg od ibuprofen 800mg tds placebo
Outcomes	Primary: endoscopically detected ulcers >=3mm Secondary: endoscopically detected ulcers >=5mm Global assessment of disease by patients (Likert 0-4); Paracetamol use Ulcer defined as mucosal break >= 3mm with unequivocal depth. Erosions defined as a mucosal break of any size with no depth
Notes	WITHDRAWAL: 278/775= 35.9% PLACEBO: 12 week cumulative rates of endoscopically detected ulcers in rofecoxib arm were similar to those seen in placebo. IBUPROFEN Rofecoxib caused fewer endoscopically detected ulcers than did ibuprofen. Patients developing ulcer were excluded from the trial QA: R=1 B=2 W=0

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Herrera 2003

Methods	30 days double-blind single centre, Venezuela POWER: 90% to detect a difference in the main variable (VAS) between the groups of 10% with alpha error of 0.05 rescue paracetamol
Participants	OA knee N= 114 >= 50 yoa (Mean age = 61.5) INCLUSION: met ACR criteria EXCLUSION: severe hepatic, renal, cardiovascular or haematological disease; prosthesis or intraarticular surgery, arthrocentesis in last 3 months prior to study; cerebrovascluar events in last two years; hypersensitivity/allergy to NSAIDs; presence or antecedents of peptic ulcer; use of analgesics during the last 5 days; pregancy or nursing. NOT PERMITTED: anticoagulants; hydantoins;oral antidiabetics; anti-malarials; immune suppressants; oral intraarticular steroids within last three months; muscle relaxants; neuroleptics; antidepressants; NSAIDs. Equivalent at baseline except 'almost all' nimisulide patients right knee and rofecoxib left knee affected
Interventions	rofecoxib 25mg od nimesulide retard 300mg od paracetamol rescue therapy
Outcomes	Investigator treatment efficacy (100mm VAS) WOMAC: daily activities; pain and stiffness paracetamol use
Notes	WITHDRAWAL: 7(6%) No standard deviations reported. Unclear number withdrawing and randomised, text of study suggests 114 was final number rather than baseline as reported in the abstract. Possibly not ITT analysis. EFFICACY:Both drugs significant improvement in efficay. Onset of analgesia faster with nimisulide (within 15 minutes significant effect occurred vs 45 minutes with rofecoxib. Nimisulide longer duration of action days 2 and 3. WOMAC and VAS QoL: SS difference on day 30 in favour of nimisulide (p=0.04). SAFETY: similar tolerability QA: R=1 B=1 W=1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kivitz 2004(MSD 085)

Methods	6 weeks double-blind, randomised, multicentre US (113 sites)

Kivitz 2004(MSD 085) *(Continued)*

	pre-trial NSAID washout RANDOMISATION: computer generated blinded allocation schedule double dummy rescue paracetamol up to 2600mg except during first 6 days or 24 hours pre efficacy assessment modified ITT analysis: baseline flare, took at least one dose of study drug and had a postbaseline efficacy assessment. low dose aspirin permitted up to 81mg/day for CV prophylaxis (10-14%) POWER: detection of clinically relevant difference between treatment groups in terms of the primary endpoint PGART; 380 patients per active group; 180 placebo estimated that the study would have 99% power to detect a difference of at least 15% between rofecoxib and nabumetone in terms of the percentage of patients with good/excellent PGART response. Statistical significance on PGART endpoint implied consistent with difference of 15 percentage points.
Participants	OA knee N= 1042 >= 40 years of age (mean 63.1; range 35-92) OA of greater than 6 months duration history of NSAID response ARC I, II or III flare with NSAID withdrawl pre-trial EXCLUSION: pregnancy; concurrent medical/arthritic disease that could alter study outcome; significant systemic disease that contra-indicated NSAIDs; CCX; misoprostol; sucralfate; histamine blockers; antacids; PPIs; analgesics; wafarin; ticlopidine; high-dose aspirin; appetite suppresants; other medications for chronic diseases; BASELINE: no differences ASPIRIN USE: rofecoixb 46/424; nabumetone 57/410; placebo 21/208
Interventions	rofecoxib 12.5mg/day nabumetone 1000mg/day placebo
Outcomes	PRIMARY: patient global response to therapy (0-4) later stated as the number of patients with good or excellent response. SECONDARY: WOMAC pain walking on a flat surface (100mm VAS); investigator global response to therapy (0-4); LOE withdrawals; SF-36 quality of life; After start of trial, protocol amended to include endpoints for the assessment of onset of efficacy (PGART and walking pain) 4 hours after taking dose on days 1-6. 55.1% of patients enrolled after this time.
Notes	WITHDRAWAL: 226 (21.7%) PLACEBO EFFICACY: Rofecoxib SS superior in number of patients with good or excellent response at 4 hours ($p<0.05$), 28hrs ($p<0.001$), 5 days (p not given) and 2, 4, and 6 wks ($p<0.05$). Patient Global Response: median time to good or excellent response rofecoxib 52hrs, placebo >124 hrs Pain walking over first 5 days rofecoxib greater improvement ($p<0.05$). NABUMETONE EFFICACY: Rofecoxib SS superior to nabumetone in number of patients with good or excellent response at 28hrs ($p<0.001$), 5 days (p not given) and 2,4,and 6 wks ($p<0.05$). Patient Global Response: median time to good or excellent response rofecoxib 52hrs, nabumetone 100hrs, placebo >124 hrs ($p=0.002$ rofecoxib vs. nabumetone, $p=0.001$ nabumetone vs. placebo). QA: R=2 B=2 W=1
Risk of bias	

Kivitz 2004(MSD 085) *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Laine 1999 (MSD 044)

Methods	12; 16-24 week double-blind US multicentre (34 sites) Paracetamol, non-NSAID pain medication and supplied antacids were permitted. No concomitant NSAIDs, aspirin, anticoagulants, sucralfate, unapproved antacids, antibiotics, PPIs or GPAs. Endoscopy, biopsy and H pylori status testing at baseline. double-dummyt randomisation: stratified by prescence/absence of history of PUB. Blocks of 4 from a computer generated list allocation concealment: sealed envelopes In order to allow for an anticipated lack of efficacy in the placebo group, 95% of patients taking placebo and 5% in the other groups were randomly selected and discontinued from the trial in a blinded manner at week 16. Study designed to provide 95% power (alpha = 0.05, 2 tailed) to detect a difference in the 12 week cumulative ulcer incidence between the rofecoxib or placebo groups and the ibuprofen groups assuming an incidence of 2.5% for the placebo and rofecoxib groups and 15% for the ibuprofen group. Predefined statistical criteria to compare ulcer rates were established for combined analysis. 2 treatments would be considered equivalent if the one-sided 95% CI upper limit of the difference in rates was <4 percentage points. Life table analysis of ulcer rates comparing first 3 months with second 3 months. Subgropu analysis: age>65; gender; race; past GI events; H pylori status; tobacco use; prior NSAID use; gastroduodenal erosions at baseline. ITT analysis Endoscopy: baseline, weeks 6, 12 and 24 and unscheduled discontinuations and for evaluation of GI symptoms.
Participants	OA N=742 >=50 yoa (Mean age 61.8, range 47-7) prior NSAID use 93% required NSAID treatment for at least 6 months Patients with history of ulcer, perforation or GI hemmorrhage, endoscopically detected gastroduodenal erosion and active H pylori infection EXCLUSION : active duodenal, gastric or oesophageal ulcers; pyloric obstruction; patients with endoscopical evidence at baseline of erosive esophagitis, UGI ulcer or pyloric obstruction, previous upper GI surgery, inflammatory bowel disease, reduced renal function, faecal occult blood, unstable medical disease, bleeding diathesis, malignancy within previous 5 years, cerebrovascular events in previous 2 years, anticoagulant therapy, CCX, ticlopidine, aspirin. No baseline differences
Interventions	rofecoxib 25 mg od rofecoxib 50 mg od ibuprofen 800mg tds placebo
Outcomes	Primary: endoscopically detected ulcers >=3mm Secondary: endoscopically detected ulcers >=5mm Patient Global assessment of disease (Likert 0-4); Paracetamol use

Laine 1999 (MSD 044) *(Continued)*

	Ulcer defined as mucosal break >= 3mm with unequivocal depth. Erosions defined as a mucosal break of any size with no depth
Notes	WITHDRAWAL: 293 = 39.5% Primary hypothesis was that 25mg rofecoxib would cause fewer gastroduodenal ulcers than 800mg ibuprofen three times a day after 12 weeks of therapy. A priori subgroup analysis indicated that age >=65 years, history of past GI events, and prescence of gastroduodenal ulcer at baseline were risk factors for the development of ulcers. No evidence that Hpylori was a risk factor (p =0.983) The cumulative incidence of endoscopically detected gastroduodenal ulcers =3mm with rofecoxib (both doses) was comparable with placebo at 12 weeks (placebo 9.9%, 25 mg rofecoxib 4.1%, 50 mg rofecoxib 14.7%, p<0.001). IBUPROFEN The cumulative incidence of endoscopically detected gastroduodenal ulcers =3mm with rofecoxib (both doses) was SS lower than with ibuprofen (placebo 9.9%, 25 mg rofecoxib 4.1%, 50 mg rofecoxib 14.7%, and ibuprofen 27.7% p<0.001). 'equivalent' individual GI AEs, GI w/d not reported QA: R=2 B=2 W=0

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

McKenna 2000

Methods	6 week double-blind, US multicentre (20 sites) Double dummy FLARE CRITERIA: absolute score of at least 40mm for patient's VAS pain assessment; 1 or more grade increase in physician's global assessment; 1 or more grade increase in patient's global assessment; 2 or more point increase in OA severity index. PERMITTED: paracetamol for non-arthritic pain (max 2 g per day); low dose aspirin (<=325mg) for cardiovascular prophylaxis; occaisional antacid use. NOT PERMITTED: anticoagulants; antirheumatic; antiulcer medication WASHOUT: 2 days or 5 half lives whichever longer RANDOMISATION: computer generated seperate schedules for those with pain assessment of <= 69mm at baseline and >= 70mm at baseline. POWER: 60 per group to provide 90% power to detect a treatment difference, using two-tailed significance test and set the alpha level of significance at 0.05. Minimum treatment expected difference between active and placebo of 15mm on 100mm VAS. ITT analysis
Participants	OA knee N=182 >=40 yoa (Mean age 62.2) INCLUSION: ACR functional class I-III at screening; flare on analgesic withdrawal (2 days or 5 half-life washout); women adequate contraception and not pregnant EXCLUSION: significant malignancy within 5 years; inflammatory arthritis or acute joint trauma of the knee; active GI, renal or hepatic disease; coagulation defect; clinically significant abnormal screening laboratory values; known hypersentivity to COX II inhibitors, sulphonamides or NSAIDs; surgery or invasive proceedure planned during the study; CCX within 8 weeks prior; intra-articular hyaluronic acid

McKenna 2000 *(Continued)*

	within 6 months; investigational medication within 30 days; diagnosed/treated for oesophageal, gastric, pyloric channel or duodenal ulcer within 30 days. No SS differences at baseline
Interventions	rofecoxib 25mg od celecoxib 200mg od placebo
Outcomes	PRIMARY: pain (100mm VAS); WOMAC total; patient global assessment of arthritis (1-5 Likert); SECONDARY: WOMAC pain, stiffness and physical functioning, total; physican global assessment of arthritis (1-5 Likert); OsteoArthritis Seveity Index (0-24): pain, walking disatance and activities of daily living.
Notes	WITHDRAWAL: 40(22%) EFFICACY: Data given as p values with some graphical presentation: No SD's in tabulated data. Both active groups equivalent improvement pain, global assessment, WOMAC, which was superior to placebo.SAFETY: RR GI adverse events = 3.05 (95% CI: 1.39, 6.68) QA: R=2 B=1 W=1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Moskowitz 2003

Methods	2 week double-blind US multicentre double-dummy ITT analysis
Participants	OA knee N=530 >=50 yoa met flare criteria
Interventions	rofecoxib 10mg per day rofecoxib 25mg per day placebo
Outcomes	PRIMARY: Pain intensity following 10minute walk(VAS) SECONDARY: "other validated OA efficacy measures" Pain intensity following 10 minute walk (VAS): baseline, 30mins, 1hour, 1hour 30mins, 2 hours, 3 hours, 4 hours 5 hours and 6 hours
Notes	Abstract only Sponsored by Pfizer

Risk of bias

Bias	Authors' judgement	Support for judgement

Moskowitz 2003 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

NAPROXEN 901 OC/OF

Methods	6 weeks double-blind, multicentre international (80 sites) paracetamol rescue up to 2.6g Randomisation: computer generated schedule stratified for history of ulcer or upper GI bleeding and use of low-dose aspirin. double dummy ITT analysis Sample size: individual studies 200 per group 95% power to demonstrate equivalence between rofecoxib and naproxen if true mean difference is zero.
Participants	OA knee or hip N=482; N=462 >=40 yoa (Mean age 61.6) Requiring regular NSAIDs; pain on moste days in previous month; radiographic evidence. At least moderate pain on NSAID withdrawal and worse physician assessment of disease status. Exclusion: inflammatory or post-traumatic arthritis; uncontrolled diabetes or hypertension; angina or CHF; malabsorption; morbid obesity; inherited bleeding disorder; positive fecal occult blood; creatinine clearance <30ml/min; serum creatinine >2.0; CCX; misoprostol; H2; PPI; warfarin; topicolone; aspirin >100mg/day; history of ulcer, upper GI bleed requiring aspirin; concomitant disease in which NSAIDS contraindicated. BASELINE: equivalent characteristics
Interventions	rofecoxib 12.5 mg od naproxen 500mg bd
Outcomes	Primary: WOMAC pain when walking; patient global response (0-4 Likert); investigator global disease status(0-4 Likert). Average response over all observation times in 6 week treatment period excluding days 2-6. Secondary: WOMAC (physical function, pain, stiffness, total score average, subscale average); patient global disease status (100mm VAS); investigator global response (0-4 Likert); time to onset of pain relief. SAFETY: spontaneously reported AE's; vital signs; laboratory tests; NSAID-related GI AEs.
Notes	WITHDRAWAL: 114 = 12.1% 2 identical studies in different continents. Analysis combined in publication. EFFICACY: no data reported. Authors report that for all efficacy endpoints treatment effects for rofecoxib and naproxen were comparable and seen at the first measures of efficacy. Subgroups equivalent. SAFETY: Authors report that both compunds were generally well tolerated with an improved gastrointestinal safety profile for rofecoxib versu naproxen. QA: R=2 B=2 W=1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Niccoli 2002

Methods	2 week assessor- blind, single centre (Italy) POWER: 30 patients in each arm to detect a 20% reduction in creatine clearance values 80% power (a=0.05). Sodium intake not controlled therefore 24 hour urinary sodium excretion not measured.
Participants	OA hip,hand and knee. N=96 60-80 years of age (Mean age 72.3). ACR classifaction criteria for OA. Treatment arms equivalent at baseline. Exclusion:unreliable in self-evaluation of symptoms; severe cardiovascular, renal or hepatic disorder; GI bleeding or peptic ulcer; hypersensitivity to NSAIDS; concomitant atnihistamines, antibiotics, NSAIDs, CCX, mucolytics, anticoagulants, antiplatelets or potentially nephrotoxic drugs; pregnancy or lactation; previous abnormalities in renal function (serum creatinine >1.5mg/dl; creatinine clearance <50ml/min).
Interventions	rofecoxib 25mg/day diclofenac 50mg tds Amtolmetin guacyl (AMG) 600mg bd 3/7 then 600mg/day Drugs taken soon after meals.
Outcomes	Primary: difference in creatinine clearance before and after treatment. Secondary: body weight; systolic and diastolic blood pressure; peripheral oedema; blood urea nitogen; serum creatinine, sodium, potassium, chlorum and uric acid; daily urine volume; creatinine clearance; blood cell count; liver function. EFFICACY: patient global pain (100mm VAS); patient global disease activity(100mm VAS); physician global disease activity(100mm VAS).
Notes	Report states: "In the case of any adverse events related to the study drug, patients were withdrawn from the study". Dropouts replaced by next eligible patient who was assigned to the same treatment arm Six patients (1 AMG; 1 diclofenac;4 rofecoxib) withdrew from the study during the first week of treatment due to intolerance or adverse events. These patients were not considered further. WITHDRAWAL: unclear - appears to be 6 (6.2%) EFFICACY: Authorts report a significant reduction all treatment groups. Multiple comparison analysis showed that diclofenac significantly reduced pain and the physician's global disease activity scores compared to rofecoxib (p<0.001). QA: R=1 B=1 W=1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Saag 1998 (MSD 033)

Methods	6 week double-blind multicentre,

Saag 1998 (MSD 033) *(Continued)*

	no aspirin or CCX rescue paracetamol double dummy comparability stated if for all 3 primary endpoints, the 95% confidence intervals of the difference in the mean treatment response between 2 treatments were within + or - 10mm on a 100mm VAS scale or 0.5 on a Likert scale 43% hypertension, 6% diabetes, 46% drug allergies,29% hypercholesterolemia, 27% hypothyroidism randomisation: computer generated schedule in a 1:4:4:4 scheme After 26 weeks, topical or systemic analgesics and CCX permitted for breakthrough pain. compliance assessed by returned tablet counts ITT analysis but only patients with baseline plus 1 treatment measurement included Analysis: average change from baseline over the six-week treatment period. POWER: to detect differences of approximately 0.86 on LIkert and 14mm on VAS between rofecoxib and placebo with 99% power (alpha=0.05, 2 tailed) , given a sample size of 50 (placebo) and 200 (rofecoxib). At least 99% power to yield the 95% CI's within the comparability ranges for the 3 primary endpoints if the true difference between rofecoxib and ibuprofen would be 0, assuming 200 patients receiving each active treatment.
Participants	OA hip and knee N=736 >= 40 years of age (Mean age 61.3 , range 39 to 91) ARA functional class I-III clinical and radiographical confirmation history of benefit from NSAIDs or paracetamol increased pain following NSAID withdrawal and patients with moderate symptoms taking paracetamol Exclusion: CCX, topical analgesics, low dose aspirin, regular antacid, H2 blocker, PPI, warfarin or ticlopidine, significant renal impairment, evidence of active GI bleed, GI malabsorption syndrome, class III/IV angina or congestive heart failure, uncontrolled hypertension, stroke, TIA within 2 years, active hepatic disease, recent neoplastic disease, allergy to NSAID or paracetamol, and any other condition that could confound results, interfere with participation or put patient at risk BASELINE: no SS differences
Interventions	rofecoxib 12.5mg od rofecoxib 25mg od ibuprofen 800mg tds placebo
Outcomes	PRIMARY: WOMAC index: pain when walking; patient global response to therapy (0-4); investigator global disease status (0-4) SECONDARY: WOMAC index: pain, stiffness, functional ability; joint tenderness (0-3); patient global disease status(10cm VAS) ; investigator global response to therapy(0-4); study joint tenderness (0-3); rescue paracetamol; LOE withdrawals
Notes	Withdrawals 111/736 = 15.1% EFFICACY: rofecoxib (both doses) SS superior to placebo (p<0.001) all OMs.SAFETY: RR GI withdrawals 12.5mg 0.79 (95% CI: ,0.16, 3.97), 25mg 1.22 (95% CI:0.26, 5.59), IBUPROFEN EFFICACY AND SAFETY: No SS differences between groups (efficacy p =0.05, ADRs p=0.1 and withdrawals due to ADRs p=0.1).RR GI withdrawals 12.5mg 0.72 (95% CI: 0.23, 2.24), 25mg 1.11 (95% CI:0.41, 3.02).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Saag 2000 (MSD 034)

Methods	52 weeks double-blind double dummy multicentre (43) international randomisation: computer generated schedule After 26 weeks, topical or systemic analgesics and CCX permitted for breakthrough pain. compliance assessed by returned tablet counts ITT analysis but only patients with baseline plus 1 treatment measurement included Primary efficacy analysis: average change from baseline over the first 12 week treatment period. Analyses also performed at 26 and 52 weeks. A secondary analysis of the last observed value in each treatment period, and an analysis of patients who completed the study were performed to confirm the findings of the primary analysis. Power: to detect differences of approximately 0.86 on the Likert scale and 14mm on the VAS between rofecoxib and placebo with 99% power (alpha=0.05, 2 tailed), given sample size of 200 in each group. Reported as at least 99% power to yeild the 95% CIs within the comparability ranges for the 3 primary end points if the true difference between rofecoxib and diclofenac would be 0, assuming 200 patients receiving each active treatment.
Participants	OA hip and knee N=693 >= 40 years of age (Mean age 62.3; range 38-85) ARA functional class I-III history of benefit from NSAIDs or paracetamol increased pain following NSAID withdrawal and patients with moderate symptoms taking paracetamol Exclusion: CCX, topical analgesics, low dose aspirin, regular antacid, H2 blocker, PPI, warfarin or ticlopidine, significant renal impairment, evidence of active GI bleed, GI malabsorption syndrome, class III/IV angina or congestive heart failure, uncontrolled hypertension, stroke, TIA within 2 years, active hepatic disease, recent neoplastic disease, allergy to NSAID or paracetamol, and any other condition that could confound results, interfere with participation or put patient at risk 34% hypertension, 5% type 2 diabetes mellitus, 3% drug allergies, 7% hypercholesterolemia, 5% hypothyroidism No significant baseline differences in gender; ARA functional class; prior NSAID use; primary study joint; age or OA duration. 66.5% completed 1year
Interventions	rofecoxib 12.5mg od rofecoxib 25mg od diclofenac 50mg tds
Outcomes	Primary: WOMAC index: pain when walking; patient global response to therapy (0-4); investigator global disease status (0-4)* Secondary: WOMAC index: pain, stiffness, functional ability; joint tenderness (0-3); patient global disease status(10cm VAS) ; investigator global response to therapy(0-4); study joint tenderness (0-3); rescue paracetamol; LOE withdrawals. Other: laboratory evaluations at each visit
Notes	WITHDRAWALS: 232/693 = 66.5% Standard deviations of the efficacy variables not avaialble in the publication. Unclear what time period the endpoints reported are from (see methods) and no data available for the 'primary efficacy analyses [which] were based on the average change from baseline over the first 12 week treatment period. Treatment period means given for response to therapy. Figure 4 states graphs for primary efficacy end points (WOMAC pain, physical function and stiffness), which conflict with those stated in the methods (see outcomes). Figure 4 also indicates that p<0.001 vs placebo, atlhough no placebo arm stated in the methods. Rofecoxib 12.5 mg signficantly less effective than diclofenac for secondary outcomes: pain

Saag 2000 (MSD 034) *(Continued)*

	when walking on a flat surface; investigator global response to therpay and patient global assesment of disease status. and use of rescue paracetamol. 25mg rofecoxib and diclofenac no significant difference. Report however states that " The 95% CIs for the difference between 12.5mg and 25mg rofecoxib versus diclofenac were contained within the prespecified comparability grounds for all of hte global assessments indicating clinical comparability of responses among the three treatments." Paper also states that " Signficant differences resulted from sample sizes, which needed to be large to ensure satisfaction of the comparability criteria." Table2 and Table 3 are conflicting in terms of numbers of patients withdrawing due to lack of efficacy. Although it states ITT analysis also states that " fewer than 1% of patients were missing sufficient data (either the baseline or all treatment period values) to exclude them from the efficacy analysis. EFFICACY AND SAFETY: Rofecoxib (both doses) of comparable efficacy and tolerability (including GI events) to diclofenac all endpoints. More patients discontinued due to ADRs in diclofenac group (SS not reported).Patient response to therapy: rofecoxib 12.5mg = -2.18, rofecoxib 25mg = -2.33, diclofenac = -2.39 (no reports of SS)RR GI withdrawals 12.5mg 0.47 (95% CI: 0.22, 1.02), 25mg 0.63 (95% CI:0.31, 1.26). QA: R=2 B=2 W=1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Schnitzer 2001

Methods	6 week double-blind paracetamol rescue
Participants	OA knee or hip N= 1082 Mean age =62 Baseline equivalent 40% history of hypertension
Interventions	rofecoxib 25mg od celecoxib 200mg od placebo
Outcomes	WOMAC Patient Global Response to Therapy Blood pressure SBP: increase >20mm Hg and SBP>140 DBP: increase >15mm Hg and DBP>90
Notes	Abstract only RESULTs: More patients on placebo discontinued prematurely, primarily due to LOE. Compared to celecoxib, rofecoxib provided SS superior relief of night pain; morning stiffness; rest pain and walking pain; WOMAC subscales pain, stiffness and physical function; good or excellent response and quicker onset of efficacy. Both active groups superior to placebo. Similar incidence of clincial AEs, drug related AEs, serious AEs and discontinuations due to AEs in active groups. (From Schnitzer poster) RESULTS (From Geba poster):

Schnitzer 2001 *(Continued)*

	patients with pre-defined changes in SCP: rofecoxib 45/471=9.6%; celecoxib 43/460 = 9.4%; placebo 5/151= 3.3% patients with pre-defined changes in DBP: rofecoxib 13/471= 2.8%; celecoxib 9/460= 2%; placebo 3/151= 2% Number of withdrawls due to hypertension = 1 rofecoxib; 0 celecoxib; 0 placebo % good or excellent patient global response to therapy; rofecoxib 273/471; celecoxib 229/460

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

SUCCESS VI

Methods	6 week double-blind, US/ Canada multicentre (101 sites) double dummy cuff BP measurements taken; arm with highest BP measurement taken PERMITTED:<= 325 mg aspirin permitted if stable dose fo 30 days prior; antiplatelets; paracetamol rescue (up to 4g); adjustment of diuretic/hypertensive at discretion of investigator not-permitted: NSAIDS, oral or injected CCX; intraarticluar hyaluronic acid; prescription/OTC antiulcer drugs. WASHOUT: 4 days minimum RANDOMISATION: computer-generated 1:1 in blocks of 4. ALLOCATION CONCEALMENT: known only by suppliers clinical packaging group. Sealed envelopes held by statistician. ITT analysis POWER: 405 patients per treatment arm to provide 90% power, with a two-sided significance level of 0.05 to detect a treatment difference if the true event rates for oedema and hypertension for patients using rofecoxib and celecoxib were 10% and 4% respectively.
Participants	OA hip, knee or hand N=810 older hypertensive patients treated with anti-hypertensive medication >=65 yoa (Mean age 74.1) INCLUSION: stable controlled hypertension; ARC criteria for OA of hip, knee or hand; would benefit from chronic daily therapy with NSAID to control symptoms. seated diastolic <=95mmHg; systolic <=160mmHg; based on cuff measurement same dose of hypertensive for minimum of 3 months EXCLUSION: active GI disease; renal, hepatic or coagulation disorder; history of New York Heart Association class III or IV heart failure; secondary hypertension; malignant hypertension; renal artery stenosis; acute joint trauma; rheumatoid arthritis; active untreated crystal induced arthropathies; known hypersensitivity to rofecoxib, celecoxib, sulphonamides, NSAIDs or related compounds; history of oesophageal, GI or duodenal ulceration within 30 days of study; use of celecoxib or rofecoxib within 30 days; serum creatinine >1.5mg/dL; blood urea nitrogen of at least 1.5 times upper limit of normal; serum potassium concentration <3.0 mmol/l or > 5.0 mmol/l. Equivalent at baseline except celceoxib greater mean duration of OA (p=0.012) and celecoxib more treated with ACE inhibitors (40% vs. 29%; p=0.002). Also more patients had a systolic BP of greater than 140mmHg at baseline in the celecoxib group (40 vs 37%)
Interventions	rofecoxib 25mg od celecoxib 200mg od
Outcomes	PRIMARY: significant peripheral oedema (0-4 Likert) ; elevated hypertension (systolic or diastolic) : elevated systolic blood pressure (>20mmHg increase with absolute >140mmHg); elevated diastolic blood pressure (>15mmHg increase with absolute >90mmHg).

SUCCESS VI *(Continued)*

	Significant oedema: increase of at least 1 grade in peripheral plus 3% weight gain; increase of 2 or more with or without weight gain; increase to 4+ oedema; initiation or increase in medication for oedema. SECONDARY: hypertension; changes in diuretic and/or hypertensive medication; change in mean diastolic or systolic; new onset or worsening CHF; clinically significant renal lab vales. POST HOC: systolic BP changes and weight gain in patients experiencing oedema.
Notes	WITHDRAWAL: 114 (14%) Cardiorenal events excluded from the overall safety analysis; therefore possibly underestimate. Suitability of pooling the results with other studies? Investigators were allowed to change diuretic/antihypertensive- no details on how many patients this occurred in. Could have biased results. Additionally more patients in the celecoxib group were receving ACE inhibitors at baseline (40% vs 29%; p=0.002). Also more patients had a systolic BP of greater than 140mmHg at baseline in the celecoxib group (40 vs 37%) although covariate analysis did not indicate this had a confounding effect. SPONSOR: Pharmacia Corporation and Pfizer Inc. SAFETY: incidence of oedema rofecoxib > celecoxib (p=0.014).Nearly 60% more patients with rofecoxib (1.6 fold increase) had increase in systolic blood pressure of =20mmHg (p<0.05) observed at week 2. At week 6 change in mean baseline bp +2.6mm rofecoxib and -0.47mm celecoxib (p=0.007). Diasatolic bp increased 2.3% rofecoxib compared to 1.2% celecoxib(p=0.29) Not all patients enrolled met current guidelines for hypertension control but were considered by investigator to have stable hypertension. QA: R=2 B=2 W=1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

SUCCESS VII

Methods	6 week double-blind, US/ Canada multicentre (107 sites) double-dummy cuff BP measurements taken; arm with highest BP measurement taken 4 day pre treatment NSAID washout PERMITTED:<= 325 mg aspirin permitted if stable dose fo 30 days prior; antiplatelets; paracetamol rescue (up to 4g); adjustment of diuretic/hypertensive at discretion of investigator; Occaisional use of paracetamol, non-NSAID analgesics, glucosamine, chondroitin or other herbal preparations permitted for pain relief not-permitted: NSAIDS, oral or injected CCX; intraarticluar hyaluronic acid; prescription/OTC antiulcer drugs. adjustment of diuretic/hypertensive at discretion of investigator RANDOMISATION: computer-generated 1:1 in blocks of 4. ITT analysis POWER: 500 patients per treatment arm to provide 80% power, with a two-sided significance level of 0.05 to detect a treatment difference in clincially significant elevations in systolic BP of 12.2% and 18.8% between celecoxib and rofecoxib respectively.
Participants	OA hip,hand and knee N=1092

SUCCESS VII *(Continued)*

	>= 65 yoa (Mean age 73.2) INCLUSION: ARC criteria for OA functional capacity I-III; stable controlled hypertension; potential benefits from chronic daily NSAID therapy. Stable dose of antihypertensive medications for >= 3months seated diastolic <=95mmHg; systolic <=160mmHg EXCLUSION: active GI disease; renal, hepatic or coagulation disorder; history of New York Heart Association class III or IV heart failure; secondary hypertension; malignant hypertension; renal artery stenosis; acute joint trauma; rheumatoid arthritis; active untreated crystal induced arthropathies; known hypersensitivity to rofecoxib, celecoxib, sulphonamides, NSAIDs or related compounds; history of oesophageal, GI or duodenal ulceration within 30 days of study; use of celecoxib or rofecoxib within 30 days; serum creatinine >1.5mg/dL; blood urea nitrogen of at least 1.5 times upper limit of normal; serum potassium concentration <3.0 mmol/l or > 5.0 mmol/l. Equivalent at baseline
Interventions	rofecoxib 25mg od celecoxib 200mg od
Outcomes	PRIMARY: significant peripheral oedema (0-4 Likert) ; elevated systolic blood pressure (>20mmHg increase with absolute >140mmHg); change from baseline in mean systolic BP. Significant oedema: increase of at least 1 grade in peripheral plus 3% weight gain; increase of 2 or more with or without weight gain; increase to 4+ oedema; initiation or increase in medication for oedema. SECONDARY: ; changes in diuretic and/or hypertensive medication; change in mean diastolic; new onset or worsening CHF; clinically significant renal lab vales; any cardiorenal clinical event. POST HOC: systolic BP changes and weight gain in patients experiencing oedema.
Notes	WITHDRAWAL: 104 (9.5%) SPONSOR: Pharmacia Corporation and Pfizer Inc. No overall rates of adverse events reported Subgroup analyses indicated that significant differences in mean systolic BP from baseline between celecoxib and rofecoxib in patients using ACE inhibitors and BB monotherapy or combined with diuretics. BP changes were minimal and not different between apteitns reeiveing calcium channel antagonists or diuretic monotherapy. Oedema more common in women receiving rofecoxib vs celecoxib 32 vs 16. In patients with clinically significant oedema, SS higher mean weight and mean diastolic BP increase occured in the rofecoxib group (+2.4kg; +10.1 mmHg) compared to the celecoxib group (+1.4kg; + 0.4mmHg). Conflicting statements in publication about numbers randomised; error in Table 1 QA: R=2 B=2 W=1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Truitt 2001(MSD 058)

Methods	6 week US multicentre (48) double-blind? aspirin permitted

Truitt 2001(MSD 058) *(Continued)*

	rescue paracetamol RANDOMISATION: centralised computer-generated schedule stratified according to low dose aspirin use and study site. Prospectively targeted group sizes: placebo, rofecoxib 25mg (target of 50 patients); rofecoxib 12.5mg and nabumetone (target of 100 patients) double dummy blinding ITT analysis POWER: 90% power to detect a difference of 13mm on the patient global assessment between rofecoxib and placebo (a=0.05, two tailed)
Participants	OA knee or hip N=341 >=80 yoa (Mean age 83, range 80-95) most painful joint designated study joint if both hip and knee affected Baseline characteristics reported as similar. INCLUSION: ambulatory; pain in study joint for at least 6 months, radiographically confirmed. ACR functional class I-III; history of positive benefit from NSAIDS or paracetamol and to have taken in previous 20/30 days; ongoing low dose aspirin up to 325 mg permitted; >24 on 'Mini Mental State Examination' at screening; able to swallow; pre study washout flare with post-washout Patient Global Assessment of Disease Status >= 40mm (100mm=very poor) EXCLUSION:prior history of inflammatory arthritis; acute ligamentous on meniscal injury to study joint within past 18 months;arthroscopy within 4 months;CCX within 3 months; other medical conditions or abnormal laboratory values that contraindicated NSAID use or could cofound; angina or CHF with symptoms at rest; decreased renal function; uncontrolled hypertension; active GI bleeding within past 3 months; history of leukaemia, lymphoma or myeloproliferative disease; hypersensitivity to aspirin or NSAIDS; postive stoll-guaiac test.
Interventions	rofecoxib 12.5 mg od rofecoxib 25mg od nabumetone 1500mg od placebo
Outcomes	PRIMARY: patient global disease status (10cm VAS); SECONDARY: WOMAC index: pain; stiffness, physical function, (pain at night, morning stiffness); investigator global disease status (0-4);LOE withdrawals; AE withdrawals;joint tenderness (0-3); laboratory testing
Notes	WITHDRAWAL: 49 (14.3%) Not stated as double blind but double dummy used and safety assessor blinded. EFFICACY: all OMs rofecoxib SS superior to placebo (p=0.001). NABUMETONE EFFICACY AND SAFETY: Results similar- but no reported results of significance tests in abstract or submission. QA: R=2 B=2 W=1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

VACT

Methods	6 weeks, double-blind, US multicentre (29 sites) 6 week average for patient calculated as mean change from baseline to weeks 2,4 and 6. ; no CCX permitted. No rescue medication permitted. double-dummy RANDOMISATION: computer generated POWER: 50 evaluable patients per treatment and subgroup, the half-width of a 95% CI would be 8.3mm, assuming a within group SD of 30mm. With 75(100) patients per group the power to detect a treatment difference of 10mm on the WOMAC scale was 52% (65%). modified ITT: all patients taking at least 1 dose of study medication included.
Participants	OA knee N=382 >=40 yoa (Mean age 62.6; range 39-91) INCLUSION: symptomatic OA for at least six months; ARA functional class I-III. NSAID responsive or regular user of paracetamol for at least 30 days prior who experienced exacerbation following withdrawal EXCLUSION: concurrent medical or arthritic disease or abnormal laboratory values that might confound results or put patient at risk; history of allergy or hypersensitivity to study drugs, aspirin, ibuprofen or NSAID, sulphonamides; investigational drug within 30days of screening. BASELINE equivalence
Interventions	rofecoxib 12.5mg od rofecoxib 25mg od celecoxib 200mg od paracetamol 1g qds
Outcomes	WOMAC (100mm VAS) [Pain on walking, night pain, pain at rest, morning stiffness, functional disability] patient global response to therapy (0-4)
Notes	WITHDRAWAL: 81(21.2%) Powered to compare rofecoxib with paracetamol Average of values over time period used for analysis rather than change from baseline No correction for multiplicity; 5 primary endpoints with 4 different comparisons; 33 individual p values EFFICACY: Rofecoxib 25mg SS superior after 5 days to paracetamol (pain walking, night pain, rest pain, pain, stiffness, functional disability (p <0.05). Rofecoxib 25mg SS superior to celecoxib (night pain, rest pain, pain, stiffness, patient global response, (p <0.05). But equivalent on other outcome measures. Rofecoxib 25mg superior to rofecoxib 12.5mg night pain. Rofecoxib 12.5mg v celecoxib: no SS difference any efficacy endpoint early or 6 weeks. SAFETY: No SS difference in ADRs between groups RR total AE = 1.19 (95% CI: 0.93, 1.53) 12.5mg and 1.00 (95% CI: 0.76, 1.32) and AE withdrawals = 1.77 (95% CI: 0.53, 5.85) 12.5mg and 1.53 (95% CI: 0.45, 5.26). GI events not reported. QA: R=2 B=2 W=1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

VACT 2

Methods	6 weeks
Participants	N=1578 (median age 62) demographics similar
Interventions	rofecoxib 12.5 or 25mg od celecoxib 200mg od paracetamol 1g qds
Outcomes	
Notes	Published in abstract only. Methods reported as being identical to VACT 1. REPORTED RESULTS: Number of patients with a good or excellent response not significantly different at week 6; signficant at weeks 2 and 4. Cumulative regression analysis of PGART was significantly greater with Rof25mg compared to CEL. Rof 12.5 mg not signficantly different to CEL. Coxibs significantly grater PGART vs ACET at any time point. Time to good or excellent PGART response was significantly quicker in for rof 25mg compared to celecoxib.All coxibs significantly quicker than paracetamol. For the four WOMAC endpoints both rof 12.5mg and 25mg had signficantly greater reductions compared to CEL and PARA. WOMAC subscales improvement greater with ROF25 compared to CEL and all coxibs greater than PAR.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

RA = rheumatoid arthritis
OA = osteo arthritis ; N= number of patients enrolled; yoa = years of age; OMs= outcome measures; SS= statistically significant; LOE= lack of efficacy; DMARD= disease modifying antirheumatic agent; CCX= corticosteroids; GCX= glucocorticoids; MTX= methotrexate; VAS= Visual Analogue Scale, AE= adverse events; RR = risk ratio; 95% CI= 95% confidence interval; US= United States; UK= United Kingdom; NHP= Nottingham Health Profile; ESR= erythrocyte sedimentation rate; # = number of; HAQ= ; CRP= C-reactive protein; VAS-= visual analogue scale, od= once daily, bd= twice daily, tds= three times a day, CHF= congestive heart failure, TIA = transient ischaemic attack; QA=quality assessment (Jadad), R=randomization, B=blinding, W=withdrawals and dropouts,* denotes primary outcome measure

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bjarnason 1998	Healthy volunteers
Eskiyurt 2001	Uncontrolled cohort study
Gertz 2002	Pooled analysis
Lanza 1999	Healthy volunteers with endpoints of impact on mucosa
Lipsky 1997	Report of results of Simon 1998
Malmstrom 1999	Dental pain
Reicin 2002	Pooled analysis

Study	Reason for exclusion
Reitblat 2002 1	Non-randomised. Examination of blood pressure elevation.
Singh 1999	Non-randomised uncontrolled study
VICOXX	Non-randomised uncontrolled cohort . Patients started on NSAIDS then transferred to rofecoxib

DATA AND ANALYSES

Comparison 1. rofecoxib versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADVERSE EVENTS*	13		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 TOTAL 12.5mg 6 weeks	3	1536	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.03, 1.29]
1.2 TOTAL 25mg 6 weeks	4	866	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.11, 1.56]
1.3 TOTAL 25mg 18 weeks	2	761	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.98, 1.14]
1.4 TOTAL 50mg 18 weeks	2	750	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.99, 1.15]
1.5 TOTAL 125mg 6 weeks	1	146	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.92, 1.77]
1.7 aged >65: TOTAL 12.5mg 6 weeks	1	632	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.85, 1.21]
1.8 Serious 12.5mg 6 weeks	3	1388	Risk Ratio (M-H, Fixed, 95% CI)	3.95 [1.06, 14.63]
1.9 Serious 25mg 6 weeks	4	658	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.11, 2.08]
1.10 Serious 125mg 6 weeks	1	146	Risk Ratio (M-H, Fixed, 95% CI)	6.81 [0.36, 129.61]
1.11 GI 12.5mg 6 weeks	1	632	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.55, 1.88]
1.12 GI 25mg 6 weeks	1	119	Risk Ratio (M-H, Fixed, 95% CI)	3.39 [1.47, 7.84]
1.13 Diarrhoea 12.5mg 6 weeks	4	1408	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.52, 1.43]
1.14 Diarrhoea 25mg 6 weeks	6	1270	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.67, 2.22]
1.15 Diarrhoea 25mg 18 weeks	2	761	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.85, 2.02]
1.16 Diarrhoea 50mg 18 weeks	2	750	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.74, 1.82]
1.17 Diarrhoea 125mg 6 weeks	1	146	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.25, 8.48]
1.18 Dyspepsia 12.5 mg 6 weeks	2	1218	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.34, 2.90]
1.19 Dyspepsia 25mg 6 weeks	2	264	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.41, 3.37]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.20 Dyspepsia 125mg 6 weeks	1	146	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.37, 10.30]
1.21 PUBS 12.5mg 6 weeks	5	1697	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.22 PUBS 25mg 6 weeks	6	1433	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.01, 4.12]
1.23 PUBS 50mg 6 weeks	1	242	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.24 PUBS 125mg 6 weeks	1	146	Risk Ratio (M-H, Fixed, 95% CI)	2.92 [0.12, 70.52]
1.29 Blood pressure increase 12.5mg 6 weeks	1	586	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.06, 36.93]
1.30 Hypertension 12.5 mg 6 weeks	2	1218	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.35, 3.61]
1.31 Hypertension 25mg 6 weeks	1	286	Risk Ratio (M-H, Fixed, 95% CI)	6.60 [0.38, 115.98]
1.32 Systolic BP increase 25mg 6 weeks	1	622	Risk Ratio (M-H, Fixed, 95% CI)	2.89 [1.17, 7.14]
1.33 Diastolic BP increase 25mg 6 weeks	1	622	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.40, 4.81]
1.34 MI 12.5mg 6 weeks	1	632	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.06, 36.06]
1.35 Headache 25mg 6 weeks	2	264	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.20, 1.11]
1.38 OEDEMA 12.5mg 6 weeks	1	586	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.03, 7.99]
1.39 OEDEMA 25mg 6 weeks	2	431	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [0.65, 9.52]
1.40 OEDEMA 125mg 6 weeks	1	146	Risk Ratio (M-H, Fixed, 95% CI)	8.76 [0.48, 159.83]
1.41 Lower extremity oedema 12.5mg 6 weeks	4	1676	Risk Ratio (M-H, Fixed, 95% CI)	2.40 [1.05, 5.48]
1.42 Lower extremity oedema 25mg 6 weeks	3	549	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [0.79, 8.37]
1.44 Lower extremity oedema 125mg 6 weeks	1	146	Risk Ratio (M-H, Fixed, 95% CI)	10.71 [0.60, 190.17]
2 WITHDRAWALS*	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 TOTAL 12.5mg 6 weeks	4	1408	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.62, 0.89]
2.3 Total 25mg 6 weeks	5	954	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.35, 0.58]
2.5 TOTAL 25mg 18/24 weeks	2	761	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.88, 1.38]
2.6 TOTAL 50mg 18/24 weeks	2	750	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.02, 1.58]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.8 Total 125mg 6 weeks	1	146	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.33, 0.87]
2.10 due to AE 5mg 6 weeks	1	294	Risk Ratio (M-H, Fixed, 95% CI)	2.92 [0.60, 14.23]
2.11 due to AE 12.5mg 6/8 weeks	6	2283	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [1.34, 3.55]
2.12 due to AE 25mg 6 weeks	7	1552	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.94, 2.59]
2.13 due to AE 25mg 18/24 weeks	2	761	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.81, 2.36]
2.14 due to AE 50mg 6 weeks	1	242	Risk Ratio (M-H, Fixed, 95% CI)	3.74 [0.74, 18.88]
2.15 due to AE 50mg 18/24 weeks	2	750	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [1.24, 3.36]
2.19 due to AE 125mg 6 weeks	1	146	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.70, 4.57]
2.35 due to CV AE 12.5 mg 6 weeks	1	288	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.02, 4.97]
2.36 due to CV AE 25 mg 6 weeks	1	296	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.06, 6.60]
2.39 due to LOE 5mg 6 weeks	1	294	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.29, 0.93]
2.40 due to LOE 12.5mg 6 weeks	4	1065	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.24, 0.54]
2.41 due to LOE 25mg 6 weeks	8	2184	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.18, 0.32]
2.42 due to LOE 25mg 18 weeks	2	761	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.25, 0.97]
2.43 due to LOE 50mg 6 weeks	1	242	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.05, 0.51]
2.44 due to LOE 50mg 18 weeks	2	750	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.13, 0.68]
2.45 due to LOE 125mg 6 weeks	1	146	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.01, 0.34]
2.46 due to GI AE 12.5 mg 6 weeks	1	288	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.16, 3.97]
2.47 due to GI AE 25 mg 6 weeks	2	415	Risk Ratio (M-H, Fixed, 95% CI)	2.32 [0.67, 8.05]
2.49 due to hypertension	1	622	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.04, 23.59]
2.50 due to lower extremity oedema AE 12.5 mg 6 weeks	1	288	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.04, 23.17]
2.51 due to lower extremity oedema 25 mg 6 weeks	1	296	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.04, 22.36]
3 Erosions (endoscoped)-change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 25mg 12 weeks	1	369	Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.45, 1.03]
3.2 50mg 12 weeks	1	364	Mean Difference (IV, Fixed, 95% CI)	0.53 [-0.22, 1.28]
4 Ulcer 12 weeks (endoscoped)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Ulcer >= 3mm rofecoxib 25mg	2	713	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.36, 1.17]
4.2 Ulcer >= 3mm rofecoxib 50mg	2	700	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.65, 1.81]
4.3 Ulcer >= 5mm rofecoxib 25mg	2	713	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.20, 0.86]
4.4 Ulcer >=5mm rofecoxib 50mg	2	700	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.59, 1.79]
4.5 Gastric Ulcer >= 3mm rofecoxib 25mg	2	713	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.31, 1.17]
4.6 Gastric Ulcer >= 3mm rofecoxib 50mg	2	700	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.52, 1.68]
4.7 Duodenal Ulcer >= 3mm rofecoxib 25mg	2	713	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.28, 2.83]
4.8 Duodenal Ulcer >= 3mm rofecoxib 50mg	2	700	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.73, 5.26]
5 EFFICACY - WOMAC scales	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 pain 12.5mg 6 weeks	2	488	Mean Difference (IV, Fixed, 95% CI)	10.97 [6.80, 15.14]
5.2 pain 25mg 6 weeks	4	855	Mean Difference (IV, Fixed, 95% CI)	2.83 [1.88, 3.77]
5.3 pain 125mg 6 weeks	1	146	Mean Difference (IV, Fixed, 95% CI)	20.93 [14.65, 27.21]
5.4 pain on walking flat surface 12.5mg 6 weeks	1	318	Mean Difference (IV, Fixed, 95% CI)	15.40 [9.88, 20.92]
5.5 pain on walking flat surface 25mg 6 weeks	1	316	Mean Difference (IV, Fixed, 95% CI)	16.15 [10.62, 21.68]
5.6 physical function 12.5mg 6 weeks	2	488	Mean Difference (IV, Fixed, 95% CI)	9.60 [5.62, 13.58]
5.7 physical function 25mg 6 weeks	4	855	Mean Difference (IV, Fixed, 95% CI)	8.67 [6.61, 10.73]

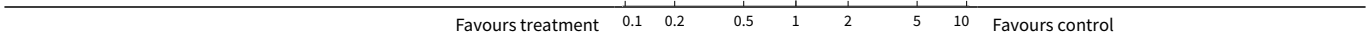
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.8 physical function 125mg 6 weeks	1	146	Mean Difference (IV, Fixed, 95% CI)	20.11 [14.27, 25.95]
5.9 stiffness 12.5mg 6 weeks	2	488	Mean Difference (IV, Fixed, 95% CI)	12.09 [7.52, 16.66]
5.10 stiffness 25mg 6 weeks	4	855	Mean Difference (IV, Fixed, 95% CI)	0.77 [0.33, 1.20]
5.11 stiffness 125mg 6 weeks	1	146	Mean Difference (IV, Fixed, 95% CI)	24.42 [17.24, 31.60]
6 EFFICACY- patient/investigator measures - continuous	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 patient global response 12.5mg 6 weeks	1	318	Mean Difference (IV, Fixed, 95% CI)	0.72 [0.48, 0.96]
6.2 patient global response 25mg 6 weeks	2	461	Mean Difference (IV, Fixed, 95% CI)	1.01 [0.82, 1.21]
6.3 patient global response 125mg 6 weeks	1	146	Mean Difference (IV, Fixed, 95% CI)	1.48 [1.15, 1.81]
6.4 patient pain 25mg 6 weeks	1	145	Mean Difference (IV, Fixed, 95% CI)	20.63 [13.69, 27.57]
6.5 patient pain 125mg 6 weeks	1	146	Mean Difference (IV, Fixed, 95% CI)	22.6 [16.10, 29.10]
6.6 patient disease status 12.5mg 6 weeks	2	488	Mean Difference (IV, Fixed, 95% CI)	15.63 [10.93, 20.34]
6.7 patient disease status 25mg 6 weeks	3	569	Mean Difference (IV, Fixed, 95% CI)	19.06 [15.12, 23.00]
6.8 patient disease status 125mg 6 weeks	1	146	Mean Difference (IV, Fixed, 95% CI)	23.68 [17.37, 29.99]
6.9 patient pain on walking 25mg 6 weeks	1	286	Mean Difference (IV, Fixed, 95% CI)	10.0 [3.41, 16.59]
6.10 investigator global disease status 12.5mg 6 weeks	2	488	Mean Difference (IV, Fixed, 95% CI)	0.47 [0.30, 0.65]
6.11 investigator global disease status 25mg 6 weeks	3	569	Mean Difference (IV, Fixed, 95% CI)	0.70 [0.54, 0.85]
6.12 investigator global disease status 125mg 6 weeks	1	146	Mean Difference (IV, Fixed, 95% CI)	1.05 [0.78, 1.32]
6.13 investigator global response 12.5mg 6 weeks	1	318	Mean Difference (IV, Fixed, 95% CI)	0.74 [0.50, 0.98]

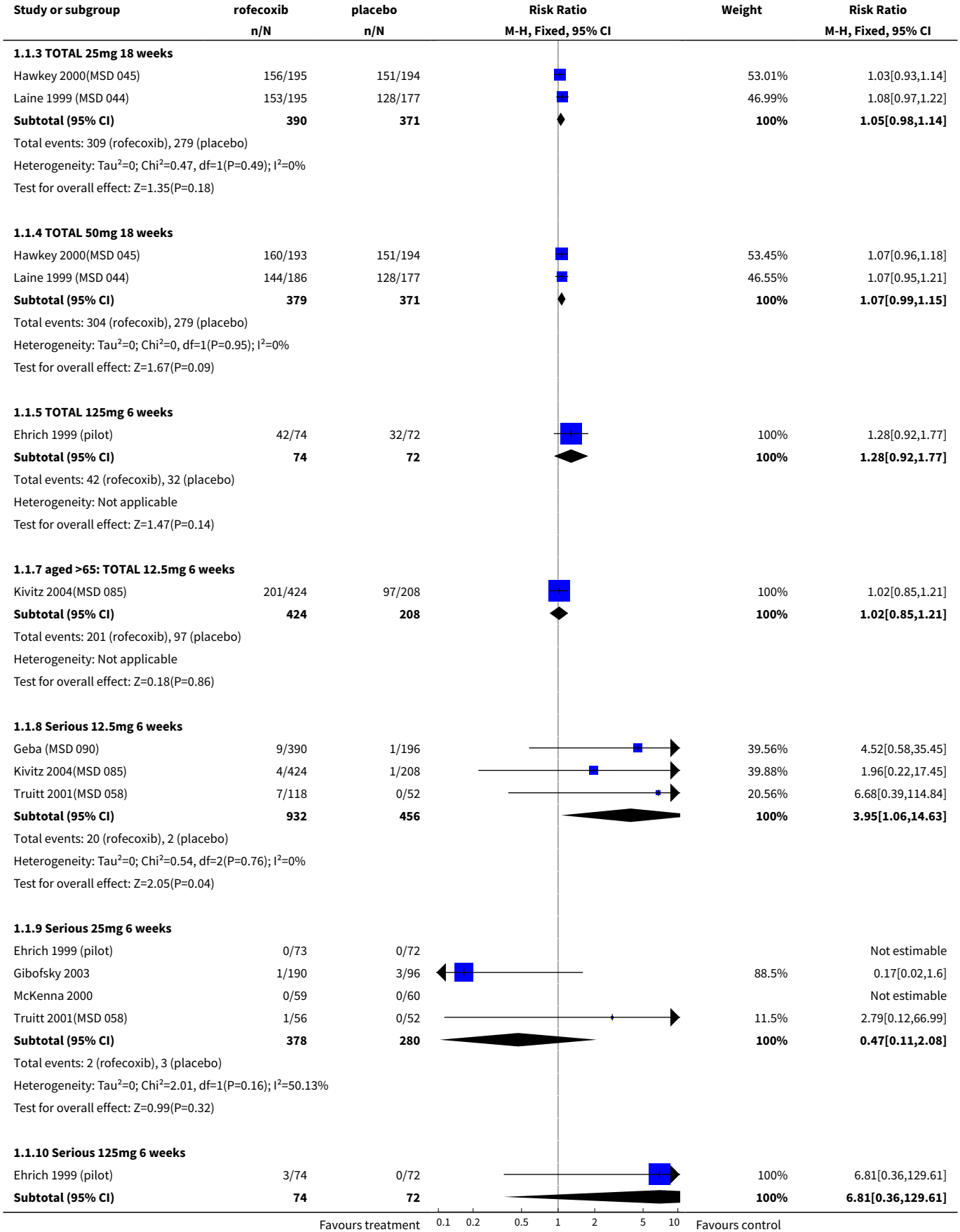
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.14 investigator global response 25mg 6 weeks	2	461	Mean Difference (IV, Fixed, 95% CI)	0.98 [0.77, 1.18]
6.15 investigator global response 125mg 6 weeks	1	146	Mean Difference (IV, Fixed, 95% CI)	1.30 [0.95, 1.65]
7 EFFICACY- patient/investigator measures- dichotomous	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 patient global- good or excellent reponse/improved 12.5 mg 6 weeks	3	1506	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.59, 2.16]
7.2 patient global- good or excellent response 25 mg 6 weeks	2	582	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.35, 2.26]
7.3 patient global- improved pain 12.5 mg 6 weeks	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.4 patient global-improved pain 25 mg 6 weeks	1	119	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.17, 2.08]
7.5 investigator global improved- 25mg 6weeks	1	286	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.96, 1.86]
7.6 investigator global- good or excellent reponse/improved 12.5 mg 6 weeks	1	632	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.50, 2.33]
8 SF 36 PHYSICAL COMPONENT: CHANGE FROM BASELINE	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 5mg	1	264	Mean Difference (IV, Fixed, 95% CI)	2.89 [0.87, 4.91]
8.2 12.5mg	1	254	Mean Difference (IV, Fixed, 95% CI)	3.17 [1.12, 5.22]
8.3 25mg	1	256	Mean Difference (IV, Fixed, 95% CI)	3.15 [1.10, 5.20]
8.4 50mg	1	218	Mean Difference (IV, Fixed, 95% CI)	4.77 [2.52, 7.02]
9 SF 36 MENTALCOMPONENT: CHANGE FROM BASELINE	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 5mg	1	264	Mean Difference (IV, Fixed, 95% CI)	2.45 [0.27, 4.63]
9.2 12.5mg	1	254	Mean Difference (IV, Fixed, 95% CI)	3.08 [0.86, 5.30]
9.3 25mg	1	256	Mean Difference (IV, Fixed, 95% CI)	4.01 [1.79, 6.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.4 50mg	1	218	Mean Difference (IV, Fixed, 95% CI)	4.12 [1.68, 6.56]
10 Use of paracetamol rescue	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 25mg 6 weeks	1	286	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.30, 1.44]
10.2 12.5mg 6 weeks	1	632	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.77, 0.90]
11 Study joint tenderness (0-3)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.1 12.5mg 6 weeks	2	488	Mean Difference (IV, Fixed, 95% CI)	0.31 [0.16, 0.45]
11.2 25mg 6 weeks	2	424	Mean Difference (IV, Fixed, 95% CI)	0.38 [0.23, 0.53]
12 Paracetamol use- tablets per day	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.1 12.5mg 6 weeks	2	488	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.70, -0.26]
12.2 25mg 6 weeks	2	424	Mean Difference (IV, Fixed, 95% CI)	-0.53 [-0.75, -0.30]

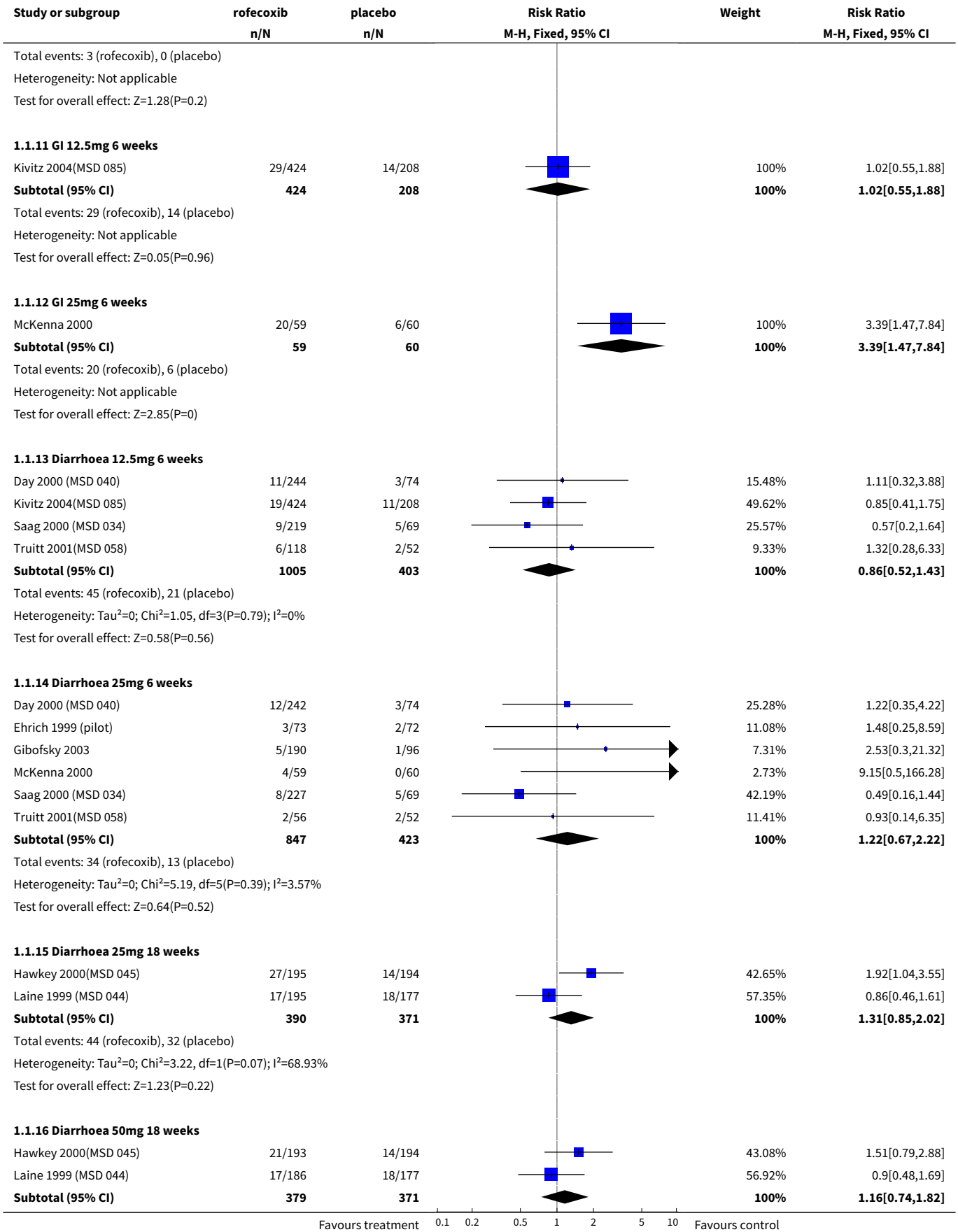
Analysis 1.1. Comparison 1 rofecoxib versus placebo, Outcome 1 ADVERSE EVENTS*.

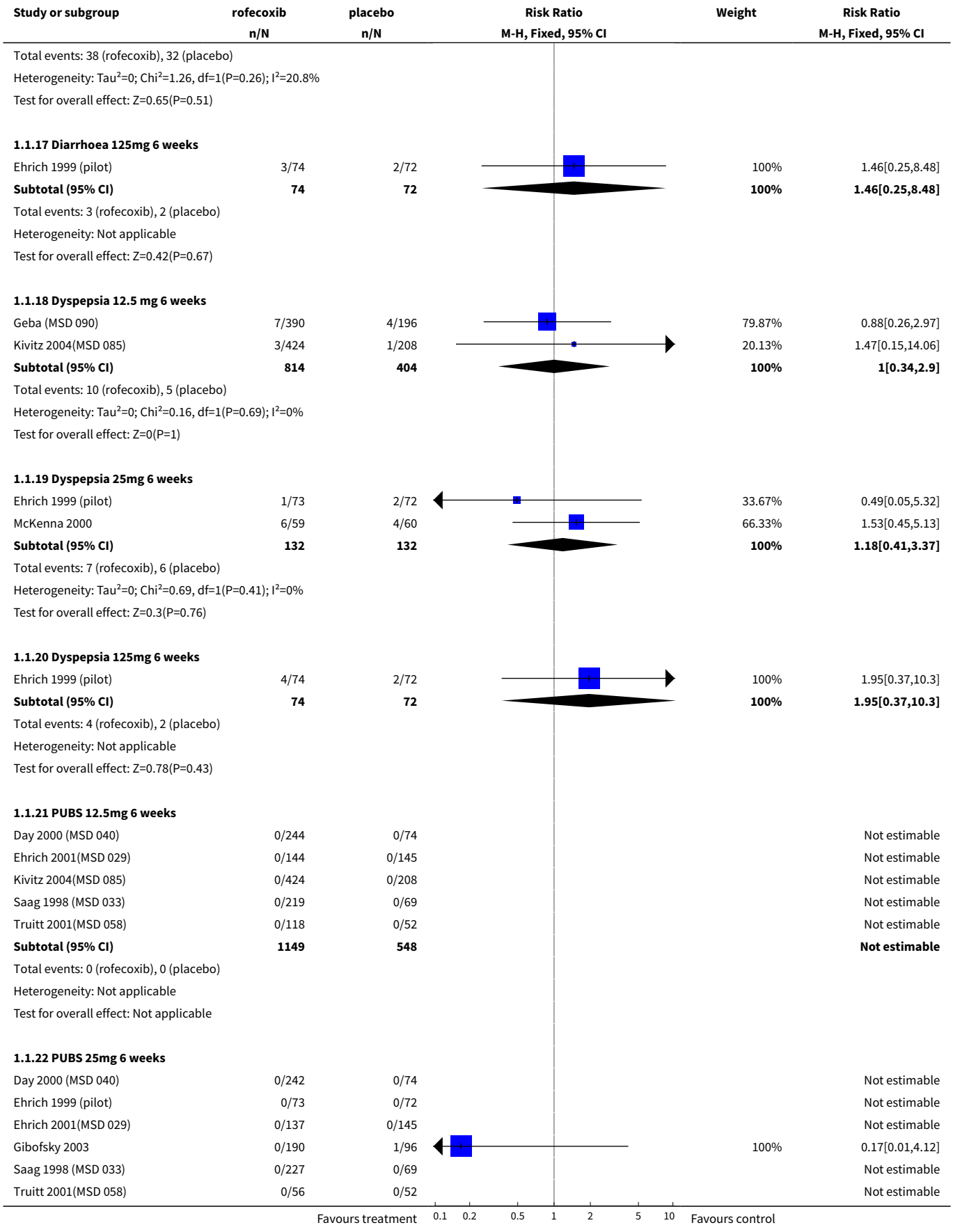
Study or subgroup	rofecoxib n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 TOTAL 12.5mg 6 weeks					
Day 2000 (MSD 040)	124/244	31/74		15.91%	1.21[0.9,1.63]
Geba (MSD 090)	220/390	84/196		37.4%	1.32[1.1,1.58]
Kivitz 2004(MSD 085)	212/424	104/208		46.68%	1[0.85,1.18]
Subtotal (95% CI)	**1058**	**478**		**100%**	**1.15[1.03,1.29]**
Total events: 556 (rofecoxib), 219 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.93, df=2(P=0.08); I^2=59.47%					
Test for overall effect: Z=2.44(P=0.01)					
1.1.2 TOTAL 25mg 6 weeks					
Day 2000 (MSD 040)	129/242	31/74		33.2%	1.27[0.95,1.71]
Ehrich 1999 (pilot)	38/73	32/72		22.53%	1.17[0.83,1.64]
Gibofsky 2003	80/190	29/96		26.94%	1.39[0.99,1.97]
McKenna 2000	36/59	25/60		17.33%	1.46[1.02,2.1]
Subtotal (95% CI)	**564**	**302**		**100%**	**1.32[1.11,1.56]**
Total events: 283 (rofecoxib), 117 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.94, df=3(P=0.82); I^2=0%					
Test for overall effect: Z=3.21(P=0)					

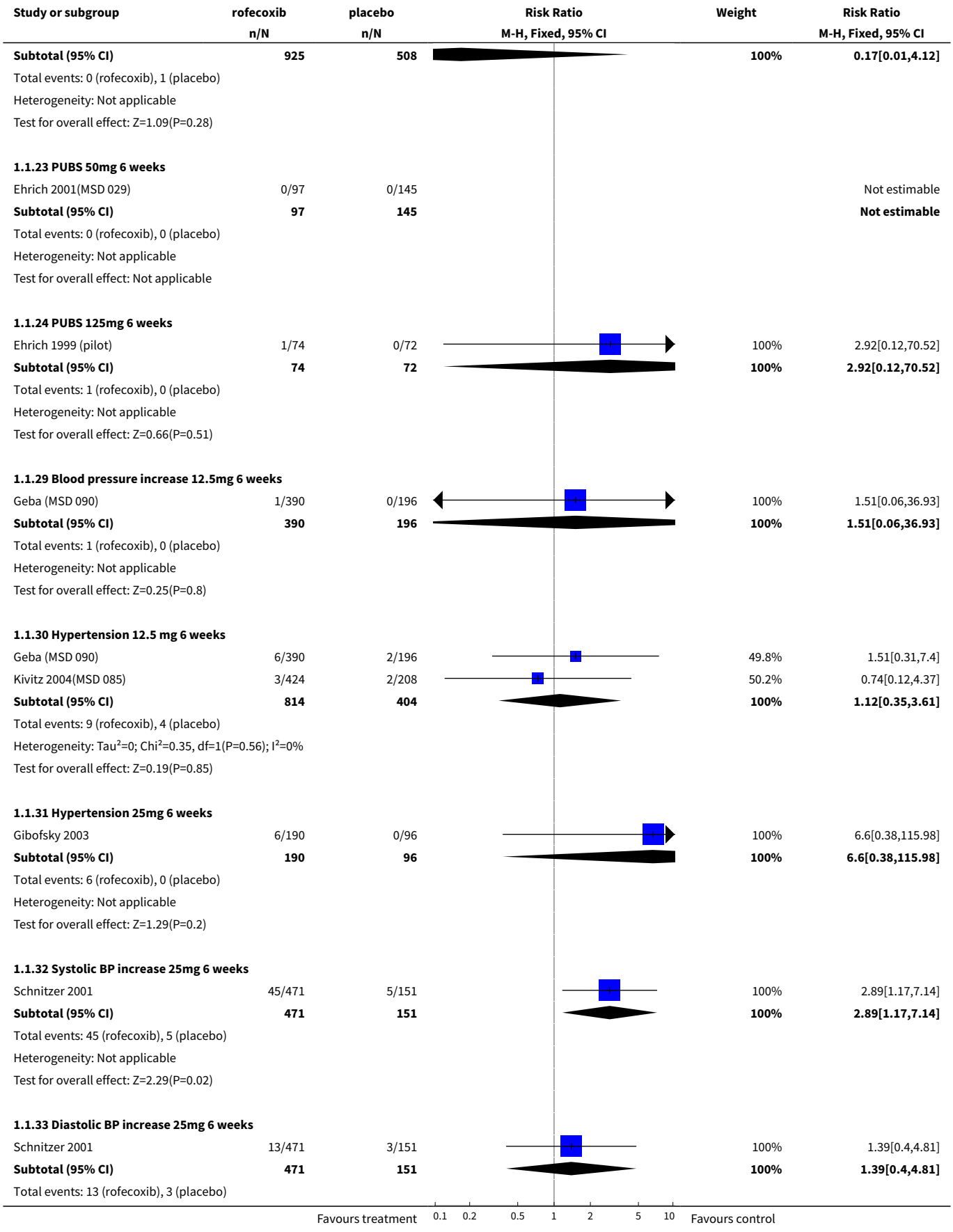


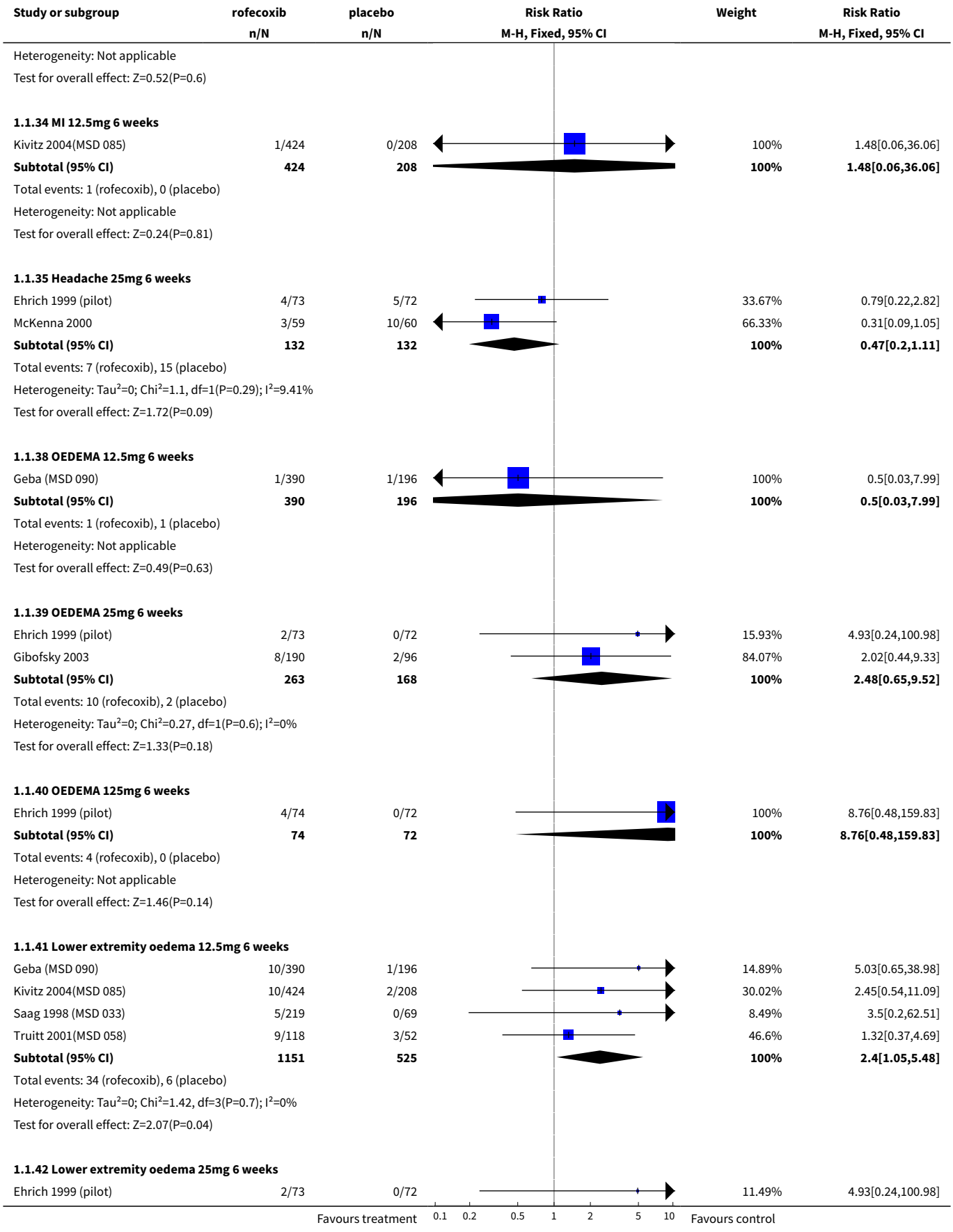


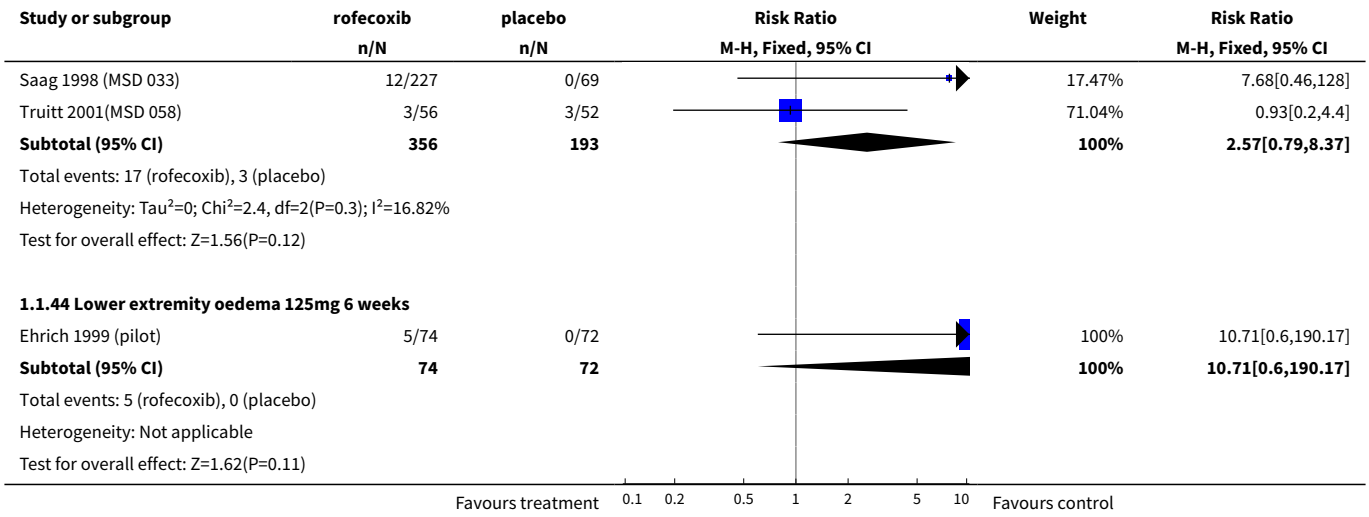
Study or subgroup	rofecoxib n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.3 TOTAL 25mg 18 weeks					
Hawkey 2000(MSD 045)	156/195	151/194		53.01%	1.03[0.93,1.14]
Laine 1999 (MSD 044)	153/195	128/177		46.99%	1.08[0.97,1.22]
Subtotal (95% CI)	**390**	**371**		**100%**	**1.05[0.98,1.14]**
Total events: 309 (rofecoxib), 279 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=1(P=0.49); I^2=0%					
Test for overall effect: Z=1.35(P=0.18)					
1.1.4 TOTAL 50mg 18 weeks					
Hawkey 2000(MSD 045)	160/193	151/194		53.45%	1.07[0.96,1.18]
Laine 1999 (MSD 044)	144/186	128/177		46.55%	1.07[0.95,1.21]
Subtotal (95% CI)	**379**	**371**		**100%**	**1.07[0.99,1.15]**
Total events: 304 (rofecoxib), 279 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.95); I^2=0%					
Test for overall effect: Z=1.67(P=0.09)					
1.1.5 TOTAL 125mg 6 weeks					
Ehrich 1999 (pilot)	42/74	32/72		100%	1.28[0.92,1.77]
Subtotal (95% CI)	**74**	**72**		**100%**	**1.28[0.92,1.77]**
Total events: 42 (rofecoxib), 32 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.47(P=0.14)					
1.1.7 aged >65: TOTAL 12.5mg 6 weeks					
Kivitz 2004(MSD 085)	201/424	97/208		100%	1.02[0.85,1.21]
Subtotal (95% CI)	**424**	**208**		**100%**	**1.02[0.85,1.21]**
Total events: 201 (rofecoxib), 97 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.18(P=0.86)					
1.1.8 Serious 12.5mg 6 weeks					
Geba (MSD 090)	9/390	1/196		39.56%	4.52[0.58,35.45]
Kivitz 2004(MSD 085)	4/424	1/208		39.88%	1.96[0.22,17.45]
Truitt 2001(MSD 058)	7/118	0/52		20.56%	6.68[0.39,114.84]
Subtotal (95% CI)	**932**	**456**		**100%**	**3.95[1.06,14.63]**
Total events: 20 (rofecoxib), 2 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.54, df=2(P=0.76); I^2=0%					
Test for overall effect: Z=2.05(P=0.04)					
1.1.9 Serious 25mg 6 weeks					
Ehrich 1999 (pilot)	0/73	0/72			Not estimable
Gibofsky 2003	1/190	3/96		88.5%	0.17[0.02,1.6]
McKenna 2000	0/59	0/60			Not estimable
Truitt 2001(MSD 058)	1/56	0/52		11.5%	2.79[0.12,66.99]
Subtotal (95% CI)	**378**	**280**		**100%**	**0.47[0.11,2.08]**
Total events: 2 (rofecoxib), 3 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.01, df=1(P=0.16); I^2=50.13%					
Test for overall effect: Z=0.99(P=0.32)					
1.1.10 Serious 125mg 6 weeks					
Ehrich 1999 (pilot)	3/74	0/72		100%	6.81[0.36,129.61]
Subtotal (95% CI)	**74**	**72**		**100%**	**6.81[0.36,129.61]**



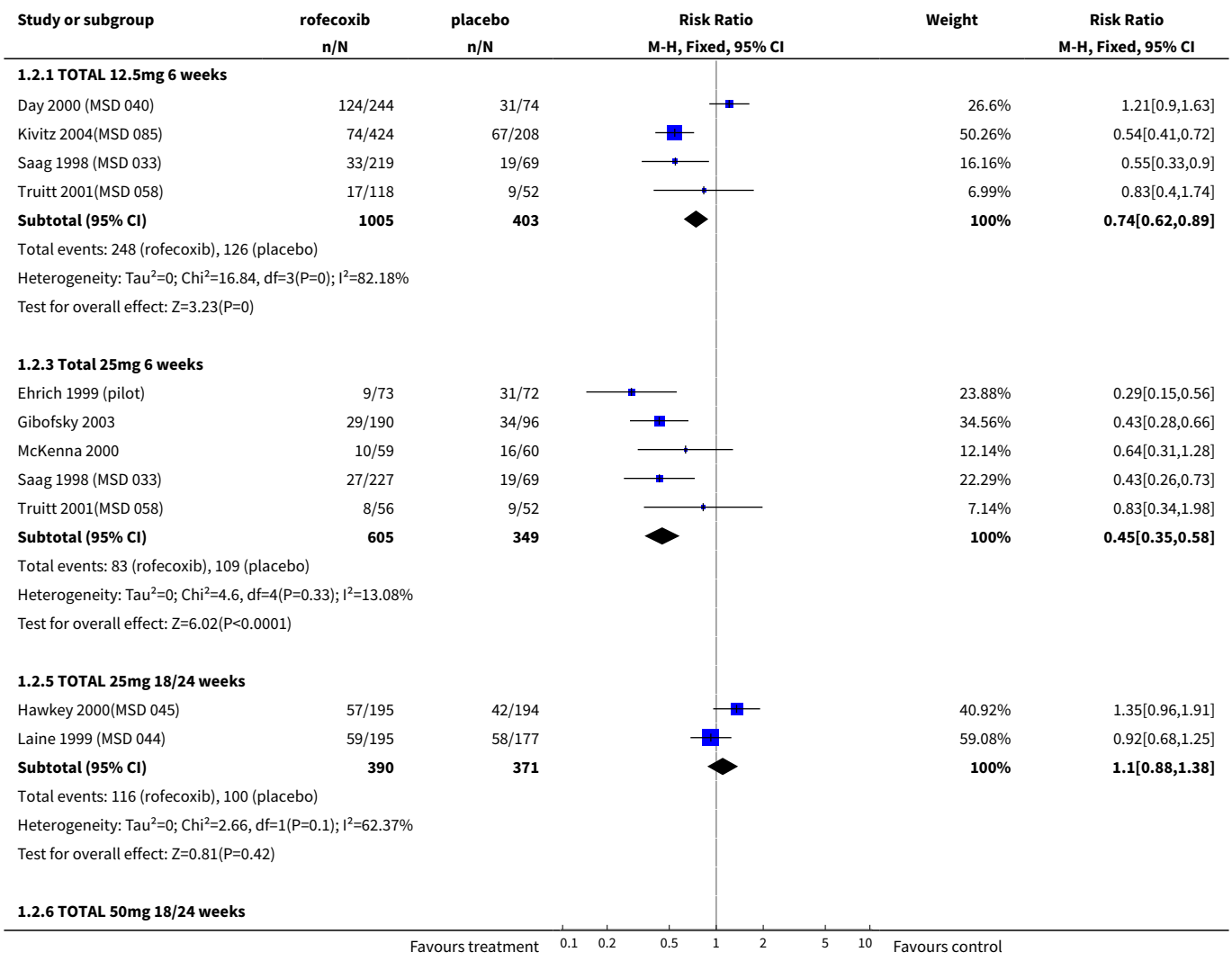


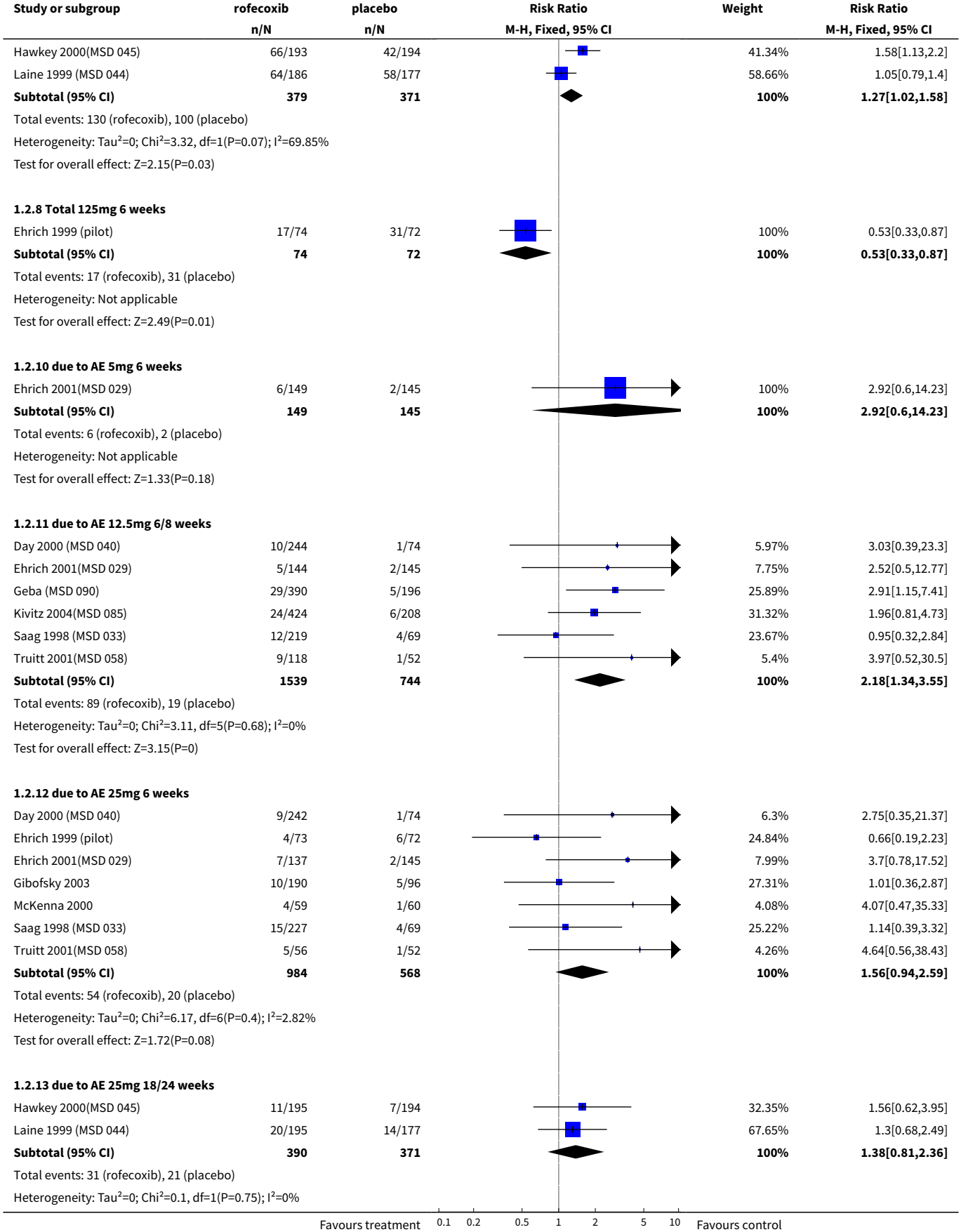




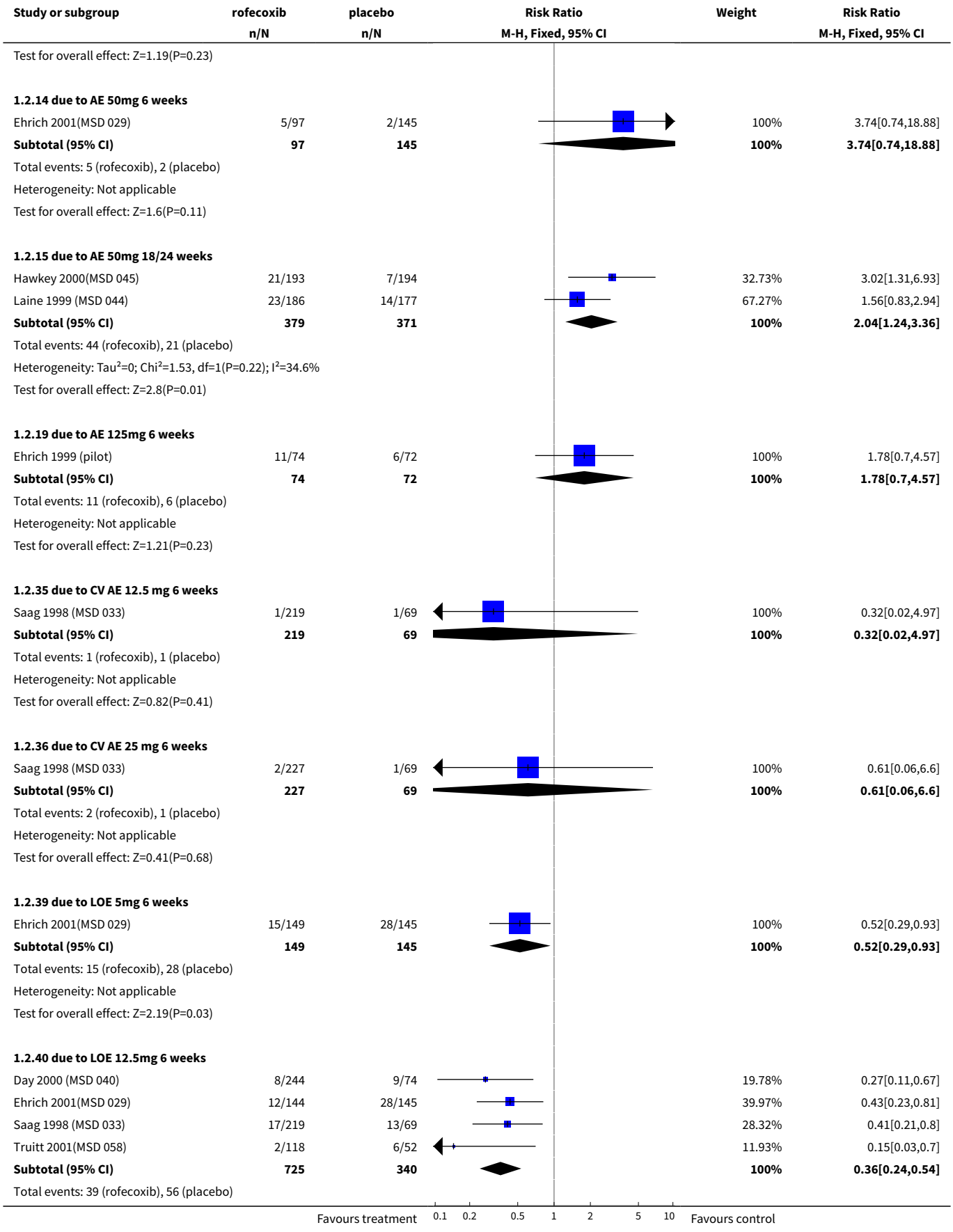


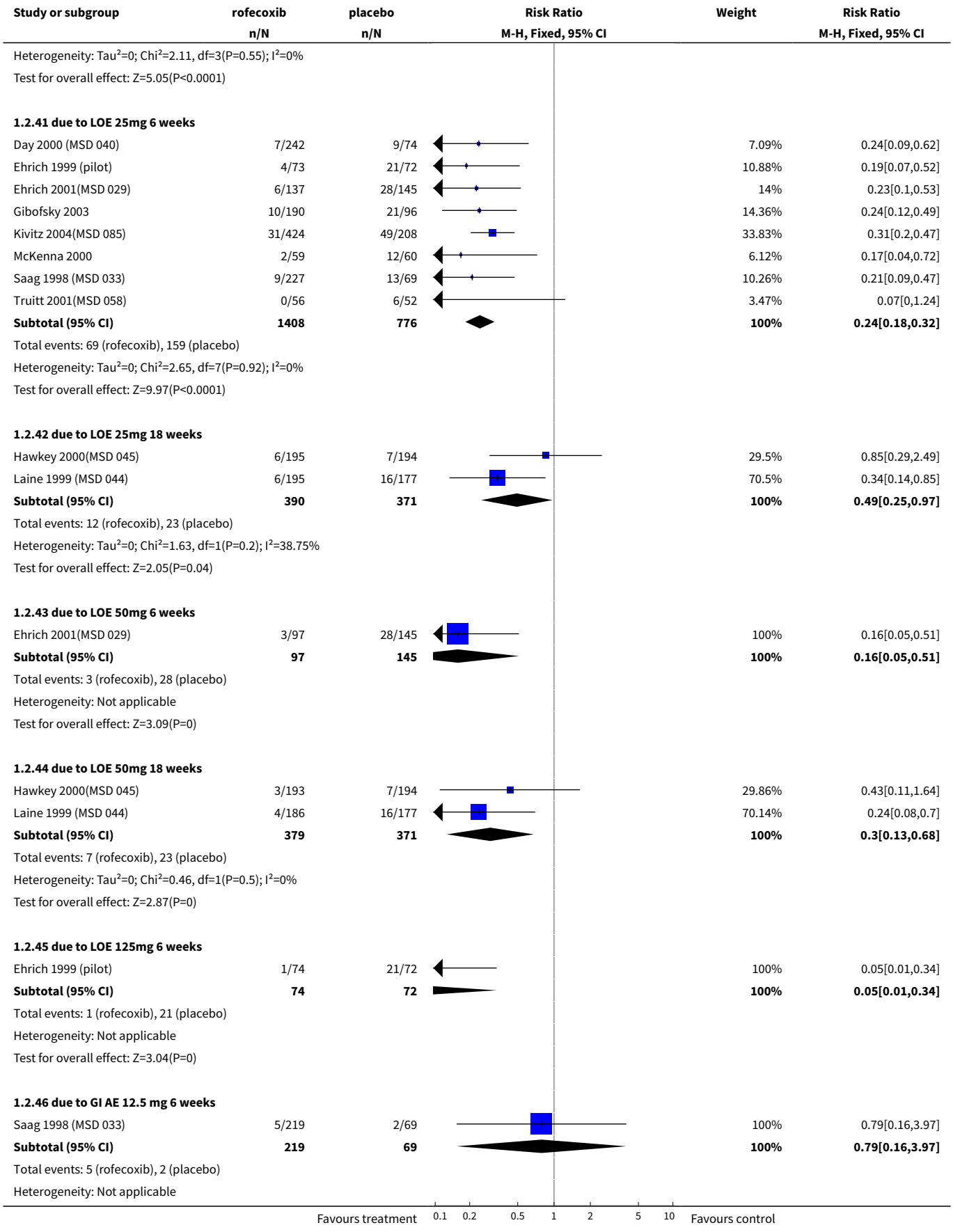
Analysis 1.2. Comparison 1 rofecoxib versus placebo, Outcome 2 WITHDRAWALS*.

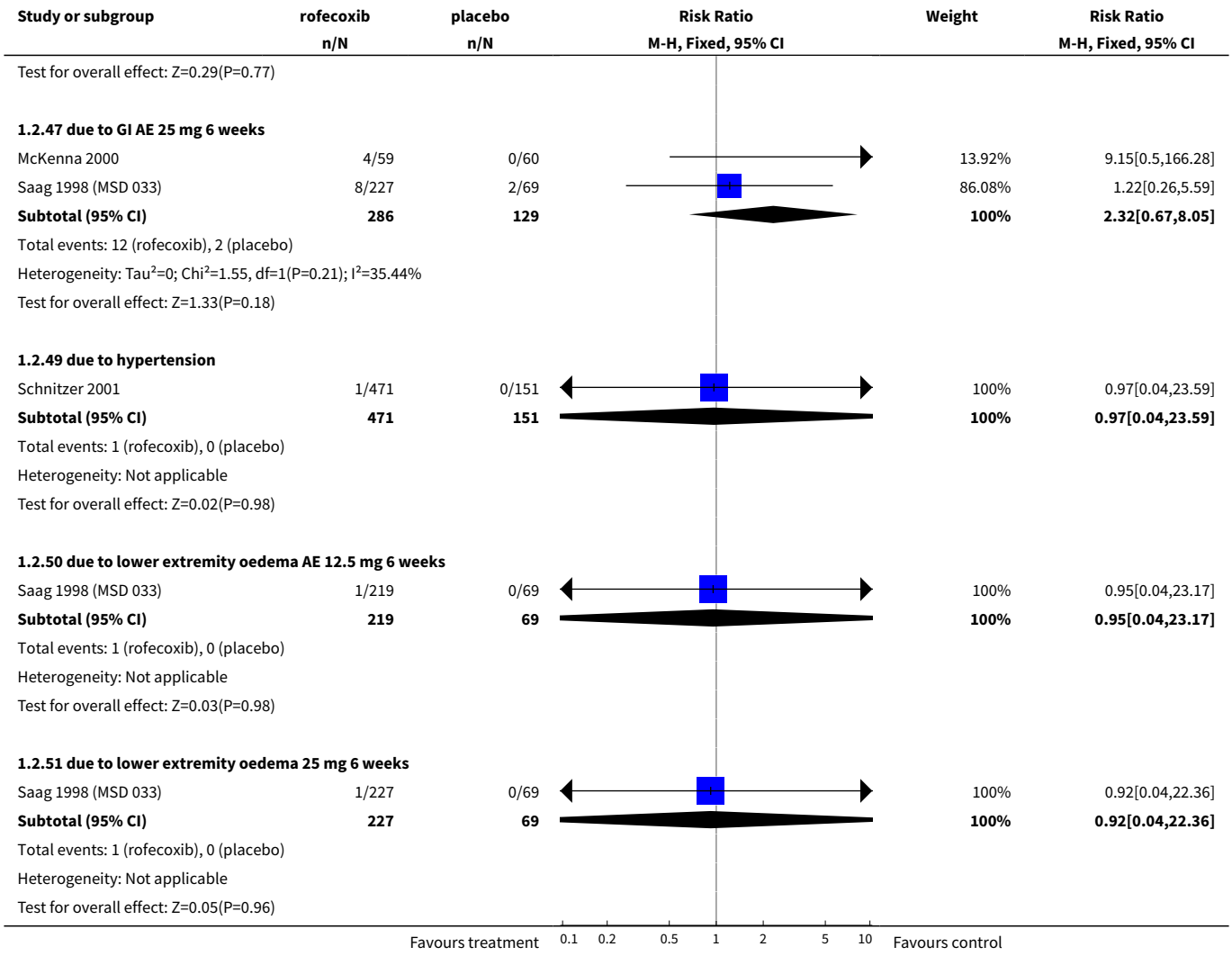




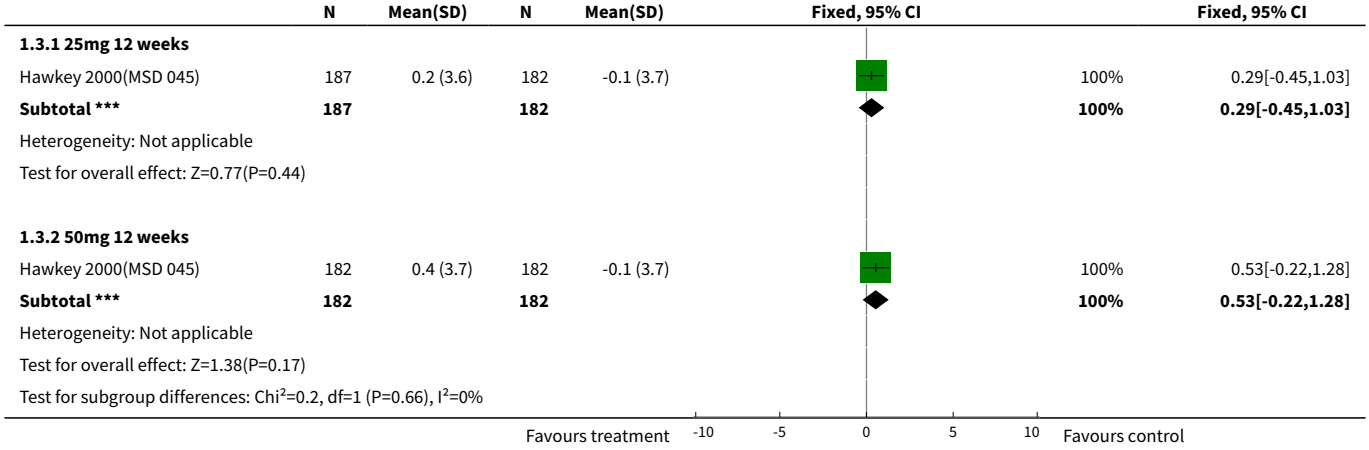
Study or subgroup	rofecoxib n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Hawkey 2000(MSD 045)	66/193	42/194		41.34%	1.58[1.13,2.2]
Laine 1999 (MSD 044)	64/186	58/177		58.66%	1.05[0.79,1.4]
Subtotal (95% CI)	**379**	**371**		**100%**	**1.27[1.02,1.58]**
Total events: 130 (rofecoxib), 100 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.32, df=1(P=0.07); I^2=69.85%					
Test for overall effect: Z=2.15(P=0.03)					
1.2.8 Total 125mg 6 weeks					
Ehrich 1999 (pilot)	17/74	31/72		100%	0.53[0.33,0.87]
Subtotal (95% CI)	**74**	**72**		**100%**	**0.53[0.33,0.87]**
Total events: 17 (rofecoxib), 31 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.49(P=0.01)					
1.2.10 due to AE 5mg 6 weeks					
Ehrich 2001(MSD 029)	6/149	2/145		100%	2.92[0.6,14.23]
Subtotal (95% CI)	**149**	**145**		**100%**	**2.92[0.6,14.23]**
Total events: 6 (rofecoxib), 2 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.33(P=0.18)					
1.2.11 due to AE 12.5mg 6/8 weeks					
Day 2000 (MSD 040)	10/244	1/74		5.97%	3.03[0.39,23.3]
Ehrich 2001(MSD 029)	5/144	2/145		7.75%	2.52[0.5,12.77]
Geba (MSD 090)	29/390	5/196		25.89%	2.91[1.15,7.41]
Kivitz 2004(MSD 085)	24/424	6/208		31.32%	1.96[0.81,4.73]
Saag 1998 (MSD 033)	12/219	4/69		23.67%	0.95[0.32,2.84]
Truitt 2001(MSD 058)	9/118	1/52		5.4%	3.97[0.52,30.5]
Subtotal (95% CI)	**1539**	**744**		**100%**	**2.18[1.34,3.55]**
Total events: 89 (rofecoxib), 19 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.11, df=5(P=0.68); I^2=0%					
Test for overall effect: Z=3.15(P=0)					
1.2.12 due to AE 25mg 6 weeks					
Day 2000 (MSD 040)	9/242	1/74		6.3%	2.75[0.35,21.37]
Ehrich 1999 (pilot)	4/73	6/72		24.84%	0.66[0.19,2.23]
Ehrich 2001(MSD 029)	7/137	2/145		7.99%	3.7[0.78,17.52]
Gibofsky 2003	10/190	5/96		27.31%	1.01[0.36,2.87]
McKenna 2000	4/59	1/60		4.08%	4.07[0.47,35.33]
Saag 1998 (MSD 033)	15/227	4/69		25.22%	1.14[0.39,3.32]
Truitt 2001(MSD 058)	5/56	1/52		4.26%	4.64[0.56,38.43]
Subtotal (95% CI)	**984**	**568**		**100%**	**1.56[0.94,2.59]**
Total events: 54 (rofecoxib), 20 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.17, df=6(P=0.4); I^2=2.82%					
Test for overall effect: Z=1.72(P=0.08)					
1.2.13 due to AE 25mg 18/24 weeks					
Hawkey 2000(MSD 045)	11/195	7/194		32.35%	1.56[0.62,3.95]
Laine 1999 (MSD 044)	20/195	14/177		67.65%	1.3[0.68,2.49]
Subtotal (95% CI)	**390**	**371**		**100%**	**1.38[0.81,2.36]**
Total events: 31 (rofecoxib), 21 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.1, df=1(P=0.75); I^2=0%					





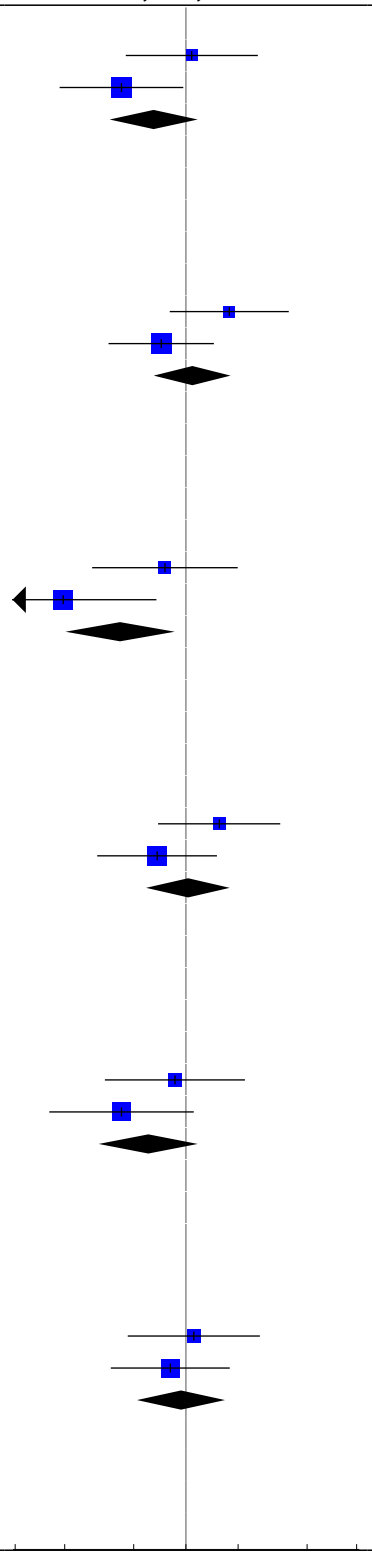


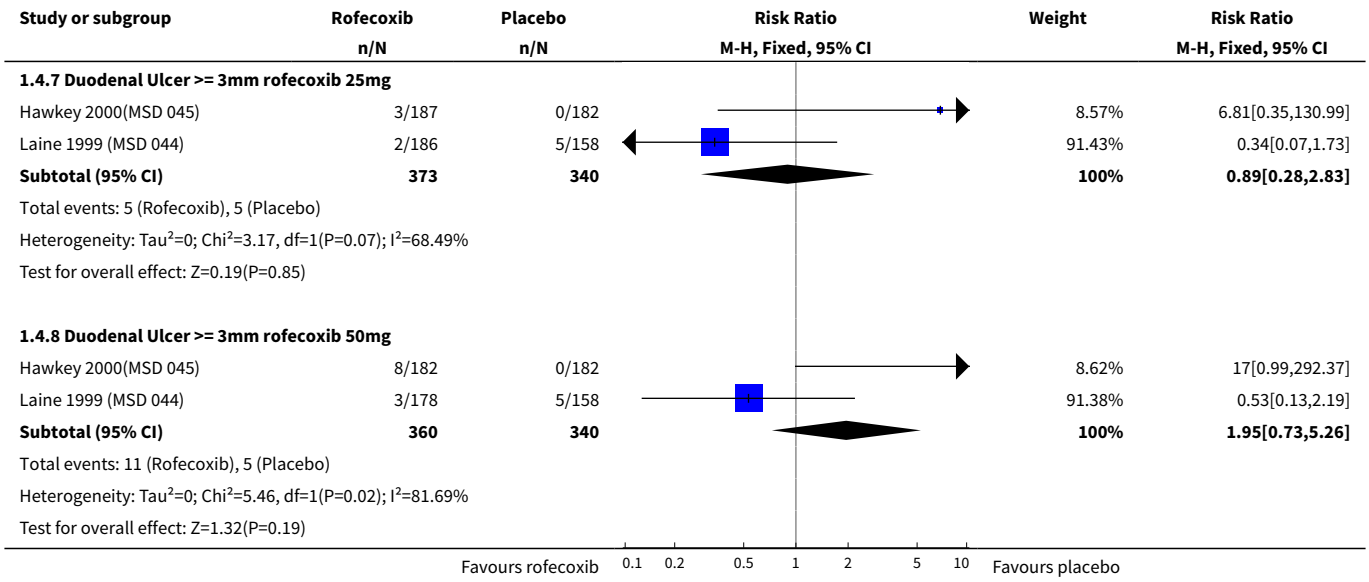
Analysis 1.3. Comparison 1 rofecoxib versus placebo, Outcome 3 Erosions (endoscoped)-change from baseline.



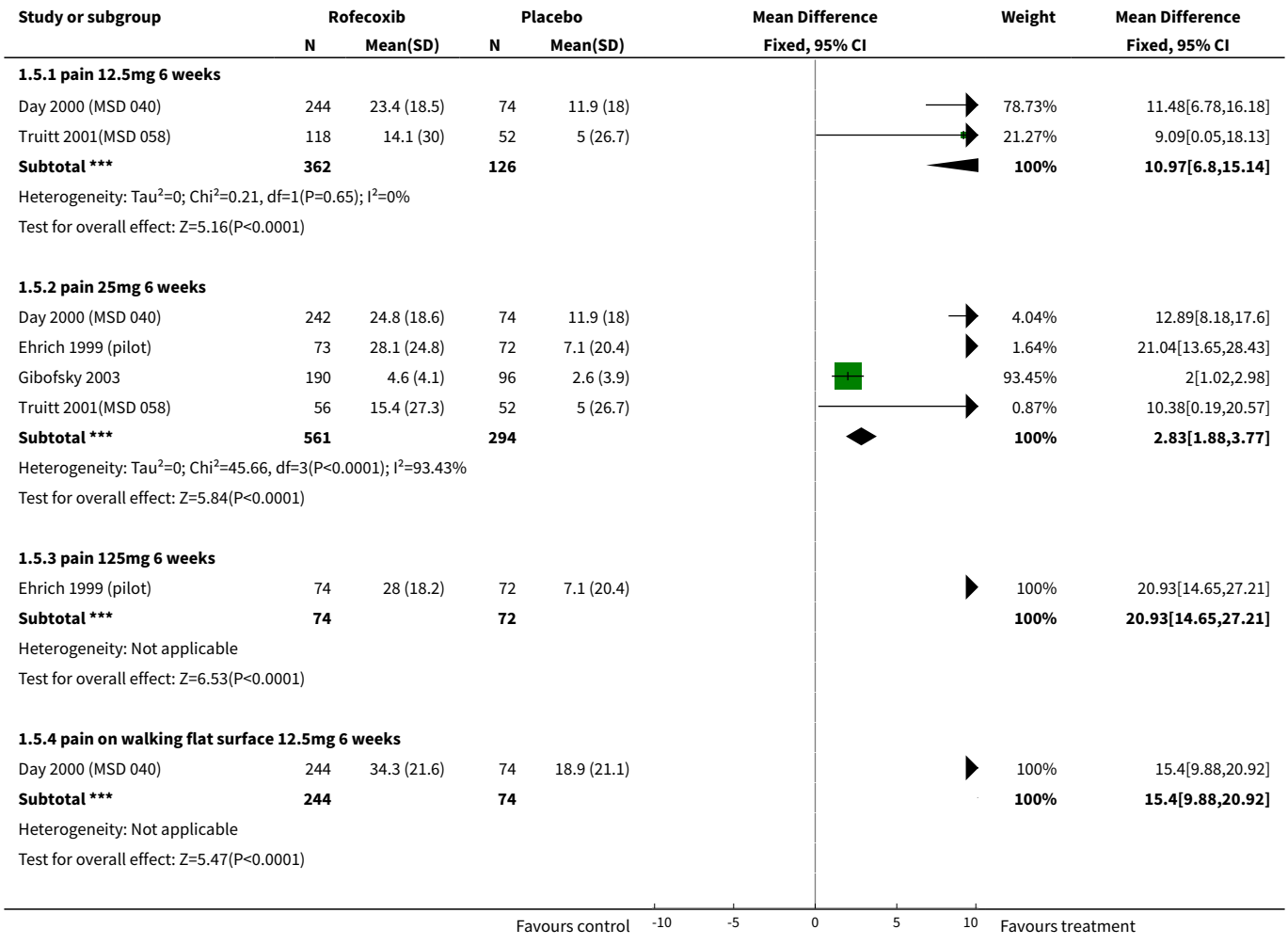
Analysis 1.4. Comparison 1 rofecoxib versus placebo, Outcome 4 Ulcer 12 weeks (endoscoped).

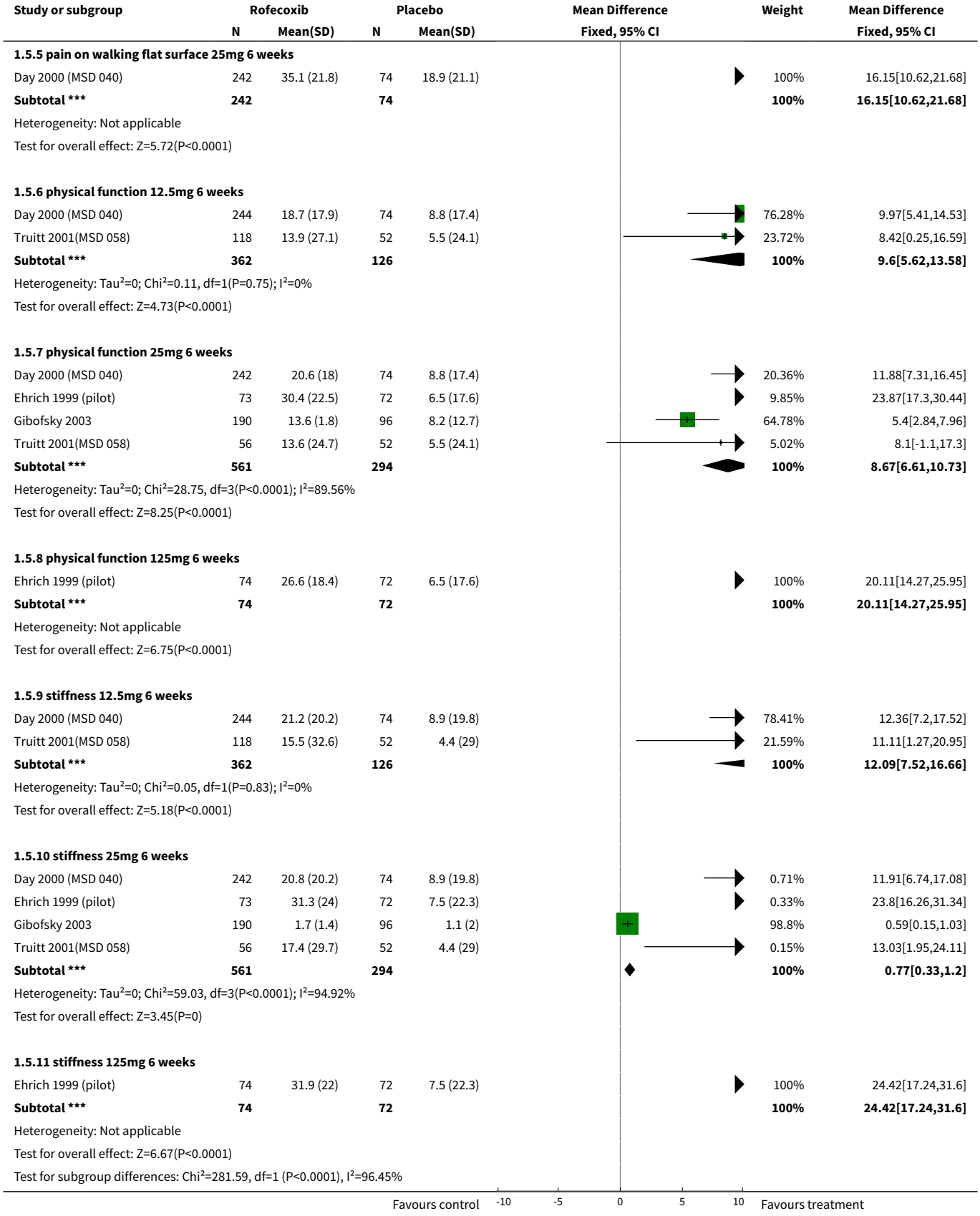
Study or subgroup	Rofecoxib n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Ulcer >= 3mm rofecoxib 25mg					
Hawkey 2000(MSD 045)	10/187	9/182		34.52%	1.08[0.45,2.6]
Laine 1999 (MSD 044)	8/186	16/158		65.48%	0.42[0.19,0.97]
Subtotal (95% CI)	**373**	**340**		**100%**	**0.65[0.36,1.17]**
Total events: 18 (Rofecoxib), 25 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.32, df=1(P=0.13); I^2=56.96%					
Test for overall effect: Z=1.44(P=0.15)					
1.4.2 Ulcer >= 3mm rofecoxib 50mg					
Hawkey 2000(MSD 045)	16/182	9/182		34.68%	1.78[0.81,3.92]
Laine 1999 (MSD 044)	13/178	16/158		65.32%	0.72[0.36,1.45]
Subtotal (95% CI)	**360**	**340**		**100%**	**1.09[0.65,1.81]**
Total events: 29 (Rofecoxib), 25 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.81, df=1(P=0.09); I^2=64.4%					
Test for overall effect: Z=0.32(P=0.75)					
1.4.3 Ulcer >= 5mm rofecoxib 25mg					
Hawkey 2000(MSD 045)	7/187	9/182		39.35%	0.76[0.29,1.99]
Laine 1999 (MSD 044)	3/186	13/158		60.65%	0.2[0.06,0.68]
Subtotal (95% CI)	**373**	**340**		**100%**	**0.42[0.2,0.86]**
Total events: 10 (Rofecoxib), 22 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.89, df=1(P=0.09); I^2=65.43%					
Test for overall effect: Z=2.36(P=0.02)					
1.4.4 Ulcer >=5mm rofecoxib 50mg					
Hawkey 2000(MSD 045)	14/182	9/182		39.52%	1.56[0.69,3.5]
Laine 1999 (MSD 044)	10/178	13/158		60.48%	0.68[0.31,1.51]
Subtotal (95% CI)	**360**	**340**		**100%**	**1.03[0.59,1.79]**
Total events: 24 (Rofecoxib), 22 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.01, df=1(P=0.16); I^2=50.37%					
Test for overall effect: Z=0.1(P=0.92)					
1.4.5 Gastric Ulcer >= 3mm rofecoxib 25mg					
Hawkey 2000(MSD 045)	8/187	9/182		41.28%	0.87[0.34,2.19]
Laine 1999 (MSD 044)	6/186	12/158		58.72%	0.42[0.16,1.11]
Subtotal (95% CI)	**373**	**340**		**100%**	**0.61[0.31,1.17]**
Total events: 14 (Rofecoxib), 21 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.09, df=1(P=0.3); I^2=8.47%					
Test for overall effect: Z=1.49(P=0.14)					
1.4.6 Gastric Ulcer >= 3mm rofecoxib 50mg					
Hawkey 2000(MSD 045)	10/182	9/182		41.45%	1.11[0.46,2.67]
Laine 1999 (MSD 044)	11/178	12/158		58.55%	0.81[0.37,1.79]
Subtotal (95% CI)	**360**	**340**		**100%**	**0.94[0.52,1.68]**
Total events: 21 (Rofecoxib), 21 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.27, df=1(P=0.6); I^2=0%					
Test for overall effect: Z=0.22(P=0.83)					





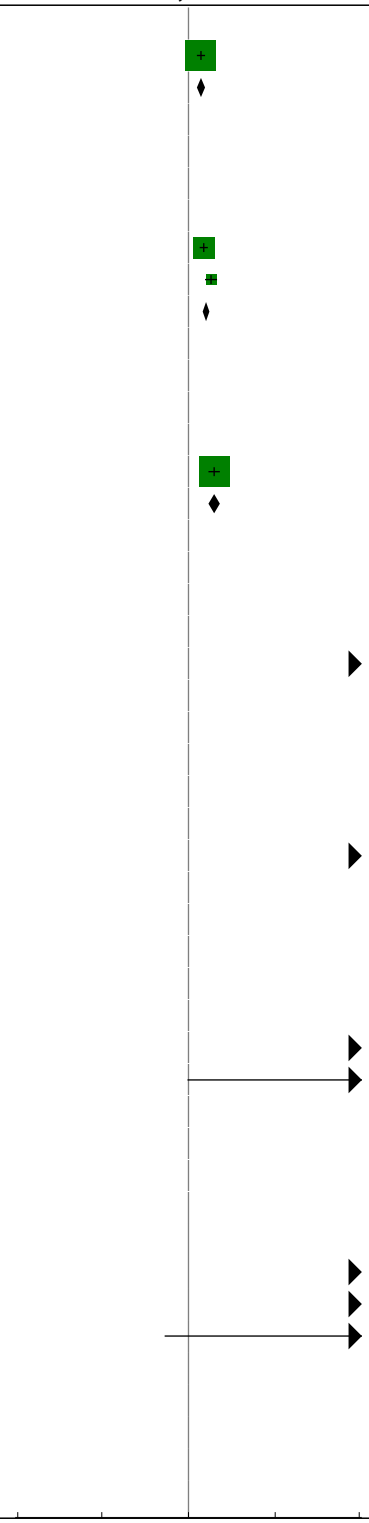
Analysis 1.5. Comparison 1 rofecoxib versus placebo, Outcome 5 EFFICACY - WOMAC scales.

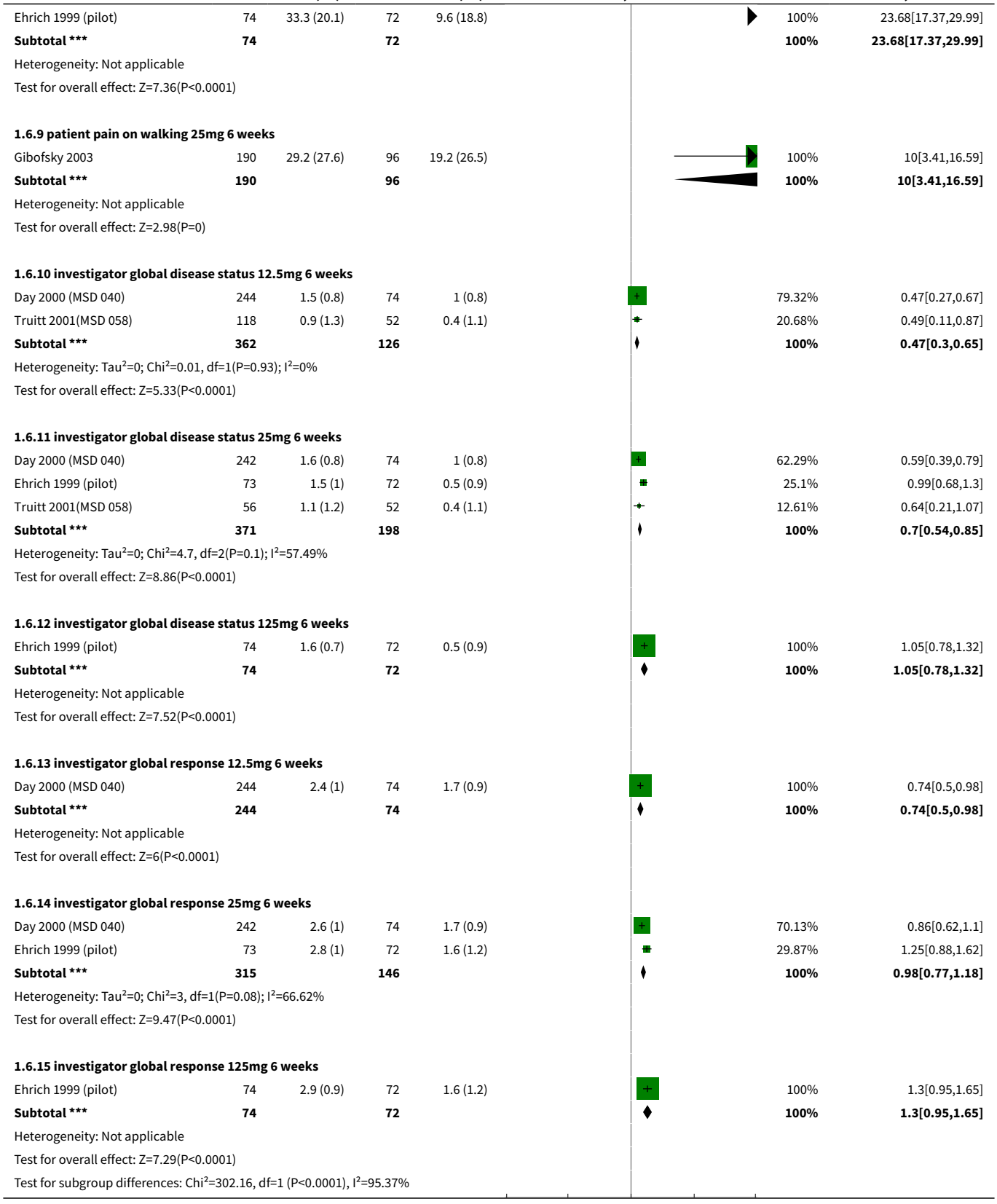




Analysis 1.6. Comparison 1 rofecoxib versus placebo, Outcome 6 EFFICACY- patient/investigator measures - continuous.

Study or subgroup	Rofecoxib N	Rofecoxib Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.6.1 patient global response 12.5mg 6 weeks							
Day 2000 (MSD 040)	244	2.3 (0.9)	74	1.6 (0.9)		100%	0.72[0.48,0.96]
Subtotal ***	**244**		**74**			**100%**	**0.72[0.48,0.96]**
Heterogeneity: Not applicable							
Test for overall effect: Z=6(P<0.0001)							
1.6.2 patient global response 25mg 6 weeks							
Day 2000 (MSD 040)	242	2.4 (0.9)	74	1.6 (0.9)		68.57%	0.88[0.65,1.11]
Ehrich 1999 (pilot)	73	2.6 (0.9)	72	1.3 (1.2)		31.43%	1.3[0.95,1.65]
Subtotal ***	**315**		**146**			**100%**	**1.01[0.82,1.21]**
Heterogeneity: Tau^2=0; Chi^2=3.86, df=1(P=0.05); I^2=74.09%							
Test for overall effect: Z=10.2(P<0.0001)							
1.6.3 patient global response 125mg 6 weeks							
Ehrich 1999 (pilot)	74	2.8 (0.8)	72	1.3 (1.2)		100%	1.48[1.15,1.81]
Subtotal ***	**74**		**72**			**100%**	**1.48[1.15,1.81]**
Heterogeneity: Not applicable							
Test for overall effect: Z=8.81(P<0.0001)							
1.6.4 patient pain 25mg 6 weeks							
Ehrich 1999 (pilot)	73	36 (21.7)	72	15.4 (21)		100%	20.63[13.69,27.57]
Subtotal ***	**73**		**72**			**100%**	**20.63[13.69,27.57]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.82(P<0.0001)							
1.6.5 patient pain 125mg 6 weeks							
Ehrich 1999 (pilot)	74	38 (19)	72	15.4 (21)		100%	22.6[16.1,29.1]
Subtotal ***	**74**		**72**			**100%**	**22.6[16.1,29.1]**
Heterogeneity: Not applicable							
Test for overall effect: Z=6.81(P<0.0001)							
1.6.6 patient disease status 12.5mg 6 weeks							
Day 2000 (MSD 040)	244	26.9 (20.6)	74	10 (20.1)		80.1%	16.91[11.65,22.17]
Truitt 2001(MSD 058)	118	25.3 (34.7)	52	14.9 (31.2)		19.9%	10.49[-0.06,21.04]
Subtotal ***	**362**		**126**			**100%**	**15.63[10.93,20.34]**
Heterogeneity: Tau^2=0; Chi^2=1.14, df=1(P=0.29); I^2=12.28%							
Test for overall effect: Z=6.51(P<0.0001)							
1.6.7 patient disease status 25mg 6 weeks							
Day 2000 (MSD 040)	242	29.1 (20.8)	74	10 (20.1)		55.86%	19.03[13.76,24.3]
Ehrich 1999 (pilot)	73	31.5 (23)	72	9.6 (18.8)		33.23%	21.9[15.07,28.73]
Truitt 2001(MSD 058)	56	25.4 (32)	52	14.9 (31.2)		10.91%	10.55[-1.37,22.47]
Subtotal ***	**371**		**198**			**100%**	**19.06[15.12,23]**
Heterogeneity: Tau^2=0; Chi^2=2.62, df=2(P=0.27); I^2=23.67%							
Test for overall effect: Z=9.48(P<0.0001)							
1.6.8 patient disease status 125mg 6 weeks							

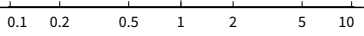




Study or subgroup	Rofecoxib N	Rofecoxib Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Ehrich 1999 (pilot)	74	33.3 (20.1)	72	9.6 (18.8)		100%	23.68[17.37,29.99]
Subtotal ***	**74**		**72**			**100%**	**23.68[17.37,29.99]**
Heterogeneity: Not applicable							
Test for overall effect: Z=7.36(P<0.0001)							
1.6.9 patient pain on walking 25mg 6 weeks							
Gibofsky 2003	190	29.2 (27.6)	96	19.2 (26.5)		100%	10[3.41,16.59]
Subtotal ***	**190**		**96**			**100%**	**10[3.41,16.59]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.98(P=0)							
1.6.10 investigator global disease status 12.5mg 6 weeks							
Day 2000 (MSD 040)	244	1.5 (0.8)	74	1 (0.8)		79.32%	0.47[0.27,0.67]
Truitt 2001(MSD 058)	118	0.9 (1.3)	52	0.4 (1.1)		20.68%	0.49[0.11,0.87]
Subtotal ***	**362**		**126**			**100%**	**0.47[0.3,0.65]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.93); I^2=0%							
Test for overall effect: Z=5.33(P<0.0001)							
1.6.11 investigator global disease status 25mg 6 weeks							
Day 2000 (MSD 040)	242	1.6 (0.8)	74	1 (0.8)		62.29%	0.59[0.39,0.79]
Ehrich 1999 (pilot)	73	1.5 (1)	72	0.5 (0.9)		25.1%	0.99[0.68,1.3]
Truitt 2001(MSD 058)	56	1.1 (1.2)	52	0.4 (1.1)		12.61%	0.64[0.21,1.07]
Subtotal ***	**371**		**198**			**100%**	**0.7[0.54,0.85]**
Heterogeneity: Tau^2=0; Chi^2=4.7, df=2(P=0.1); I^2=57.49%							
Test for overall effect: Z=8.86(P<0.0001)							
1.6.12 investigator global disease status 125mg 6 weeks							
Ehrich 1999 (pilot)	74	1.6 (0.7)	72	0.5 (0.9)		100%	1.05[0.78,1.32]
Subtotal ***	**74**		**72**			**100%**	**1.05[0.78,1.32]**
Heterogeneity: Not applicable							
Test for overall effect: Z=7.52(P<0.0001)							
1.6.13 investigator global response 12.5mg 6 weeks							
Day 2000 (MSD 040)	244	2.4 (1)	74	1.7 (0.9)		100%	0.74[0.5,0.98]
Subtotal ***	**244**		**74**			**100%**	**0.74[0.5,0.98]**
Heterogeneity: Not applicable							
Test for overall effect: Z=6(P<0.0001)							
1.6.14 investigator global response 25mg 6 weeks							
Day 2000 (MSD 040)	242	2.6 (1)	74	1.7 (0.9)		70.13%	0.86[0.62,1.1]
Ehrich 1999 (pilot)	73	2.8 (1)	72	1.6 (1.2)		29.87%	1.25[0.88,1.62]
Subtotal ***	**315**		**146**			**100%**	**0.98[0.77,1.18]**
Heterogeneity: Tau^2=0; Chi^2=3, df=1(P=0.08); I^2=66.62%							
Test for overall effect: Z=9.47(P<0.0001)							
1.6.15 investigator global response 125mg 6 weeks							
Ehrich 1999 (pilot)	74	2.9 (0.9)	72	1.6 (1.2)		100%	1.3[0.95,1.65]
Subtotal ***	**74**		**72**			**100%**	**1.3[0.95,1.65]**
Heterogeneity: Not applicable							
Test for overall effect: Z=7.29(P<0.0001)							
Test for subgroup differences: Chi^2=302.16, df=1 (P<0.0001), I^2=95.37%							

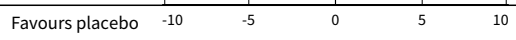
Analysis 1.7. Comparison 1 rofecoxib versus placebo, Outcome 7 EFFICACY- patient/investigator measures- dichotomous.

Study or subgroup	Rofecoxib n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 patient global- good or excellent reponse/improved 12.5 mg 6 weeks					
Geba (MSD 090)	197/390	58/196		41.55%	1.71[1.35,2.16]
Kivitz 2004(MSD 085)	235/424	56/208		40.44%	2.06[1.62,2.62]
Saag 1998 (MSD 033)	120/219	22/69		18.01%	1.72[1.19,2.48]
Subtotal (95% CI)	**1033**	**473**		**100%**	**1.85[1.59,2.16]**
Total events: 552 (Rofecoxib), 136 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.36, df=2(P=0.51); I^2=0%					
Test for overall effect: Z=7.89(P<0.0001)					
1.7.2 patient global- good or excellent response 25 mg 6 weeks					
Gibofsky 2003	82/190	26/96		50.59%	1.59[1.1,2.3]
Saag 1998 (MSD 033)	138/227	22/69		49.41%	1.91[1.33,2.73]
Subtotal (95% CI)	**417**	**165**		**100%**	**1.75[1.35,2.26]**
Total events: 220 (Rofecoxib), 48 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=1(P=0.49); I^2=0%					
Test for overall effect: Z=4.26(P<0.0001)					
1.7.3 patient global- improved pain 12.5 mg 6 weeks					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Rofecoxib), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.7.4 patient global-improved pain 25 mg 6 weeks					
McKenna 2000	46/59	30/60		100%	1.56[1.17,2.08]
Subtotal (95% CI)	**59**	**60**		**100%**	**1.56[1.17,2.08]**
Total events: 46 (Rofecoxib), 30 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.03(P=0)					
1.7.5 investigator global improved- 25mg 6weeks					
Gibofsky 2003	82/190	31/96		100%	1.34[0.96,1.86]
Subtotal (95% CI)	**190**	**96**		**100%**	**1.34[0.96,1.86]**
Total events: 82 (Rofecoxib), 31 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.71(P=0.09)					
1.7.6 investigator global- good or excellent reponse/improved 12.5 mg 6 weeks					
Kivitz 2004(MSD 085)	244/424	64/208		100%	1.87[1.5,2.33]
Subtotal (95% CI)	**424**	**208**		**100%**	**1.87[1.5,2.33]**
Total events: 244 (Rofecoxib), 64 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=5.59(P<0.0001)					



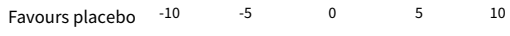
Analysis 1.8. Comparison 1 rofecoxib versus placebo, Outcome 8 SF 36 PHYSICAL COMPONENT: CHANGE FROM BASELINE.

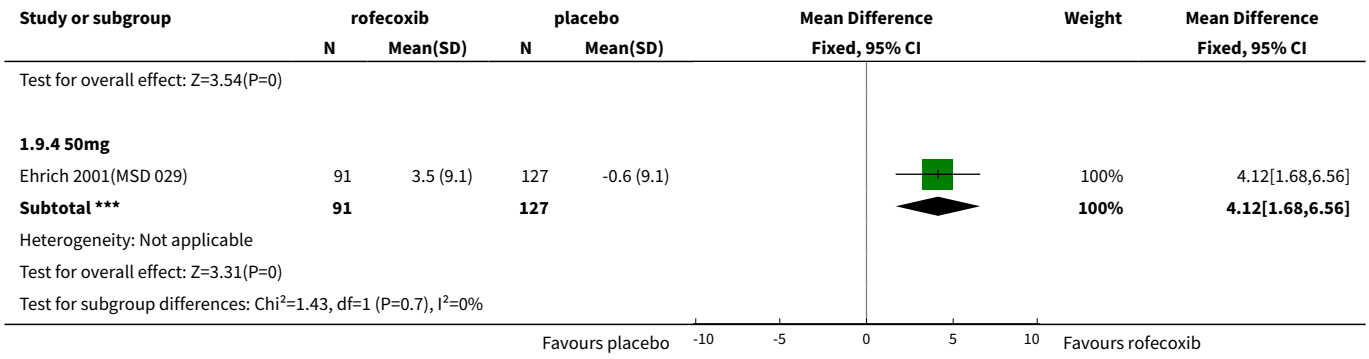
Study or subgroup	rofecoxib N	rofecoxib Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.8.1 5mg							
Ehrich 2001(MSD 029)	137	6 (8.4)	127	3.1 (8.4)		100%	2.89[0.87,4.91]
Subtotal ***	**137**		**127**			**100%**	**2.89[0.87,4.91]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.8(P=0.01)							
1.8.2 12.5mg							
Ehrich 2001(MSD 029)	127	6.2 (8.3)	127	3.1 (8.4)		100%	3.17[1.12,5.22]
Subtotal ***	**127**		**127**			**100%**	**3.17[1.12,5.22]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.02(P=0)							
1.8.3 25mg							
Ehrich 2001(MSD 029)	129	6.2 (8.4)	127	3.1 (8.4)		100%	3.15[1.1,5.2]
Subtotal ***	**129**		**127**			**100%**	**3.15[1.1,5.2]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.01(P=0)							
1.8.4 50mg							
Ehrich 2001(MSD 029)	91	7.8 (8.4)	127	3.1 (8.4)		100%	4.77[2.52,7.02]
Subtotal ***	**91**		**127**			**100%**	**4.77[2.52,7.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.15(P<0.0001)							
Test for subgroup differences: Chi^2=1.77, df=1 (P=0.62), I^2=0%							



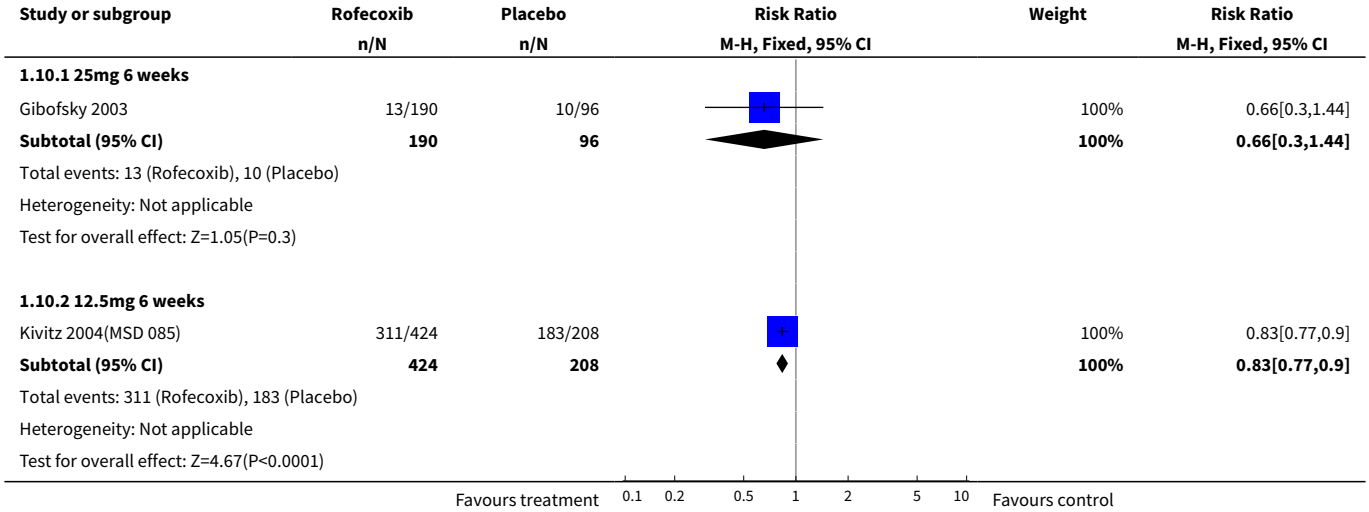
Analysis 1.9. Comparison 1 rofecoxib versus placebo, Outcome 9 SF 36 MENTALCOMPONENT: CHANGE FROM BASELINE.

Study or subgroup	rofecoxib N	rofecoxib Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.9.1 5mg							
Ehrich 2001(MSD 029)	137	1.8 (9)	127	-0.6 (9.1)		100%	2.45[0.27,4.63]
Subtotal ***	**137**		**127**			**100%**	**2.45[0.27,4.63]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.2(P=0.03)							
1.9.2 12.5mg							
Ehrich 2001(MSD 029)	127	2.5 (9)	127	-0.6 (9.1)		100%	3.08[0.86,5.3]
Subtotal ***	**127**		**127**			**100%**	**3.08[0.86,5.3]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.71(P=0.01)							
1.9.3 25mg							
Ehrich 2001(MSD 029)	129	3.4 (9)	127	-0.6 (9.1)		100%	4.01[1.79,6.23]
Subtotal ***	**129**		**127**			**100%**	**4.01[1.79,6.23]**
Heterogeneity: Not applicable							

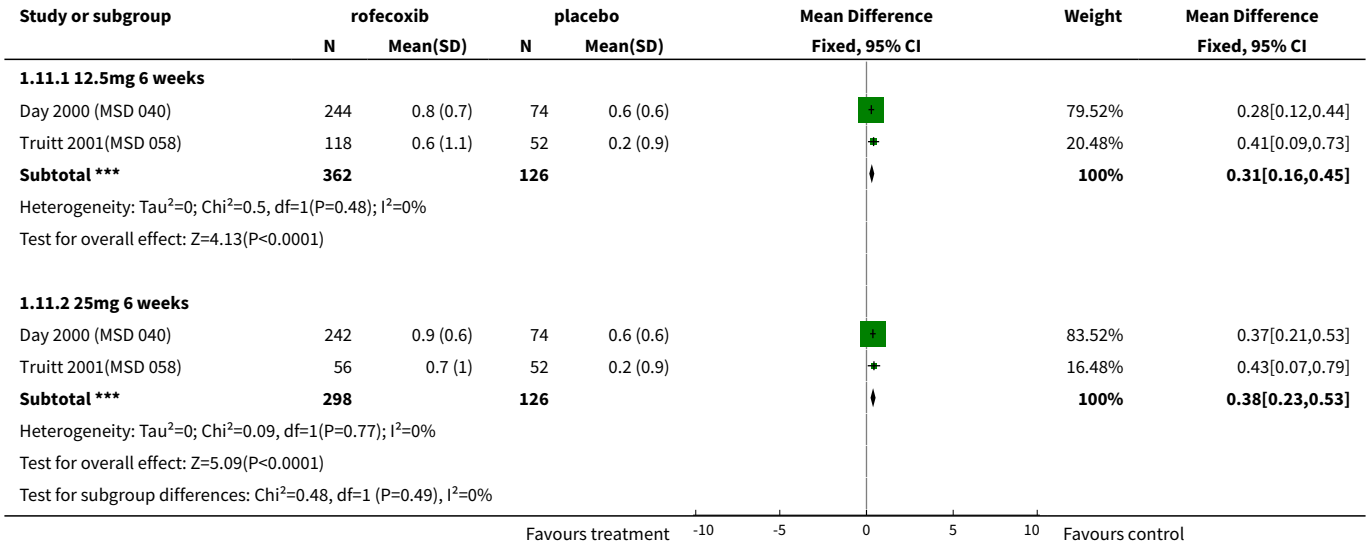




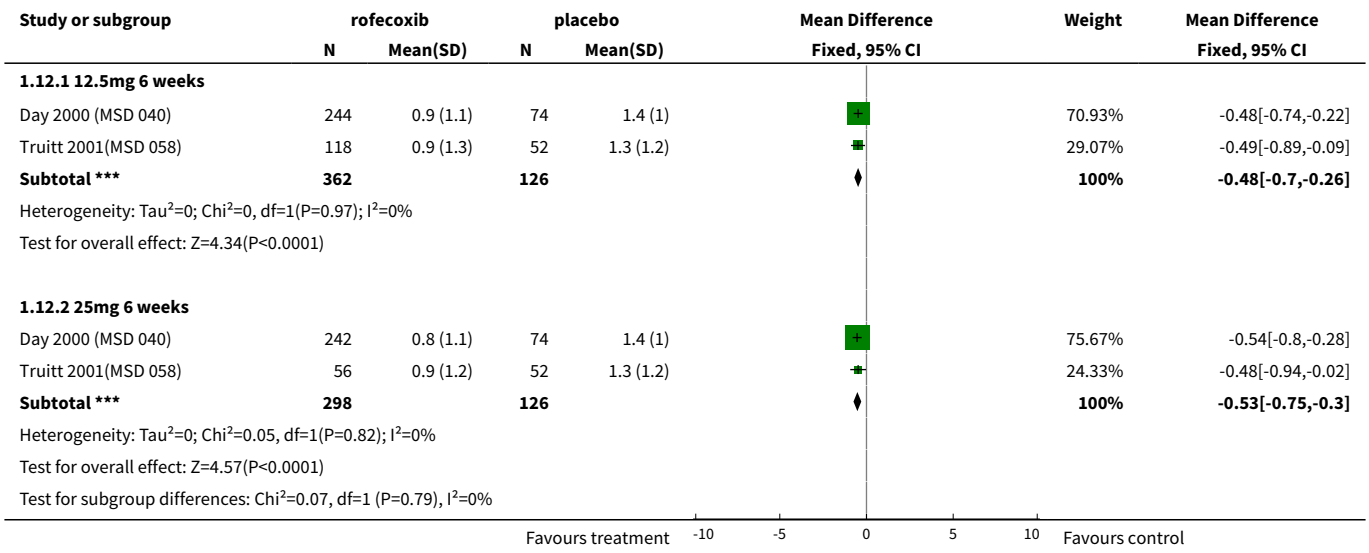
Analysis 1.10. Comparison 1 rofecoxib versus placebo, Outcome 10 Use of paracetamol rescue.



Analysis 1.11. Comparison 1 rofecoxib versus placebo, Outcome 11 Study joint tenderness (0-3).



Analysis 1.12. Comparison 1 rofecoxib versus placebo, Outcome 12 Paracetamol use- tablets per day.



Comparison 2. rofecoxib dose comparison

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADVERSE EVENTS*	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 TOTAL 25 mg v 12.5mg 6 weeks	2	677	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.85, 1.13]
1.2 TOTAL 25mg v 50mg 18 weeks	2	769	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.94, 1.09]
1.4 TOTAL 25mg v 12.5mg 52 weeks	1	516	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.90, 1.04]
1.5 TOTAL 125mg v 25mg 6 weeks	1	147	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.81, 1.47]
1.7 Serious 25mg v 12.5 mg 6 weeks	2	365	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.13, 2.05]
1.10 CV 25mg v 12.5mg 52 weeks	1	516	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.43, 5.29]
1.11 Serious 125mg v 25mg 6 weeks	1	147	Risk Ratio (M-H, Fixed, 95% CI)	6.91 [0.36, 131.40]
1.13 Diarrhoea 25mg v 12.5mg 6 weeks	4	1297	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.51, 1.38]
1.15 Diarrhoea 25mg v 50mg 18 weeks	2	769	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.59, 1.33]
1.16 Diarrhoea 25mg v 12.5mg 52 weeks	1	516	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [1.00, 3.02]

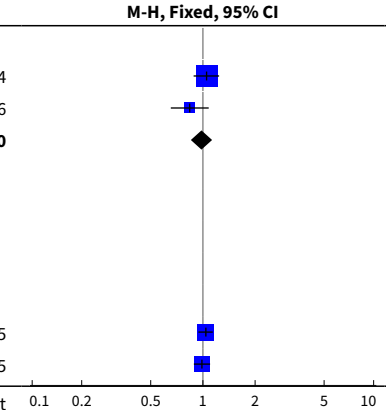
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.17 Diarrhoea 125mg v 25mg 6 weeks	1	147	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.21, 4.73]
1.18 Dyspepsia 25mg v 12.5 mg 6 weeks	1	191	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.15]
1.19 Dyspepsia 25mg v 12.5mg 52 weeks	1	463	Risk Ratio (M-H, Fixed, 95% CI)	4.98 [0.24, 103.14]
1.20 Dyspepsia 125mg v 25mg 6 weeks	1	147	Risk Ratio (M-H, Fixed, 95% CI)	3.95 [0.45, 34.47]
1.21 PUBS 25mg v 12.5mg 6 weeks	2	677	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.22 PUBS 25mg v 12.5 mg 52 weeks	1	516	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.14, 7.10]
1.25 Thromboembolic CV events 25mg v 12.5mg 52 weeks	1	516	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.43, 5.29]
1.31 Hypertension 25mg v 12.5mg 6 weeks	1	191	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.48]
1.39 OEDEMA 25mg v 12.5 mg 52 weeks	1	516	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.17, 1.45]
1.41 Lower extremity oedema 25mg v 12.5mg 52 weeks	1	516	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.17, 1.45]
1.42 Lower extremity oedema 25mg v 12.5mg 6 weeks	3	811	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.60, 2.46]
1.44 Lower extremity oedema 125mg v 25mg 6 weeks	1	147	Risk Ratio (M-H, Fixed, 95% CI)	2.47 [0.49, 12.31]
1.45 MI 25mg v 12.5mg 52 weeks	1	516	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 16.03]
2 WITHDRAWALS*	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 TOTAL 25mg v 12.5mg 6 weeks	4	813	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.26]
2.2 Total 12.5mg v 5mg 6 weeks	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Total 125mg v 25mg 6 weeks	1	147	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [0.89, 3.91]
2.5 TOTAL 50mg v 25mg 18 weeks	2	769	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.94, 1.42]
2.7 Total 25mg v 12.5mg 52 weeks	2	979	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.90, 1.24]
2.9 due to AE 50mg v 25mg 18 weeks	2	769	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.95, 2.27]
2.10 due to AE 12.5mg v 5mg 6 weeks	1	293	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.27, 2.76]

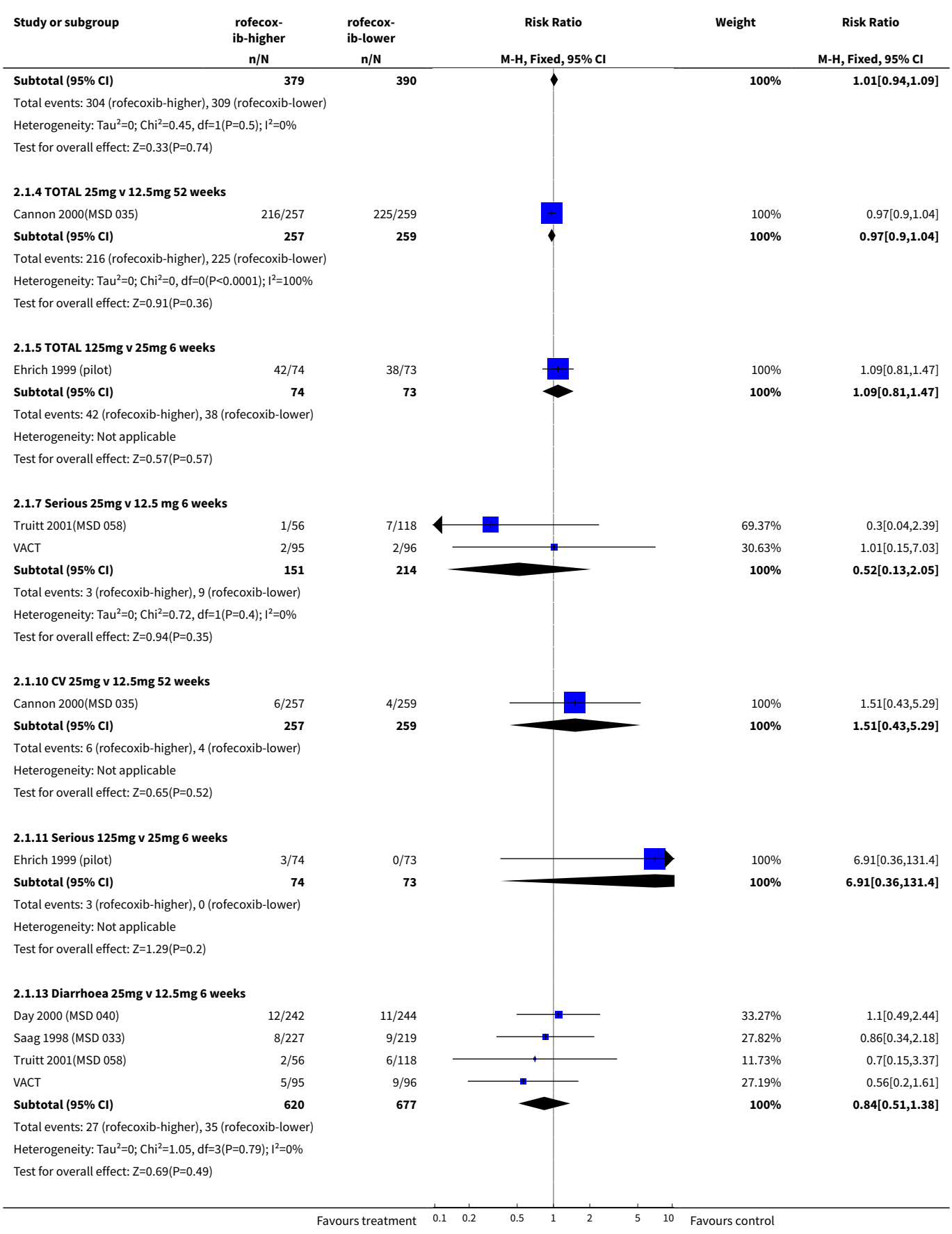
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.11 due to AE 25mg v 12.5mg 6 weeks	5	1578	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.73, 1.67]
2.12 due to AE 25mg v 5mg 6 weeks	1	286	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.44, 3.68]
2.13 due to AE 50mg v 25mg 6 weeks	1	234	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.33, 3.09]
2.14 due to AE 50mg v 5mg 6 weeks	1	246	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.40, 4.08]
2.15 due to AE 50mg v 12.5 mg 6 weeks	1	241	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.44, 4.99]
2.18 due to AE 25mg v 12.5mg 52 weeks	2	979	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.70, 1.39]
2.19 due to AE 125mg v 25mg 6 weeks	1	147	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [0.91, 8.13]
2.37 due to LOE 12.5mg v 5mg 6 weeks	1	293	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.40, 1.71]
2.38 due to LOE 25mg v 5mg 6 weeks	1	286	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.17, 1.09]
2.39 due to LOE 50mg v 5mg 6 weeks	1	246	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.09, 1.03]
2.40 due to LOE 25mg v 12.5mg 6 weeks	5	1578	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.42, 1.03]
2.41 due to LOE 50mg v 12.5 mg 6 weeks	1	241	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.11, 1.28]
2.42 due to LOE 50mg v 25mg 6 weeks	1	234	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.18, 2.75]
2.43 due to LOE 25mg v 12.5mg 52 weeks	2	979	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.95, 1.74]
2.45 due to LOE 125mg v 25mg 6 weeks	1	147	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.15]
2.46 due to LOE 50mg v 25mg 18 weeks	2	769	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.24, 1.51]
2.48 due to GI AE 25mg v 12.5 mg 6 weeks	1	446	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.51, 4.65]
2.49 due to GI AE 25mg v 12.5mg 52 weeks	2	979	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.52, 1.74]
2.50 due to lower extremity oedema 25mg v 12.5 mg 6 weeks	2	637	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.22, 12.28]

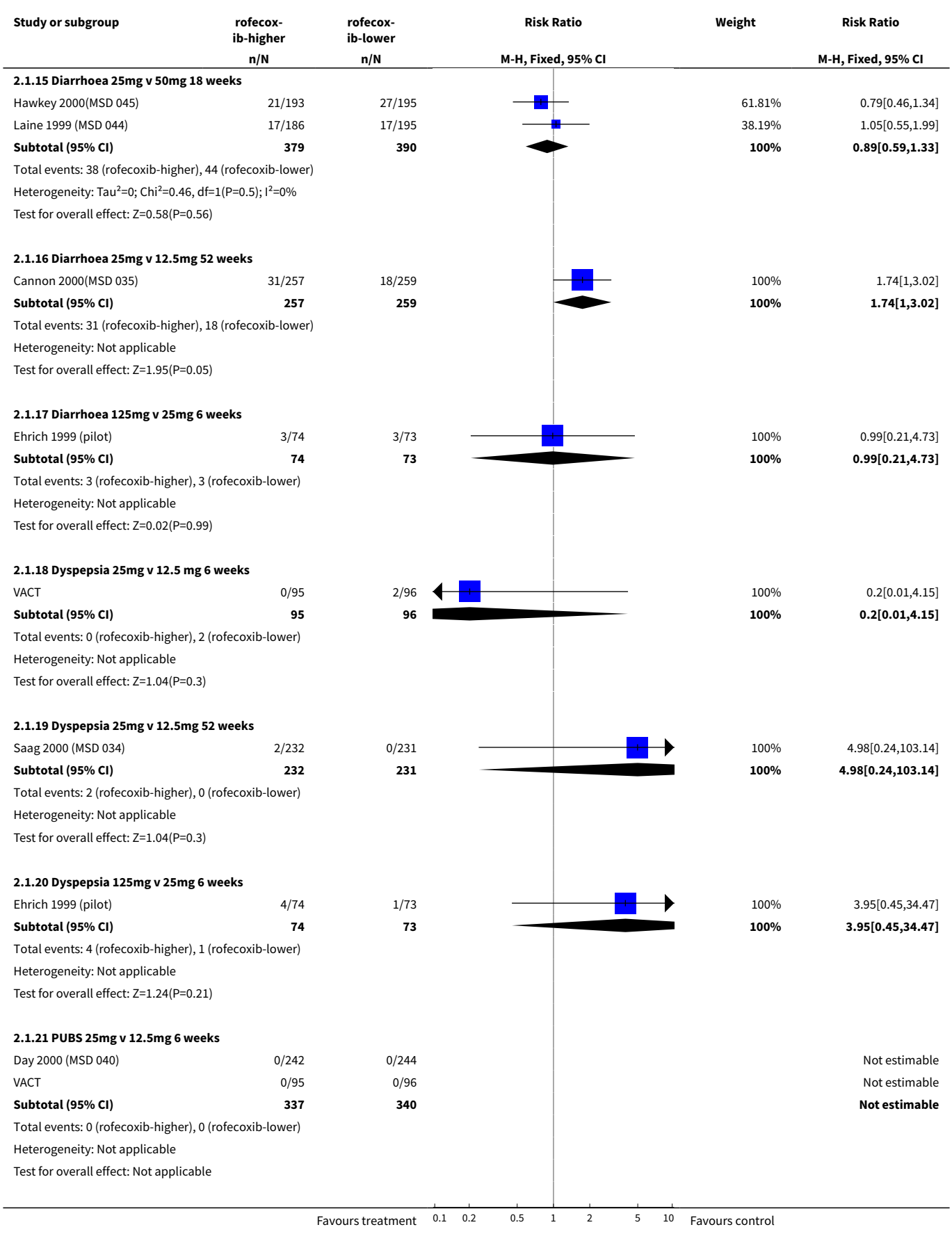
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.51 due to lower extremity oedema 125 mg v 25 mg 6 weeks	1	147	Risk Ratio (M-H, Fixed, 95% CI)	6.91 [0.36, 131.40]
2.52 due to lower extremity oedema 25mg v 12.5mg 52 weeks	1	463	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.11]
2.53 due to MI 25mg v 12.5 mg 52 weeks	1	516	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 16.03]
2.54 due to CV AE 25mg v 12.5 mg 52 weeks	2	979	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.57, 3.15]
2.55 due to CV AE 25mg v12.5mg 6 weeks	1	446	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [0.18, 21.13]
3 Ulcer 12 weeks (endoscoped) 50mg vs 25mg 6 weeks	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Ulcer >= 3mm rofecoxib	2	733	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.94, 2.95]
3.4 Ulcer >=5mm rofecoxib 50mg	2	733	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [1.21, 5.11]
3.6 Gastric Ulcer >= 3mm rofecoxib 50mg	2	733	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.80, 3.01]
3.8 Duodenal Ulcer >= 3mm rofecoxib 50mg	2	733	Risk Ratio (M-H, Fixed, 95% CI)	2.27 [0.80, 6.48]
4 Erosions (endoscoped)-change from baseline 50mg v 25mg 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Hawkey	1	369	Mean Difference (IV, Fixed, 95% CI)	0.24 [-0.50, 0.98]

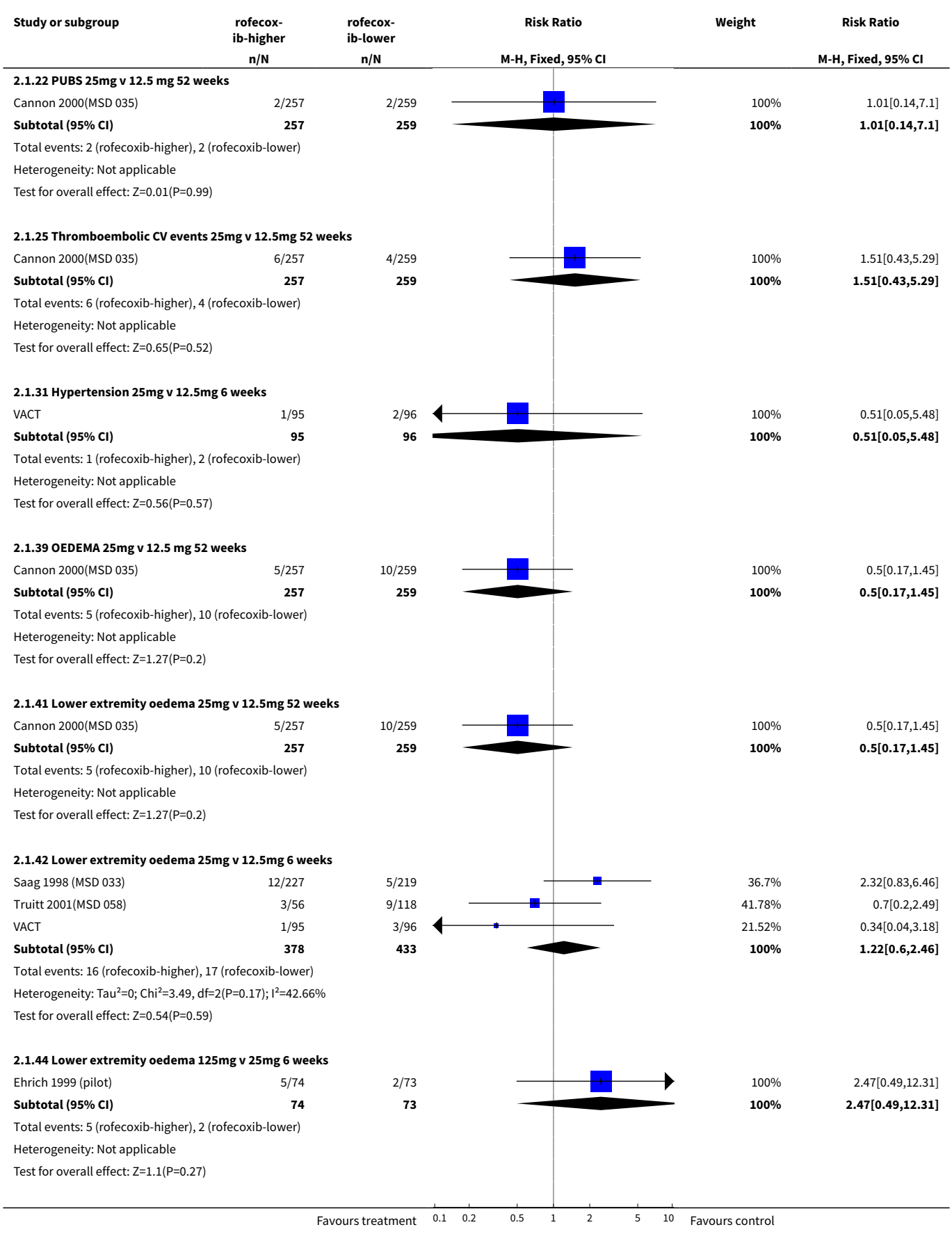
Analysis 2.1. Comparison 2 rofecoxib dose comparison, Outcome 1 ADVERSE EVENTS*.

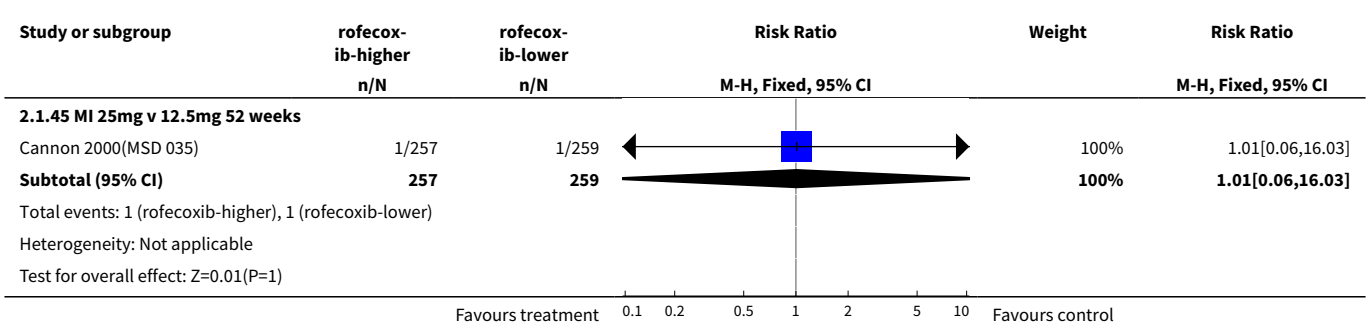
Study or subgroup	rofecoxib-higher n/N	rofecoxib-lower n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 TOTAL 25 mg v 12.5mg 6 weeks					
Day 2000 (MSD 040)	129/242	124/244		67.78%	1.05[0.88,1.24]
VACT	49/95	59/96		32.22%	0.84[0.65,1.08]
Subtotal (95% CI)	**337**	**340**		**100%**	**0.98[0.85,1.13]**
Total events: 178 (rofecoxib-higher), 183 (rofecoxib-lower)					
Heterogeneity: Tau^2=0; Chi^2=2.08, df=1(P=0.15); I^2=51.81%					
Test for overall effect: Z=0.26(P=0.79)					
2.1.2 TOTAL 25mg v 50mg 18 weeks					
Hawkey 2000(MSD 045)	160/193	156/195		50.95%	1.04[0.94,1.14]
Laine 1999 (MSD 044)	144/186	153/195		49.05%	0.99[0.89,1.1]



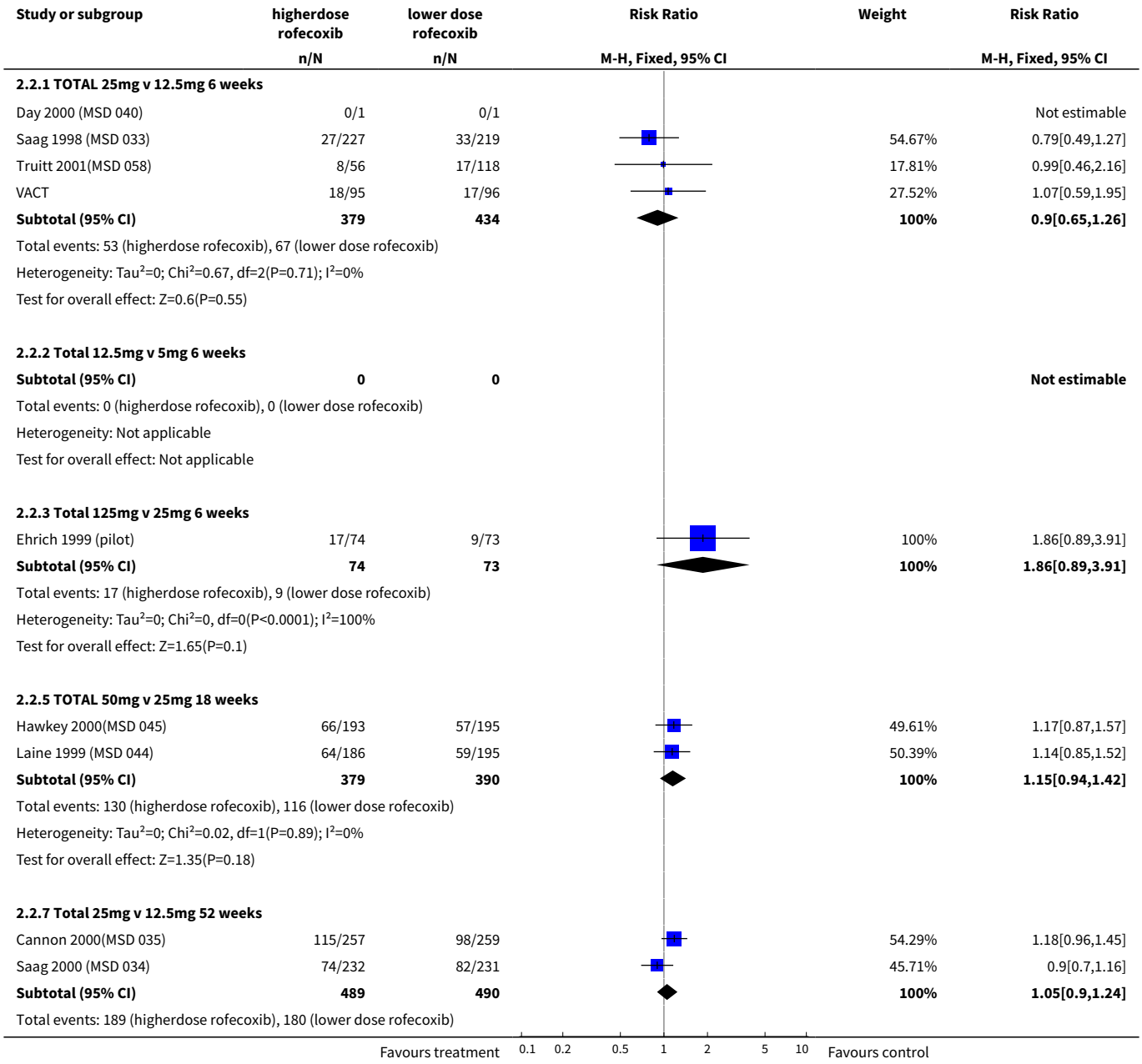


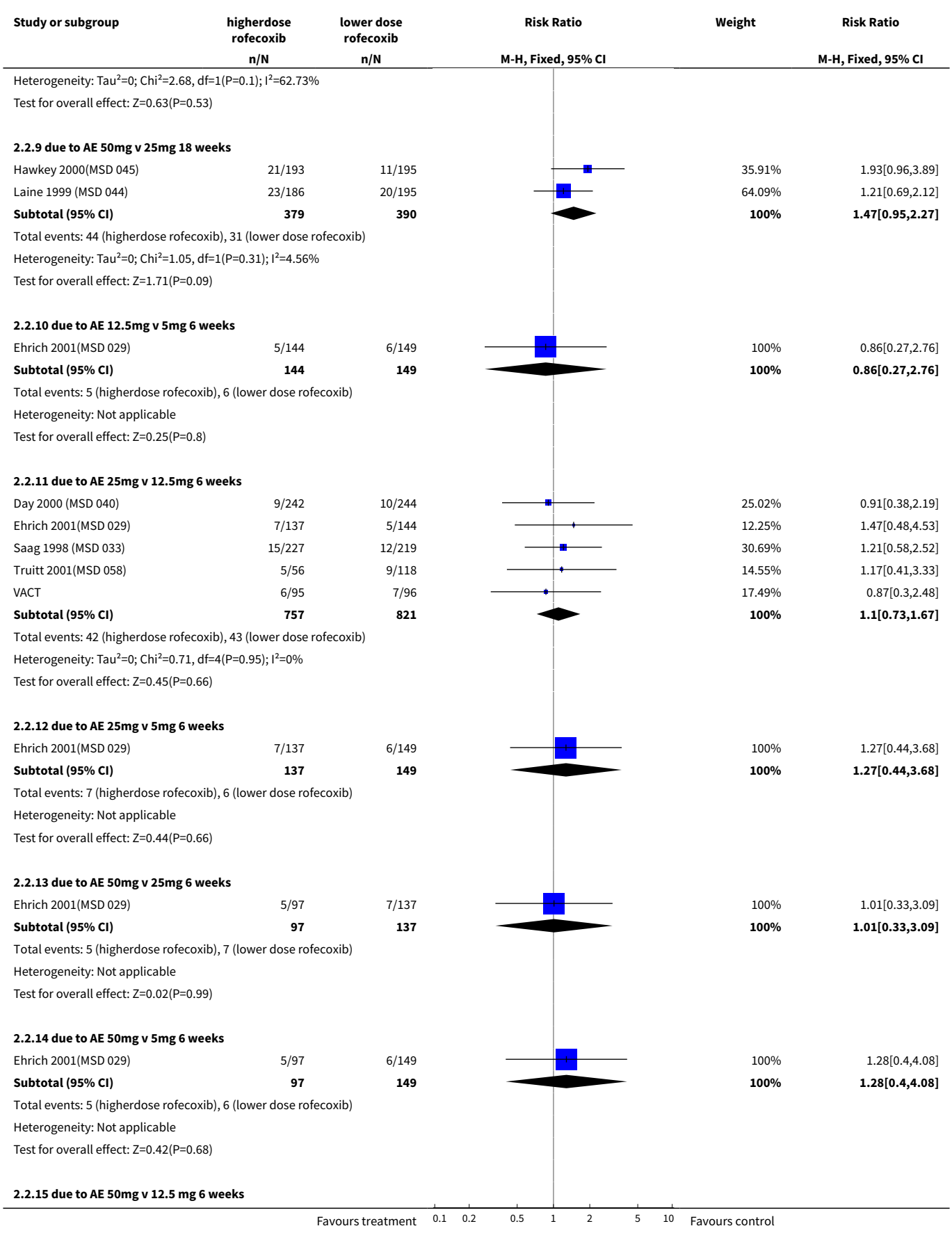


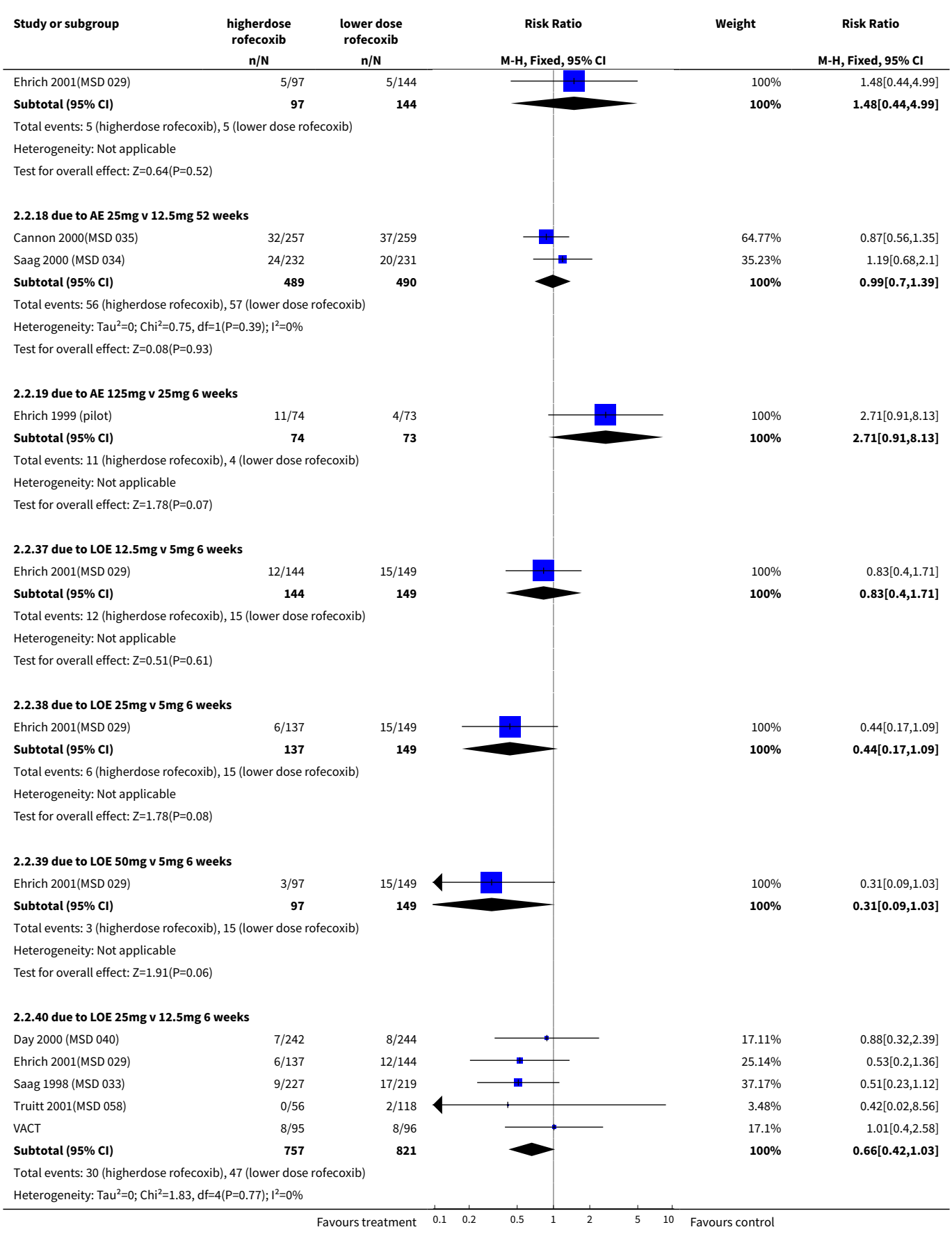


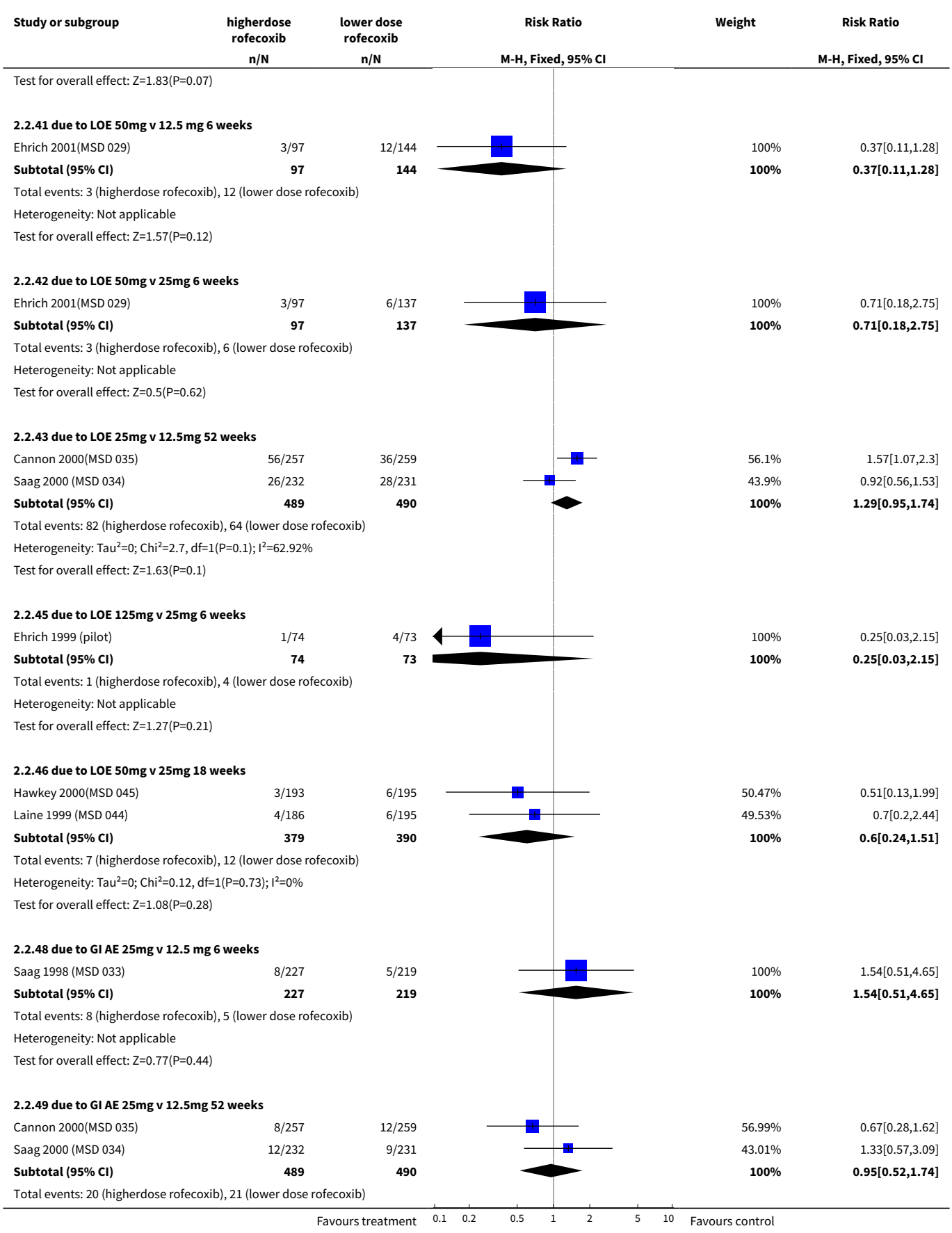


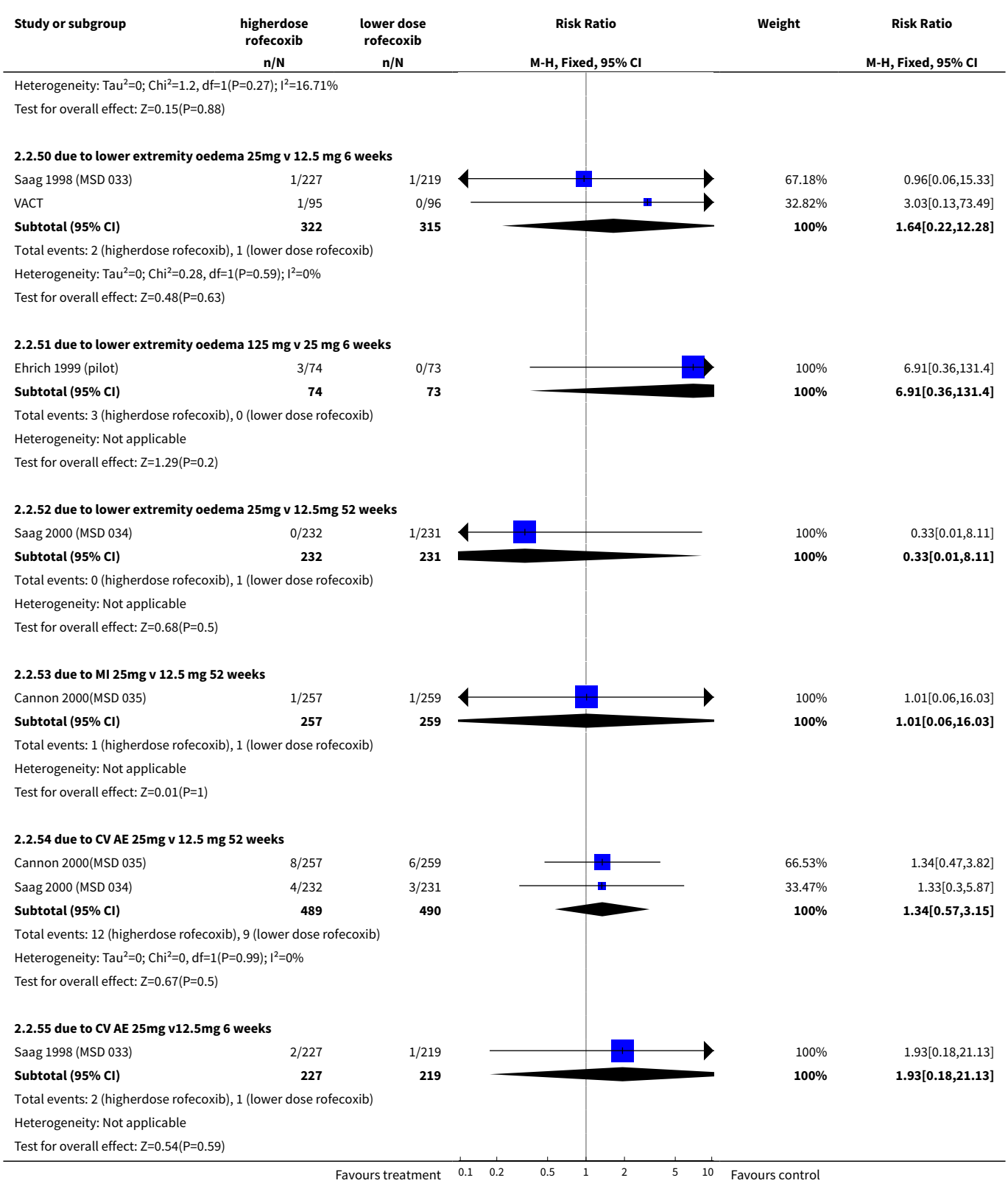
Analysis 2.2. Comparison 2 rofecoxib dose comparison, Outcome 2 WITHDRAWALS*.











Analysis 2.3. Comparison 2 rofecoxib dose comparison, Outcome 3 Ulcer 12 weeks (endoscoped) 50mg vs 25mg 6 weeks.

Study or subgroup	Rofecoxib 50mg n/N	rofecoxib 25mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Ulcer >= 3mm rofecoxib					
Hawkey 2000(MSD 045)	16/182	10/187		55.77%	1.64[0.77,3.53]
Laine 1999 (MSD 044)	13/178	8/186		44.23%	1.7[0.72,4]
Subtotal (95% CI)	**360**	**373**		**100%**	**1.67[0.94,2.95]**
Total events: 29 (Rofecoxib 50mg), 18 (rofecoxib 25mg)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.96); I^2=0%					
Test for overall effect: Z=1.76(P=0.08)					
2.3.4 Ulcer >=5mm rofecoxib 50mg					
Hawkey 2000(MSD 045)	14/182	7/187		70.18%	2.05[0.85,4.97]
Laine 1999 (MSD 044)	10/178	3/186		29.82%	3.48[0.97,12.45]
Subtotal (95% CI)	**360**	**373**		**100%**	**2.48[1.21,5.11]**
Total events: 24 (Rofecoxib 50mg), 10 (rofecoxib 25mg)					
Heterogeneity: Tau^2=0; Chi^2=0.45, df=1(P=0.5); I^2=0%					
Test for overall effect: Z=2.47(P=0.01)					
2.3.6 Gastric Ulcer >= 3mm rofecoxib 50mg					
Hawkey 2000(MSD 045)	10/182	8/187		57.35%	1.28[0.52,3.18]
Laine 1999 (MSD 044)	11/178	6/186		42.65%	1.92[0.72,5.07]
Subtotal (95% CI)	**360**	**373**		**100%**	**1.55[0.8,3.01]**
Total events: 21 (Rofecoxib 50mg), 14 (rofecoxib 25mg)					
Heterogeneity: Tau^2=0; Chi^2=0.35, df=1(P=0.56); I^2=0%					
Test for overall effect: Z=1.31(P=0.19)					
2.3.8 Duodenal Ulcer >= 3mm rofecoxib 50mg					
Hawkey 2000(MSD 045)	8/182	3/187		60.21%	2.74[0.74,10.17]
Laine 1999 (MSD 044)	3/178	2/186		39.79%	1.57[0.27,9.27]
Subtotal (95% CI)	**360**	**373**		**100%**	**2.27[0.8,6.48]**
Total events: 11 (Rofecoxib 50mg), 5 (rofecoxib 25mg)					
Heterogeneity: Tau^2=0; Chi^2=0.25, df=1(P=0.62); I^2=0%					
Test for overall effect: Z=1.54(P=0.12)					

Analysis 2.4. Comparison 2 rofecoxib dose comparison, Outcome 4 Erosions (endoscoped)-change from baseline 50mg v 25mg 12 weeks.

Study or subgroup	Rofecoxib 50mg N	Rofecoxib 50mg Mean(SD)	Rofecoxib 25mg N	Rofecoxib 25mg Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.4.1 Hawkey							
Hawkey 2000(MSD 045)	182	0.4 (3.7)	187	0.2 (3.6)		100%	0.24[-0.5,0.98]
Subtotal ***	**182**		**187**			**100%**	**0.24[-0.5,0.98]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.64(P=0.52)							

Comparison 3. rofecoxib versus diclofenac

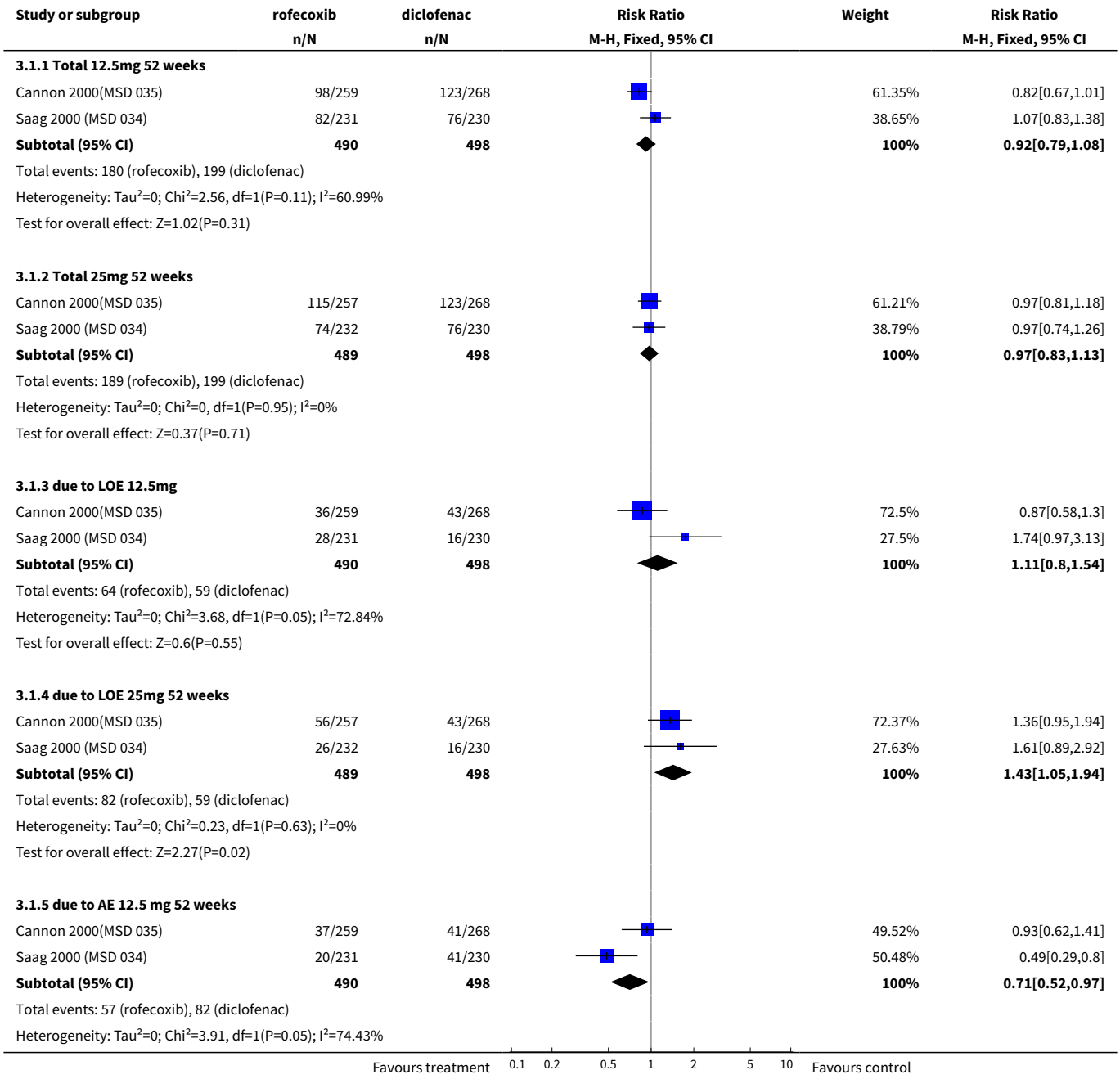
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 WITHDRAWALS	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Total 12.5mg 52 weeks	2	988	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.79, 1.08]
1.2 Total 25mg 52 weeks	2	987	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.83, 1.13]
1.3 due to LOE 12.5mg	2	988	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.80, 1.54]
1.4 due to LOE 25mg 52 weeks	2	987	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.05, 1.94]
1.5 due to AE 12.5 mg 52 weeks	2	988	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.52, 0.97]
1.6 due to AE 25mg 52 weeks	2	987	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.51, 0.95]
1.7 due to GI AE 12.5 mg 52 weeks	2	988	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.42, 1.27]
1.8 due to GI AE 25 mg 52 weeks	2	987	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.40, 1.21]
1.9 due to CV AE 12.5 mg 52 weeks	2	988	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.31, 1.64]
1.10 due to CV AE 25 mg 52 weeks	2	987	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.44, 2.06]
1.11 Total 25mg 2 weeks	1	65	Risk Ratio (M-H, Fixed, 95% CI)	3.65 [0.43, 30.89]
1.12 due to GI AE 25mg 2 weeks	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.01, 7.22]
1.13 due to renal AE 25mg 2 weeks	1	65	Risk Ratio (M-H, Fixed, 95% CI)	8.23 [0.46, 146.90]
1.14 due to lab AE 12.5mg 52 weeks	1	527	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.01, 0.56]
1.15 due to lab AE 25mg 52 weeks	1	525	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.03, 0.65]
1.16 due to elevated transaminase 25mg 52 weeks	1	461	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 0.77]
2 ADVERSE EVENTS	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.3 TOTAL 12.5mg 52 weeks	1	527	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.94, 1.08]
2.4 TOTAL 25mg 52 weeks	1	525	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.91, 1.05]
2.5 MI 12.5mg 52 weeks	1	527	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.05, 5.67]
2.6 MI 25mg 52 weeks	1	525	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.05, 5.72]

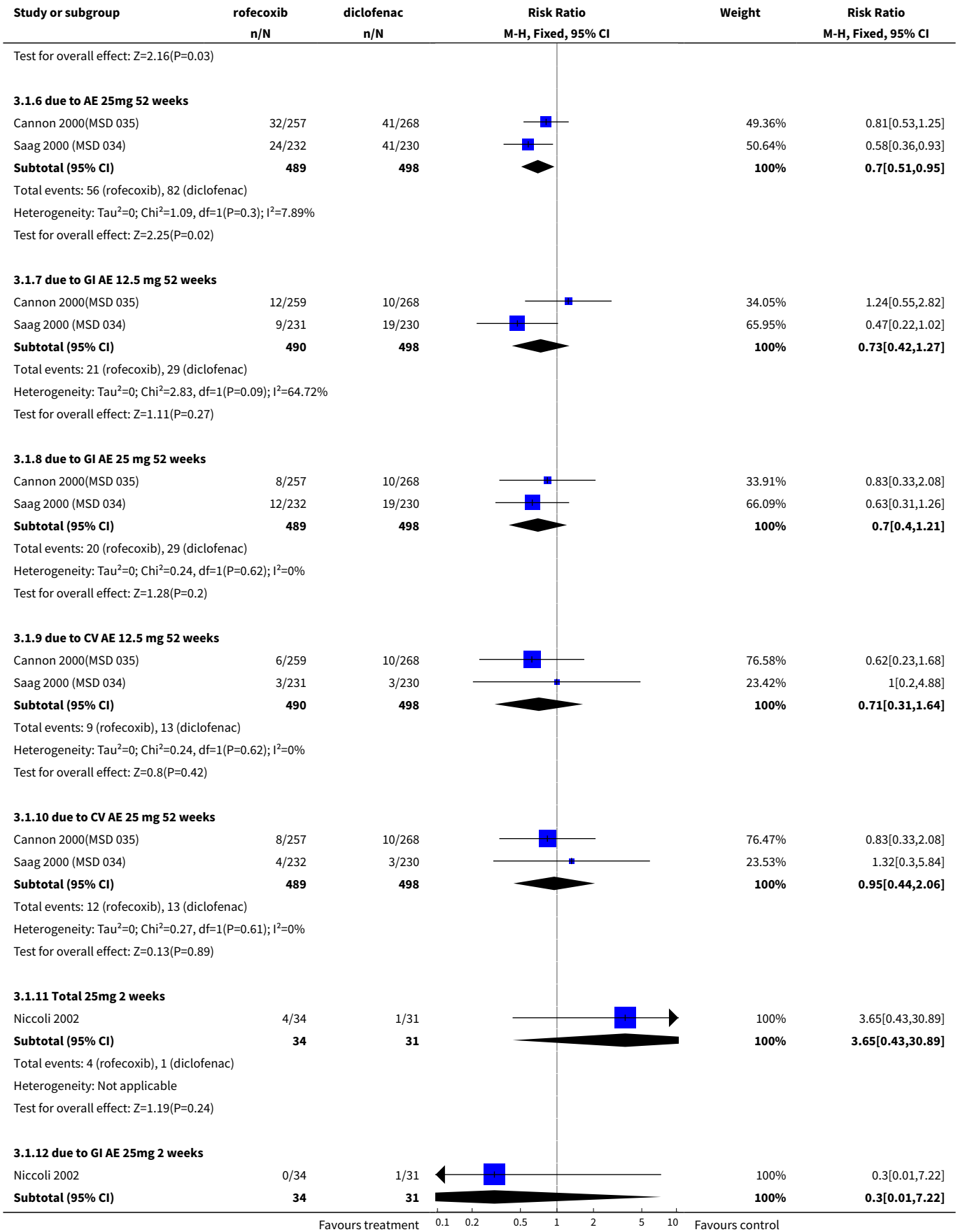
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.7 PUBS 12.5mg 52 weeks	1	527	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.12, 4.09]
2.8 PUBS 25mg 52 weeks	1	525	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.12, 4.13]
2.9 OEDEMA 12.5mg 52 weeks	1	527	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.47, 2.78]
2.10 OEDEMA 25mg 52 weeks	1	525	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.20, 1.71]
2.11 CV 12.5mg 52 weeks	1	527	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.14, 1.47]
2.12 CV 25mg 52 weeks	1	525	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.25, 1.93]
2.13 Oedema 25mg 2 weeks	1	65	Risk Ratio (M-H, Fixed, 95% CI)	19.2 [1.17, 314.55]
2.14 GI 25mg 2 weeks	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.00, 0.79]
2.15 Hypertension 25mg 2 weeks	1	65	Risk Ratio (M-H, Fixed, 95% CI)	15.54 [0.93, 258.58]
2.16 Weight gain 25mg 2 weeks	1	65	Risk Ratio (M-H, Fixed, 95% CI)	19.2 [1.17, 314.55]
2.17 Oliguria 25mg 2 weeks	1	65	Risk Ratio (M-H, Fixed, 95% CI)	11.89 [0.70, 202.66]
3 EFFICACY - WOMAC	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.5 pain 12.5 mg 52 weeks	1	527	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.30, 0.05]
3.6 pain 25mg 52 weeks	1	525	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.27, 0.07]
3.7 physical function (100mm VAS) 12.5 mg 52 weeks	1	527	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.27, 0.08]
3.8 physical function (100mm VAS) 25mg 52 weeks	1	525	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.25, 0.09]
3.9 stiffness (100mm VAS) 12.5 mg 52 weeks	1	527	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.29, 0.05]
3.10 stiffness (100mm VAS) 25mg 52 weeks	1	525	Std. Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.27, 0.08]
4 EFFICACY- patient/investigator- continuous	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 patient assessed pain (100mm VAS) 25mg 2 weeks	1	60	Mean Difference (IV, Fixed, 95% CI)	-6.26 [-10.78, -1.74]
4.2 patient global disease activity (100mm VAS) 25mg 2 weeks	1	60	Mean Difference (IV, Fixed, 95% CI)	-6.39 [-10.87, -1.91]

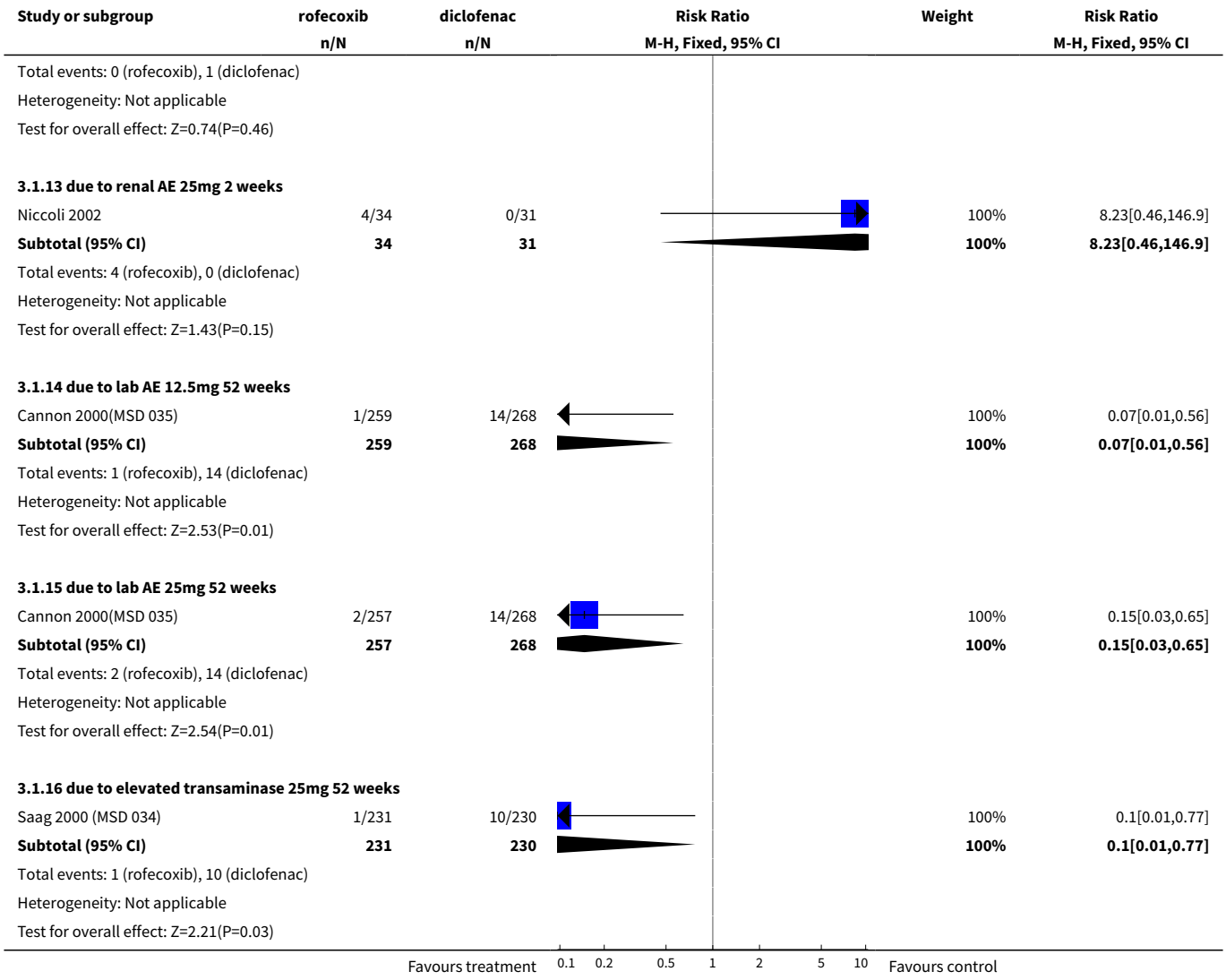
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 physician global disease activity (100mm VAS) 25mg 2 weeks	1	60	Mean Difference (IV, Fixed, 95% CI)	-5.08 [-9.66, -0.50]
4.4 Patient Global Status (100mm VAS) 12.5 mg 52 weeks	1	527	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-7.53, 1.53]
4.5 Patient Global Status (100mm VAS) 25mg 52 weeks	1	525	Mean Difference (IV, Fixed, 95% CI)	-4.40 [-8.93, 0.13]
4.6 Investigator Global response(0-4 Likert) 12.5 mg 26 weeks	1	527	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.49, -0.11]
4.7 Investigator Global response (0-4 Likert) 25 mg 26 weeks	1	525	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.49, -0.11]
4.8 joint tenderness (0-3 Likert) 12.5 mg 52 weeks	1	527	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.14, 0.14]
4.9 joint tenderness (0-3 Likert) 25mg 52 weeks	1	525	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.04, 0.24]
5 Use of concomitant OA treatment post 26 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 12.5mg 52 weeks	1	461	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.54, 2.10]
5.2 25mg 52 weeks	1	462	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.38, 1.66]
6 Renal function 2 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Body weight (kg)	1	60	Mean Difference (IV, Fixed, 95% CI)	1.17 [-1.96, 4.30]
6.2 Systolic blood pressure (mmHg)	1	60	Mean Difference (IV, Fixed, 95% CI)	8.0 [3.00, 13.00]
6.3 Diastolic blood pressure (mmHg)	1	60	Mean Difference (IV, Fixed, 95% CI)	8.0 [4.47, 11.53]
6.4 Blood urea nitrogen	1	60	Mean Difference (IV, Fixed, 95% CI)	-6.05 [-8.25, -3.85]
6.5 Creatinine	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.26, -0.12]
6.6 sodium (mEq/l)	1	60	Mean Difference (IV, Fixed, 95% CI)	1.25 [0.41, 2.09]
6.7 potassium (mEq/l)	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.57 [-0.77, -0.37]
6.8 chlorum (mEq/l)	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.41 [-1.25, 0.43]
6.9 uric acid (mg/dl)	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.74 [-1.26, -0.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.10 24 hour urine (ml)	1	60	Mean Difference (IV, Fixed, 95% CI)	131.18 [7.77, 254.59]
6.11 Creatinine clearance (ml/min)	1	60	Mean Difference (IV, Fixed, 95% CI)	9.45 [2.95, 15.95]

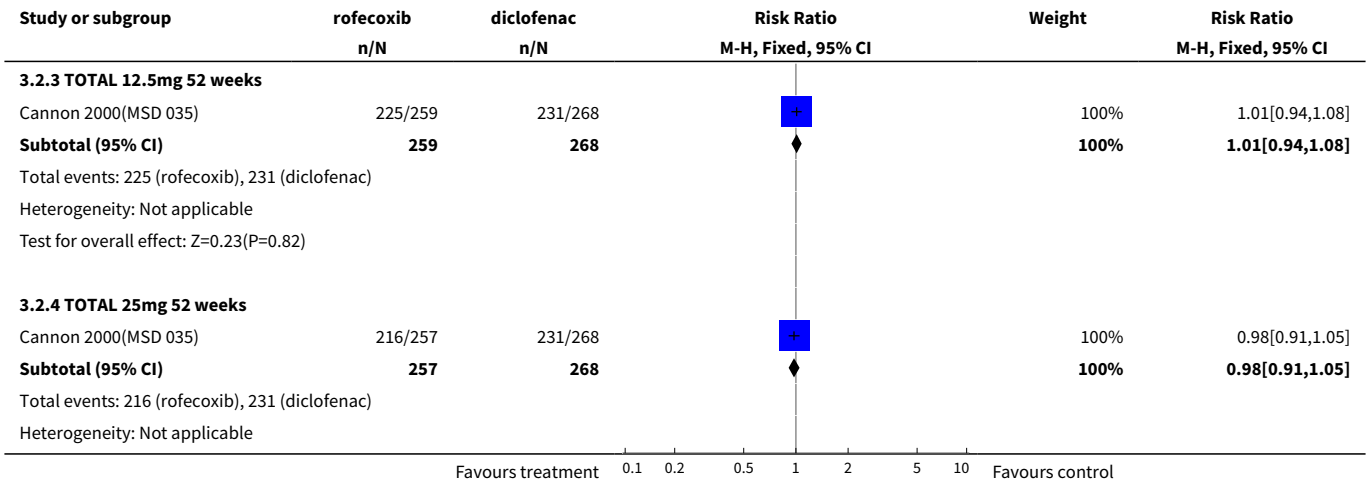
Analysis 3.1. Comparison 3 rofecoxib versus diclofenac, Outcome 1 WITHDRAWALS.



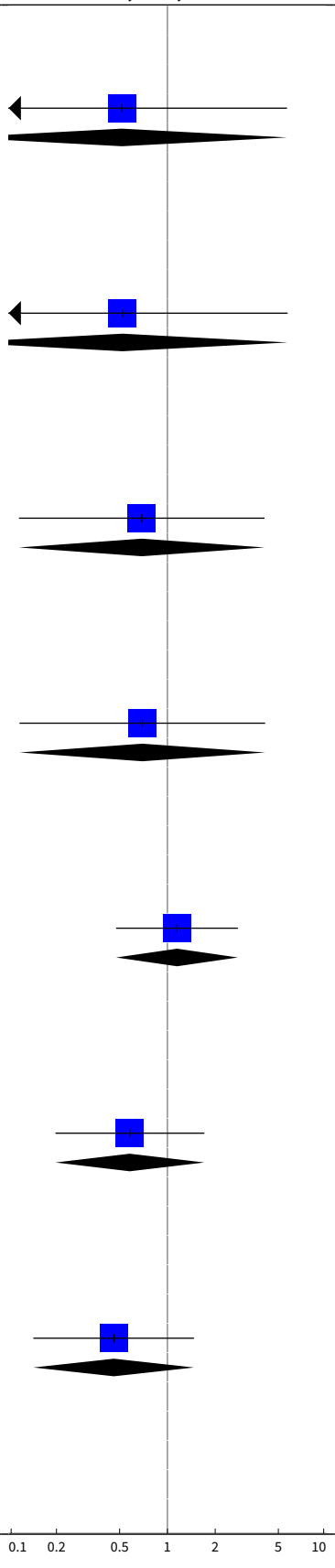


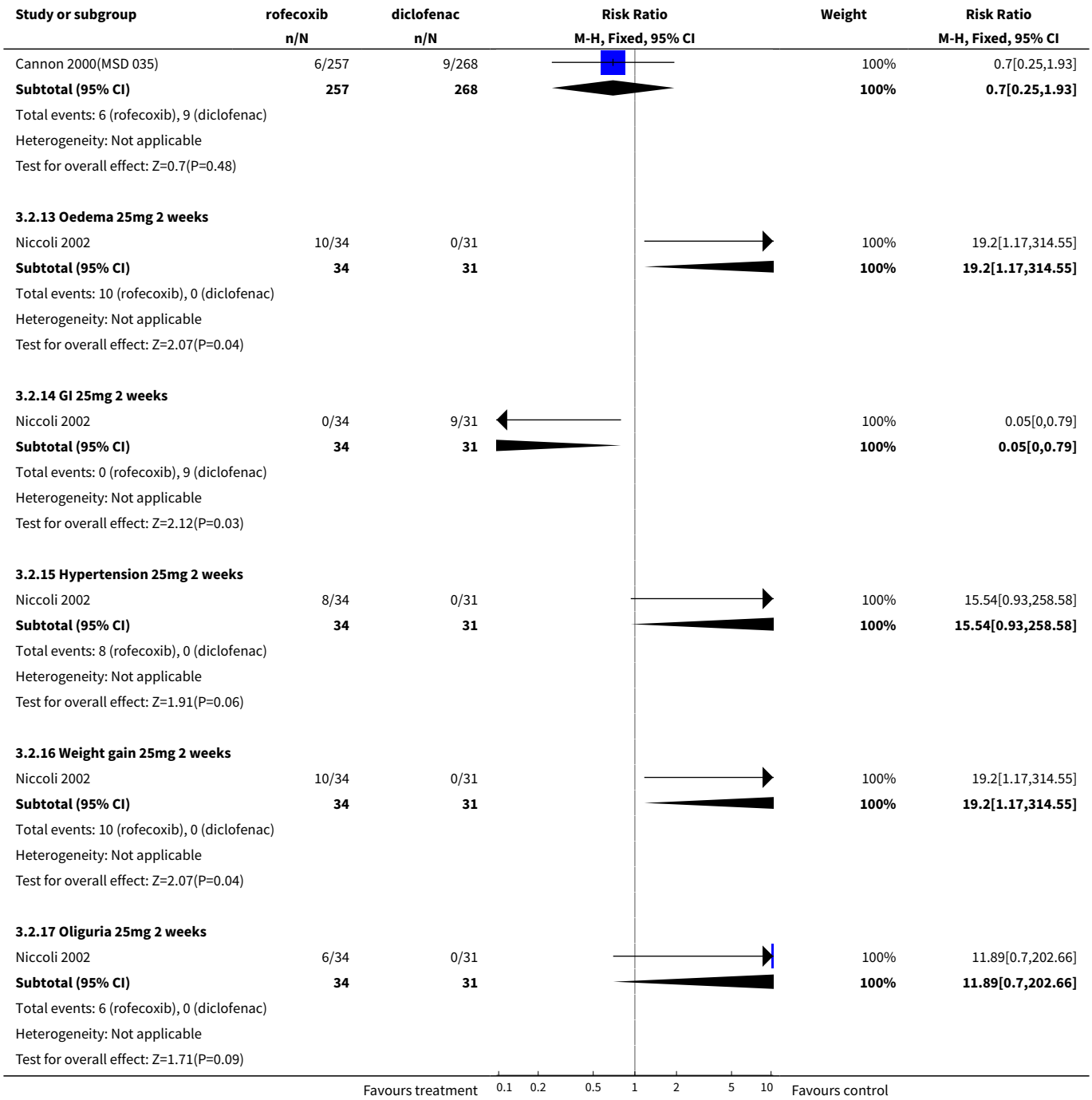


Analysis 3.2. Comparison 3 rofecoxib versus diclofenac, Outcome 2 ADVERSE EVENTS.

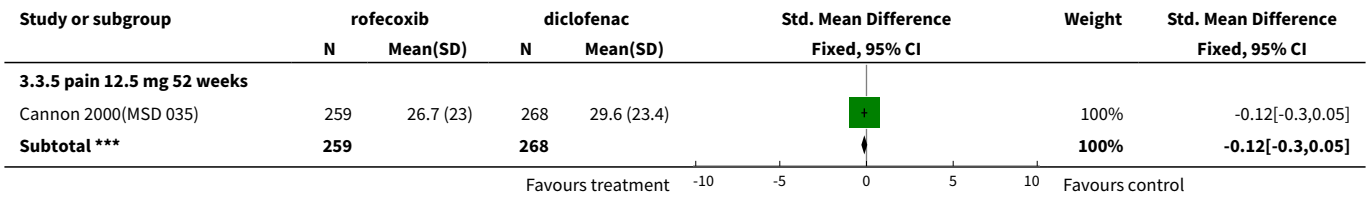


Study or subgroup	rofecoxib n/N	diclofenac n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.69(P=0.49)					
3.2.5 MI 12.5mg 52 weeks					
Cannon 2000(MSD 035)	1/259	2/268		100%	0.52[0.05,5.67]
Subtotal (95% CI)	**259**	**268**		**100%**	**0.52[0.05,5.67]**
Total events: 1 (rofecoxib), 2 (diclofenac)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					
3.2.6 MI 25mg 52 weeks					
Cannon 2000(MSD 035)	1/257	2/268		100%	0.52[0.05,5.72]
Subtotal (95% CI)	**257**	**268**		**100%**	**0.52[0.05,5.72]**
Total events: 1 (rofecoxib), 2 (diclofenac)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.53(P=0.59)					
3.2.7 PUBS 12.5mg 52 weeks					
Cannon 2000(MSD 035)	2/259	3/268		100%	0.69[0.12,4.09]
Subtotal (95% CI)	**259**	**268**		**100%**	**0.69[0.12,4.09]**
Total events: 2 (rofecoxib), 3 (diclofenac)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.41(P=0.68)					
3.2.8 PUBS 25mg 52 weeks					
Cannon 2000(MSD 035)	2/257	3/268		100%	0.7[0.12,4.13]
Subtotal (95% CI)	**257**	**268**		**100%**	**0.7[0.12,4.13]**
Total events: 2 (rofecoxib), 3 (diclofenac)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.4(P=0.69)					
3.2.9 OEDEMA 12.5mg 52 weeks					
Cannon 2000(MSD 035)	10/259	9/268		100%	1.15[0.47,2.78]
Subtotal (95% CI)	**259**	**268**		**100%**	**1.15[0.47,2.78]**
Total events: 10 (rofecoxib), 9 (diclofenac)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.31(P=0.76)					
3.2.10 OEDEMA 25mg 52 weeks					
Cannon 2000(MSD 035)	5/257	9/268		100%	0.58[0.2,1.71]
Subtotal (95% CI)	**257**	**268**		**100%**	**0.58[0.2,1.71]**
Total events: 5 (rofecoxib), 9 (diclofenac)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.99(P=0.32)					
3.2.11 CV 12.5mg 52 weeks					
Cannon 2000(MSD 035)	4/259	9/268		100%	0.46[0.14,1.47]
Subtotal (95% CI)	**259**	**268**		**100%**	**0.46[0.14,1.47]**
Total events: 4 (rofecoxib), 9 (diclofenac)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.31(P=0.19)					
3.2.12 CV 25mg 52 weeks					

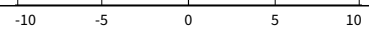




Analysis 3.3. Comparison 3 rofecoxib versus diclofenac, Outcome 3 EFFICACY - WOMAC.

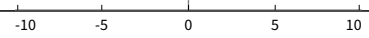


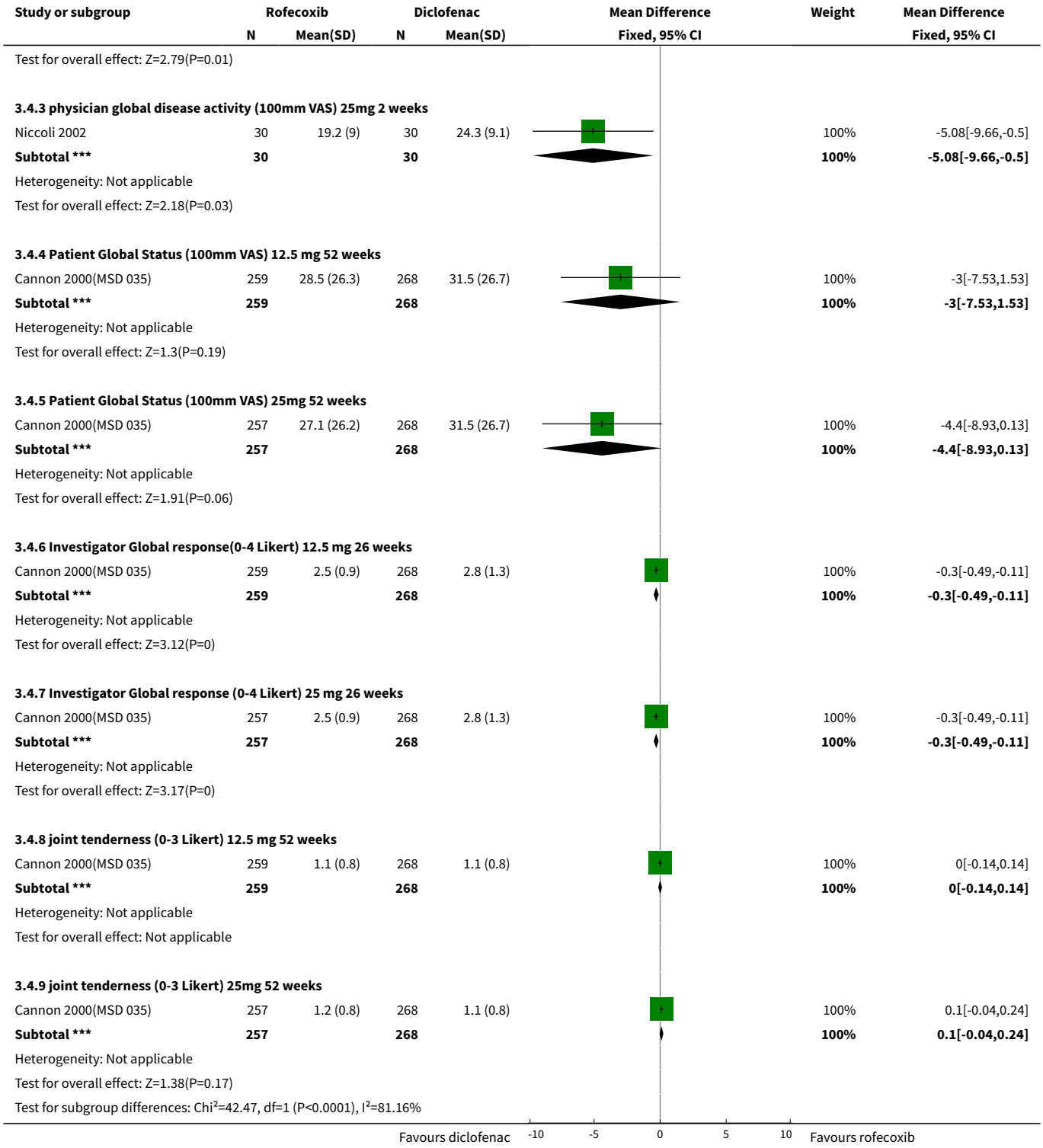
Study or subgroup	rofecoxib N	rofecoxib Mean(SD)	diclofenac N	diclofenac Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Heterogeneity: Not applicable							
Test for overall effect: Z=1.43(P=0.15)							
3.3.6 pain 25mg 52 weeks							
Cannon 2000(MSD 035)	257	27.3 (23.2)	268	29.6 (23.4)		100%	-0.1[-0.27,0.07]
Subtotal ***	**257**		**268**			**100%**	**-0.1[-0.27,0.07]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.13(P=0.26)							
3.3.7 physical function (100mm VAS) 12.5 mg 52 weeks							
Cannon 2000(MSD 035)	259	23.4 (24.6)	268	25.8 (25.5)		100%	-0.1[-0.27,0.08]
Subtotal ***	**259**		**268**			**100%**	**-0.1[-0.27,0.08]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.1(P=0.27)							
3.3.8 physical function (100mm VAS) 25mg 52 weeks							
Cannon 2000(MSD 035)	257	23.8 (25)	268	25.8 (25.5)		100%	-0.08[-0.25,0.09]
Subtotal ***	**257**		**268**			**100%**	**-0.08[-0.25,0.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.91(P=0.36)							
3.3.9 stiffness (100mm VAS) 12.5 mg 52 weeks							
Cannon 2000(MSD 035)	259	24.5 (26.3)	268	27.7 (26.7)		100%	-0.12[-0.29,0.05]
Subtotal ***	**259**		**268**			**100%**	**-0.12[-0.29,0.05]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.38(P=0.17)							
3.3.10 stiffness (100mm VAS) 25mg 52 weeks							
Cannon 2000(MSD 035)	257	25.2 (26.2)	268	27.7 (26.7)		100%	-0.09[-0.27,0.08]
Subtotal ***	**257**		**268**			**100%**	**-0.09[-0.27,0.08]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.08(P=0.28)							
Test for subgroup differences: Chi^2=0.2, df=1 (P=1), I^2=0%							



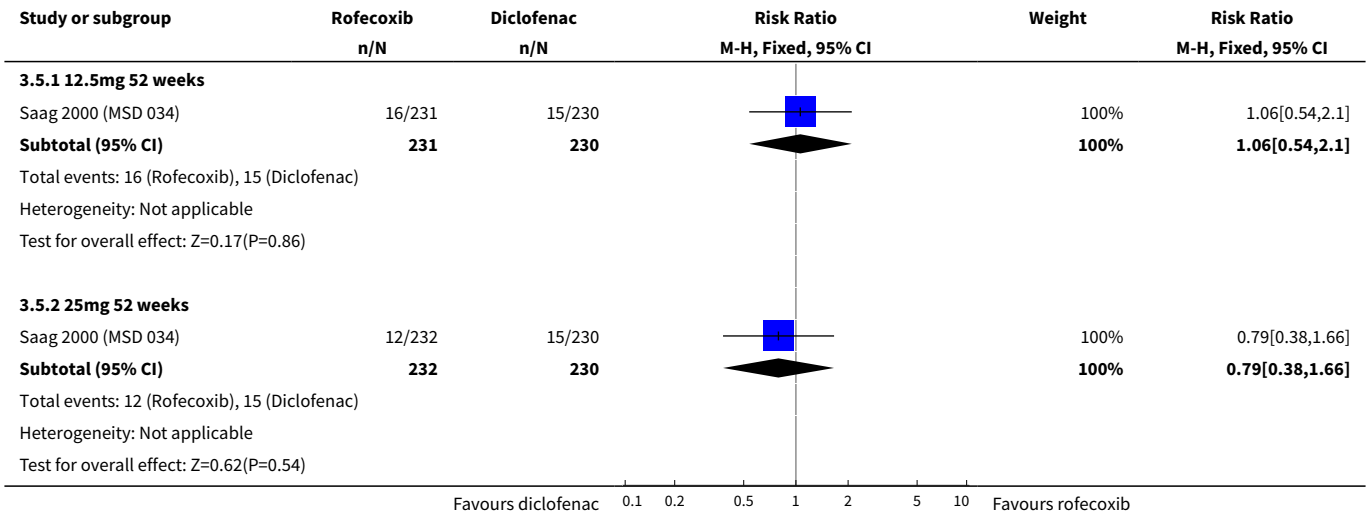
Analysis 3.4. Comparison 3 rofecoxib versus diclofenac, Outcome 4 EFFICACY- patient/investigator- continuous.

Study or subgroup	Rofecoxib N	Rofecoxib Mean(SD)	Diclofenac N	Diclofenac Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.4.1 patient assessed pain (100mm VAS) 25mg 2 weeks							
Niccoli 2002	30	16.2 (8.5)	30	22.4 (9.4)		100%	-6.26[-10.78,-1.74]
Subtotal ***	**30**		**30**			**100%**	**-6.26[-10.78,-1.74]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.71(P=0.01)							
3.4.2 patient global disease activity (100mm VAS) 25mg 2 weeks							
Niccoli 2002	30	16.5 (8.5)	30	22.9 (9.2)		100%	-6.39[-10.87,-1.91]
Subtotal ***	**30**		**30**			**100%**	**-6.39[-10.87,-1.91]**
Heterogeneity: Not applicable							

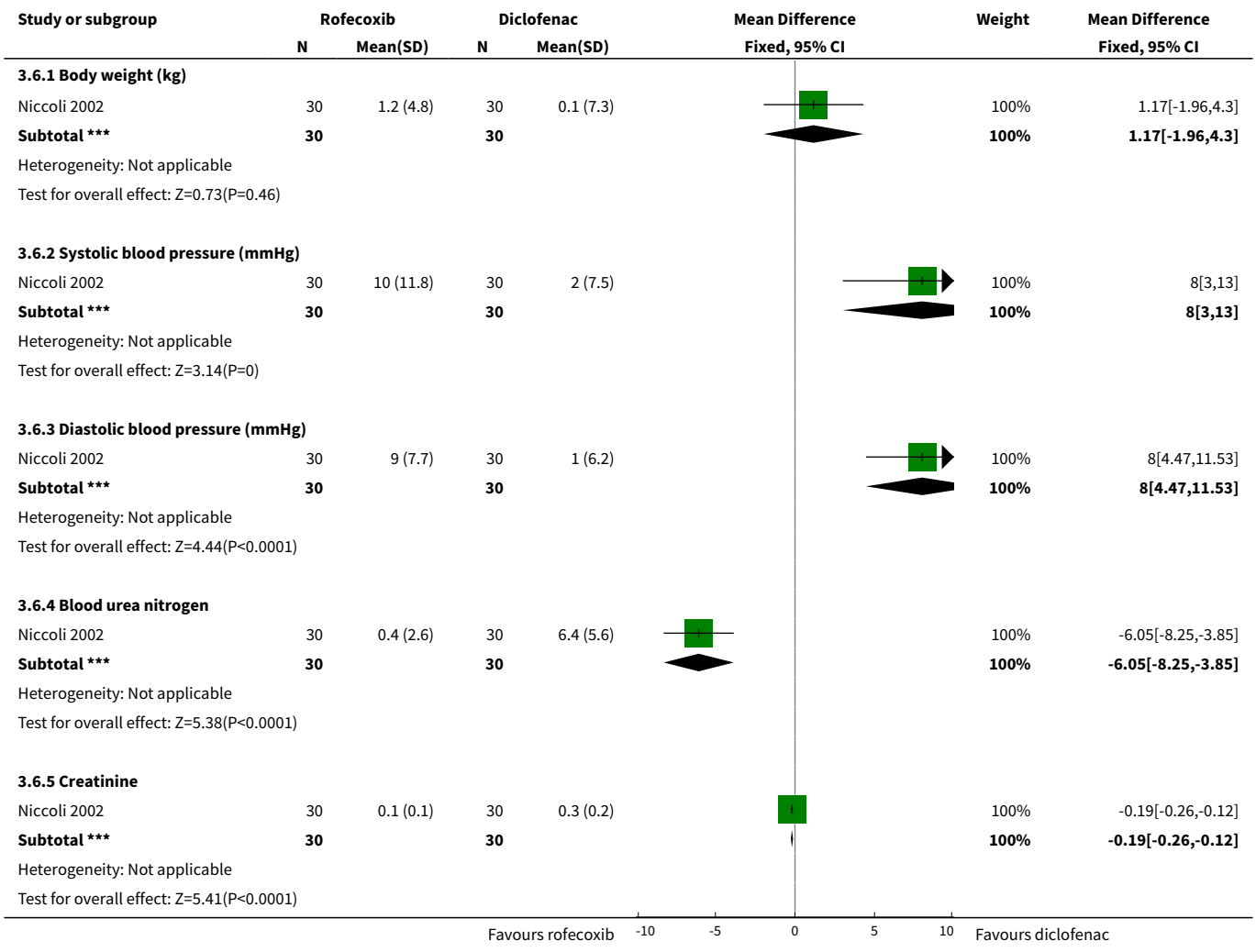


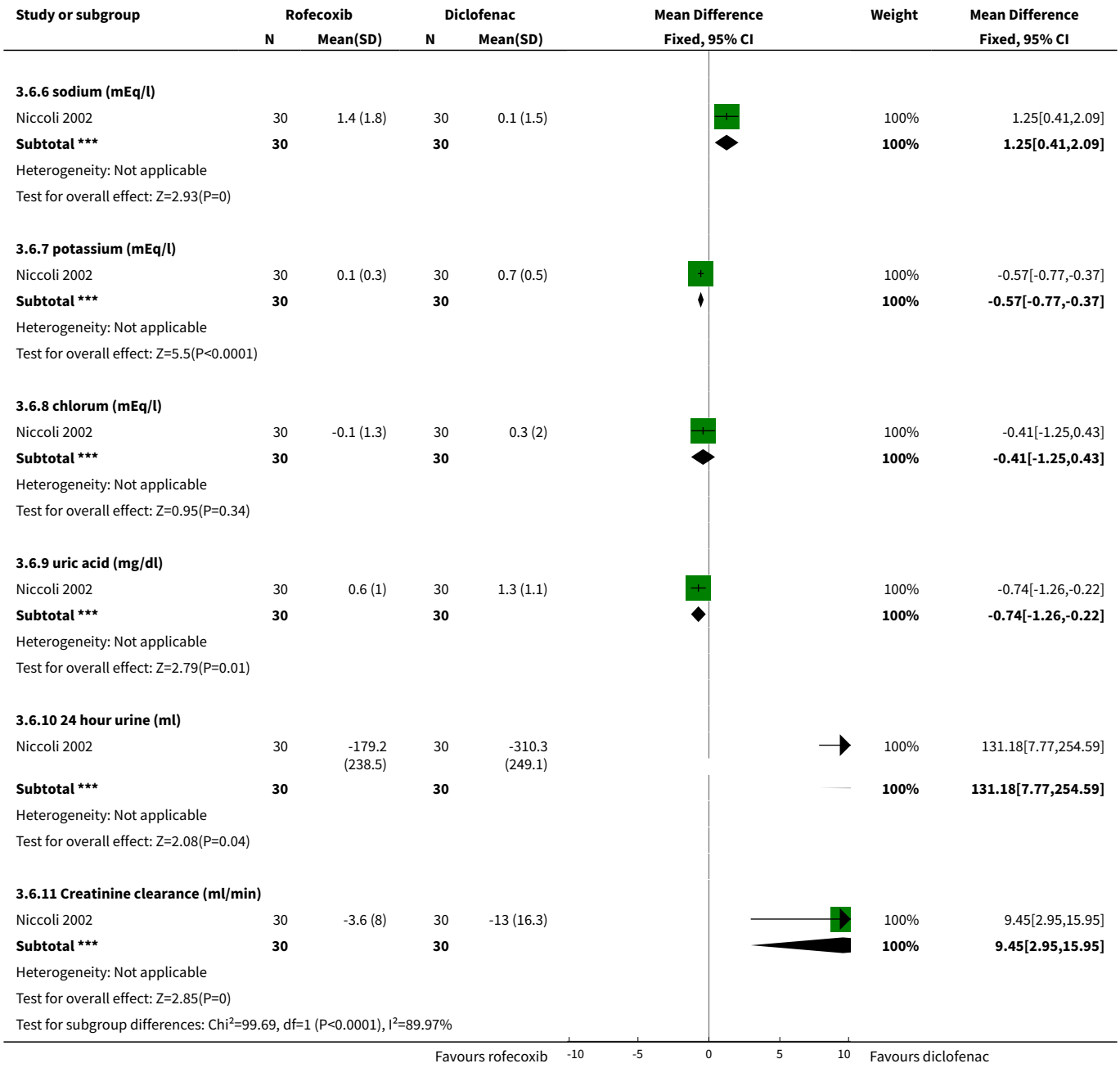


Analysis 3.5. Comparison 3 rofecoxib versus diclofenac, Outcome 5 Use of concomitant OA treatment post 26 weeks.



Analysis 3.6. Comparison 3 rofecoxib versus diclofenac, Outcome 6 Renal function 2 weeks.





Comparison 4. rofecoxib versus ibuprofen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADVERSE EVENTS*	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Total 12.5mg 6 weeks	1	493	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.17]
1.2 Total 25mg 6 weeks	1	491	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.87, 1.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7 Total 25mg 18 weeks	2	766	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.95, 1.10]
1.8 Total 50 mg 18 weeks	2	755	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.96, 1.12]
1.13 Diarrhoea 12.5mg	2	933	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.58, 1.98]
1.14 Diarrhoea 25mg	2	939	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.57, 1.96]
1.15 Diarrhoea 25mg 18 weeks	2	766	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.67, 1.47]
1.16 Diarrhoea 50mg 18 weeks	2	755	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.58, 1.32]
1.25 PUBs 12.5mg 6 weeks	2	933	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.26]
1.26 PUBs 25mg 6 weeks	2	939	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.25]
1.30 lower extremity oedema 12.5mg 6 weeks	1	440	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.30, 3.44]
1.31 lower extremity oedema 25mg 6 weeks	1	448	Risk Ratio (M-H, Fixed, 95% CI)	2.34 [0.84, 6.52]
2 WITHDRAWALS*	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Total 12.5mg 6 weeks	1	440	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.66, 1.63]
2.2 Total 25mg 6 weeks	1	448	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.51, 1.32]
2.3 Total 25mg 18/24 weeks	2	766	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.42, 0.59]
2.4 Total 50mg 18/24 weeks	2	755	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.49, 0.67]
2.5 due to AE 12.5mg 6 weeks	2	933	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.44, 1.27]
2.6 due to AE 25mg 6 weeks	2	939	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.47, 1.36]
2.7 due to AE 25mg 16 weeks	2	766	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.42, 0.99]
2.8 due to AE 50mg 18/24 weeks	2	755	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.64, 1.40]
2.11 due to LOE 12.5mg 6 weeks	2	933	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.54, 1.52]
2.12 due to LOE 25mg 6 weeks	2	939	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.31, 1.03]
2.13 due to LOE 25mg 16 weeks	2	766	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.39, 1.75]
2.14 due to LOE 50mg 16 weeks	2	755	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.20, 1.21]
2.25 due to GI AE 12.5 mg 6 weeks	1	440	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.23, 2.24]
2.26 due to GI AE 25 mg 6 weeks	1	448	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.41, 3.02]

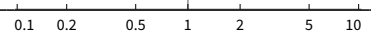
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.30 due to lower extremity oedema 12.5 mg 6 weeks	1	440	Risk Ratio (M-H, Fixed, 95% CI)	3.03 [0.12, 73.91]
2.31 due to lower extremity oedema 25 mg 6 weeks	1	448	Risk Ratio (M-H, Fixed, 95% CI)	2.92 [0.12, 71.32]
2.32 due to CV AE 12.5 mg	1	440	Risk Ratio (M-H, Fixed, 95% CI)	3.03 [0.12, 73.91]
2.33 due to CV AE 25 mg	1	448	Risk Ratio (M-H, Fixed, 95% CI)	4.87 [0.24, 100.84]
2.34 due to diarrhoea 12.5 mg 6 weeks	1	440	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.35 due to diarrhoea 25 mg 6 weeks	1	448	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Ulcer 12 weeks (endoscoped)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Ulcer >= 3mm rofecoxib 25mg	2	727	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.11, 0.27]
3.2 Ulcer >= 3mm rofecoxib 50mg	2	714	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.19, 0.42]
3.3 Ulcer >= 5mm rofecoxib 25mg	2	727	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.07, 0.24]
3.4 Ulcer >=5mm rofecoxib 50mg	2	714	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.20, 0.49]
3.5 Gastric Ulcer >= 3mm rofecoxib 25mg	2	727	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.09, 0.25]
3.6 Gastric Ulcer >= 3mm rofecoxib 50mg	2	714	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.14, 0.36]
3.7 Duodenal Ulcer >= 3mm rofecoxib 25mg	2	727	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.09, 0.63]
3.8 Duodenal Ulcer >= 3mm rofecoxib 50mg	2	714	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.27, 1.12]
4 EFFICACY- patient/investigator- dicotomous	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Patient global- good or excellent response 12.5 mg 6 weeks	1	440	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.81, 1.13]
4.2 Patient global- good or excellent response 25 mg 6 weeks	1	448	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.91, 1.25]
5 EFFICACY-WOMAC	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 WOMAC pain on walking 12.5mg 6 weeks	1	493	Mean Difference (IV, Fixed, 95% CI)	0.77 [-3.07, 4.61]

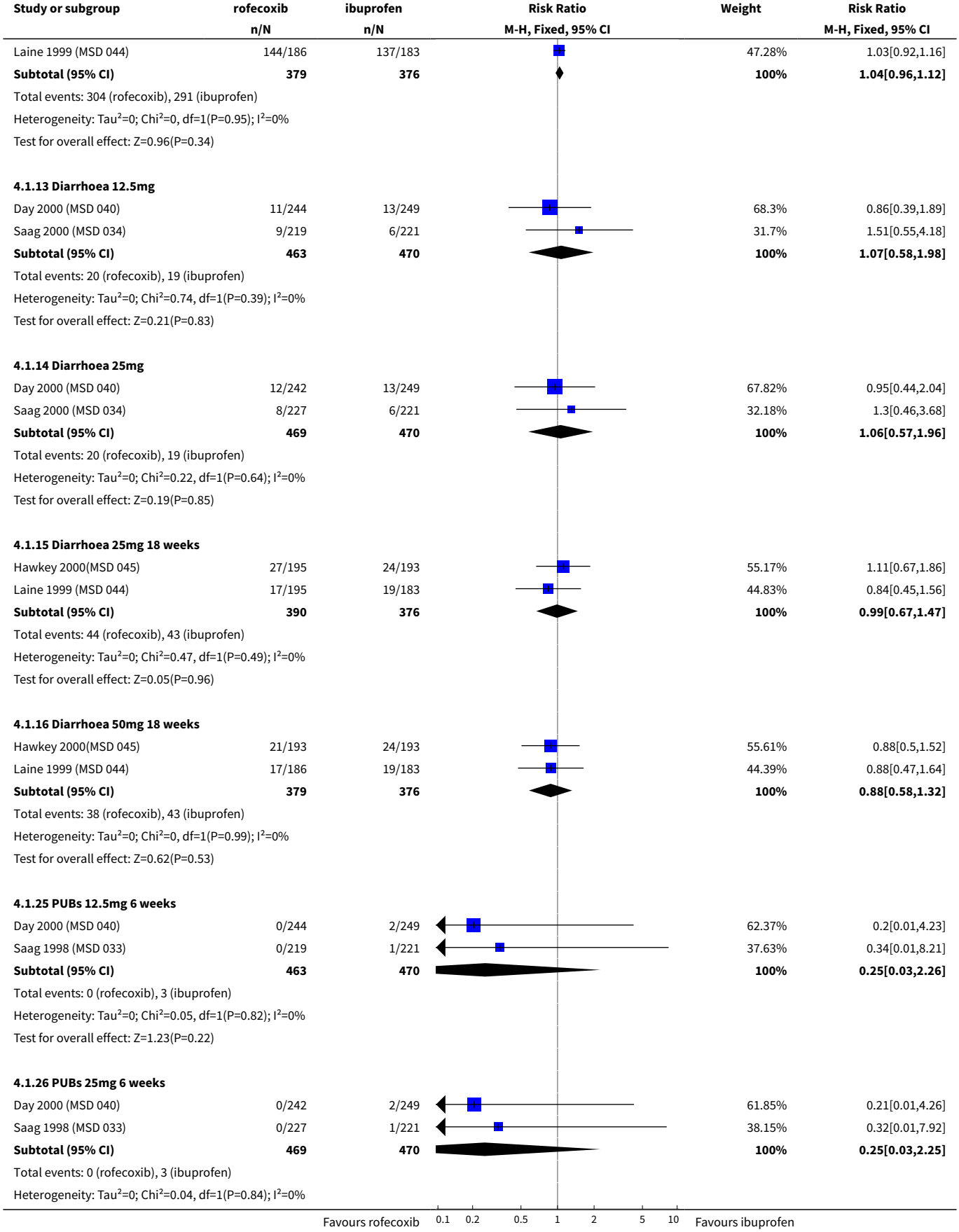
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 WOMAC pain on walking 25mg 6 weeks	1	491	Mean Difference (IV, Fixed, 95% CI)	1.52 [-2.34, 5.38]
5.3 WOMAC physical function subscale 12.5mg 6 weeks	1	493	Mean Difference (IV, Fixed, 95% CI)	0.67 [-2.50, 3.84]
5.4 WOMAC physical function subscale 25mg 6 weeks	1	491	Mean Difference (IV, Fixed, 95% CI)	2.58 [-0.61, 5.77]
5.5 pain 12.5mg 6 weeks	1	493	Mean Difference (IV, Fixed, 95% CI)	0.48 [-2.79, 3.75]
5.6 pain 25mg 6 weeks	1	491	Mean Difference (IV, Fixed, 95% CI)	1.89 [-1.41, 5.19]
5.7 stiffness 12.5mg 6 weeks	1	493	Mean Difference (IV, Fixed, 95% CI)	1.07 [-2.50, 4.64]
5.8 stiffness 25mg 6 weeks	1	491	Mean Difference (IV, Fixed, 95% CI)	0.62 [-2.96, 4.20]
6 EFFICACY- patient/investigator measured- continuous	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Patient Global Response 12.5mg 6 weeks	1	493	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.10, 0.22]
6.2 Patient Global Response 25mg 6 weeks	1	491	Mean Difference (IV, Fixed, 95% CI)	0.22 [0.06, 0.38]
6.3 Investigator Global Disease Status 12.5mg 6 weeks	1	493	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.06, 0.20]
6.4 Investigator Global Disease Status 25mg 6 weeks	1	491	Mean Difference (IV, Fixed, 95% CI)	0.19 [0.06, 0.32]
6.5 patient disease status 12.5mg 6 weeks	1	493	Mean Difference (IV, Fixed, 95% CI)	1.65 [-2.01, 5.31]
6.6 patient disease status 25mg 6 weeks	1	491	Mean Difference (IV, Fixed, 95% CI)	3.77 [0.09, 7.45]
6.7 investigator global response 12.5mg 6 weeks	1	493	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.13, 0.21]
6.8 Investigator global response 25mg 6 weeks	1	491	Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.01, 0.33]
7 Sudy joint tenderness (0-3)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 12.5mg 6 weeks	1	493	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.10, 0.14]

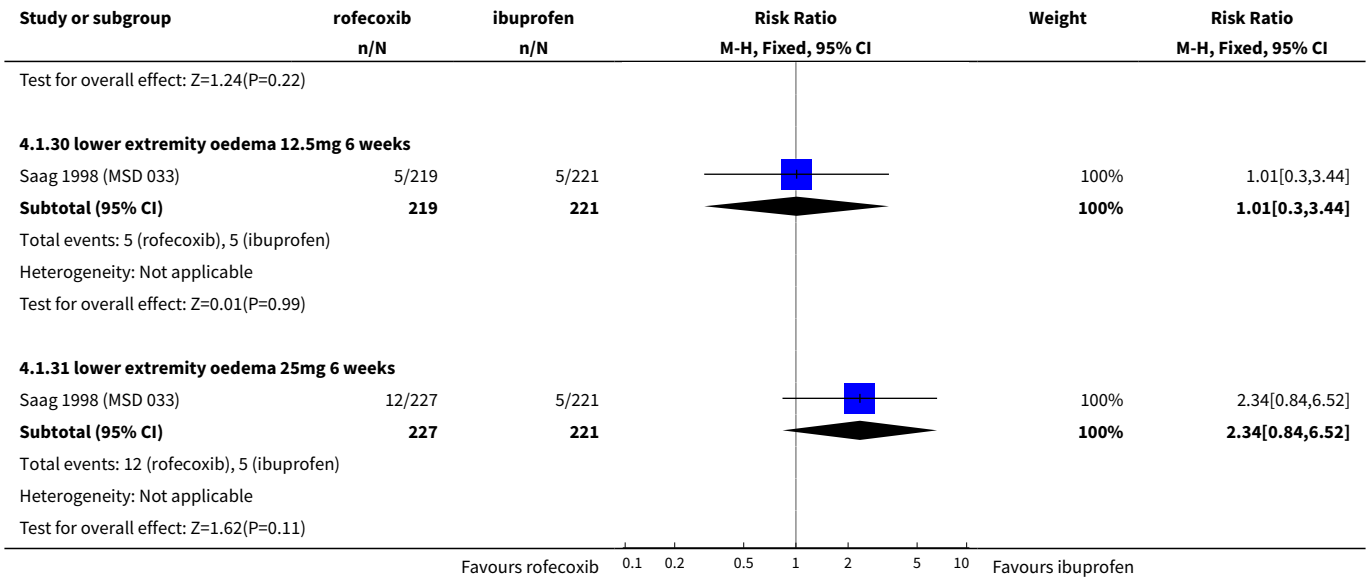
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 25mg 6 weeks	1	491	Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.00, 0.22]
8 Paracetamol use- tablets per day	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 12.5mg 6 weeks	1	493	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.30, 0.08]
8.2 25mg 6 weeks	1	491	Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.36, 0.02]
9 Erosions (endoscoped)-change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 25mg 12 weeks	1	374	Mean Difference (IV, Fixed, 95% CI)	-2.98 [-3.71, -2.25]
9.2 50mg 12 weeks	1	369	Mean Difference (IV, Fixed, 95% CI)	-2.74 [-3.48, -2.00]

Analysis 4.1. Comparison 4 rofecoxib versus ibuprofen, Outcome 1 ADVERSE EVENTS*.

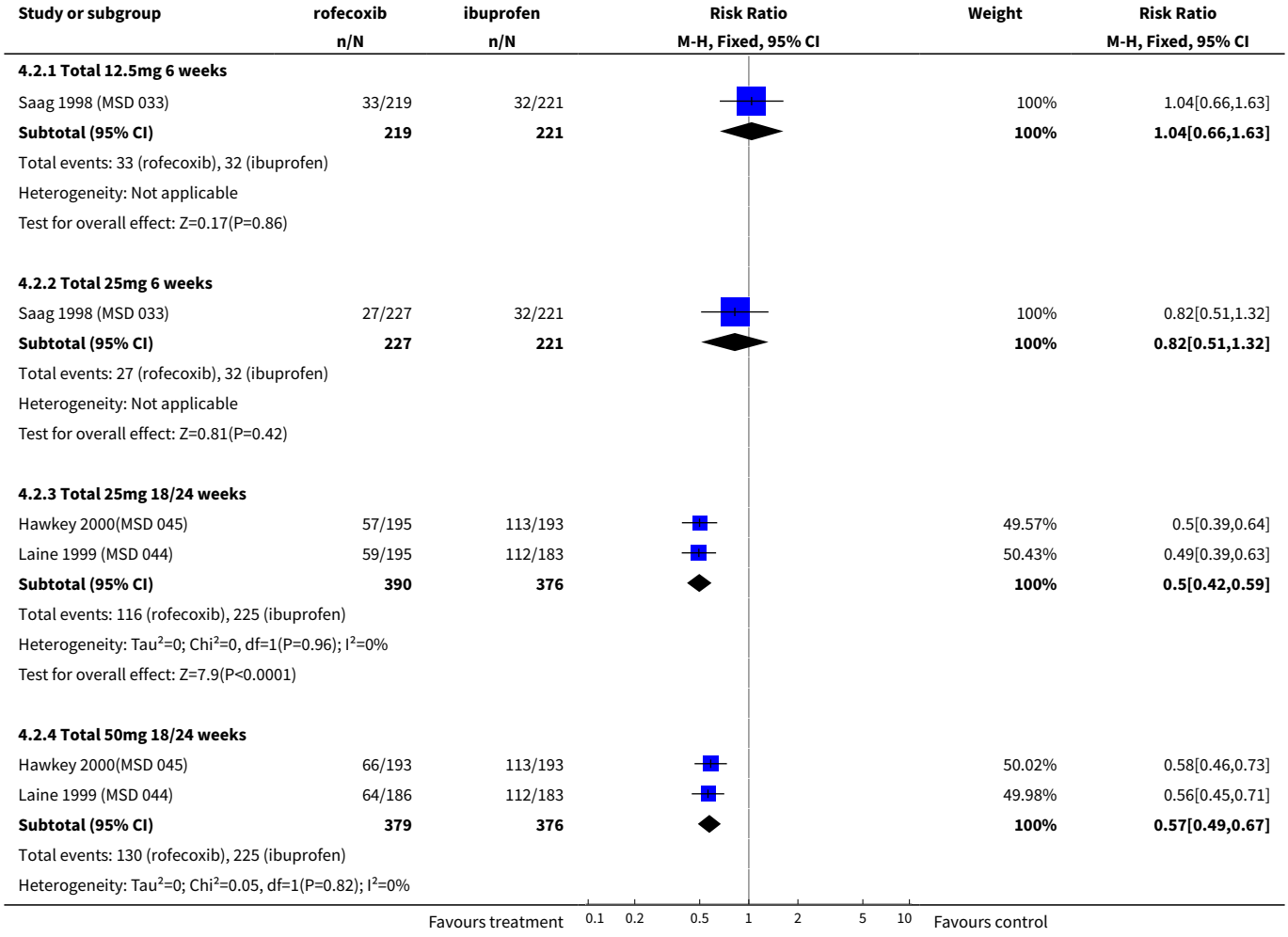
Study or subgroup	rofecoxib n/N	ibuprofen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Total 12.5mg 6 weeks					
Day 2000 (MSD 040)	124/244	129/249		100%	0.98[0.83,1.17]
Subtotal (95% CI)	**244**	**249**		**100%**	**0.98[0.83,1.17]**
Total events: 124 (rofecoxib), 129 (ibuprofen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.22(P=0.83)					
4.1.2 Total 25mg 6 weeks					
Day 2000 (MSD 040)	129/242	129/249		100%	1.03[0.87,1.22]
Subtotal (95% CI)	**242**	**249**		**100%**	**1.03[0.87,1.22]**
Total events: 129 (rofecoxib), 129 (ibuprofen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.33(P=0.74)					
4.1.7 Total 25mg 18 weeks					
Hawkey 2000(MSD 045)	156/195	154/193		52.27%	1[0.91,1.11]
Laine 1999 (MSD 044)	153/195	137/183		47.73%	1.05[0.94,1.17]
Subtotal (95% CI)	**390**	**376**		**100%**	**1.02[0.95,1.1]**
Total events: 309 (rofecoxib), 291 (ibuprofen)					
Heterogeneity: Tau^2=0; Chi^2=0.34, df=1(P=0.56); I^2=0%					
Test for overall effect: Z=0.63(P=0.53)					
4.1.8 Total 50 mg 18 weeks					
Hawkey 2000(MSD 045)	160/193	154/193		52.72%	1.04[0.94,1.14]

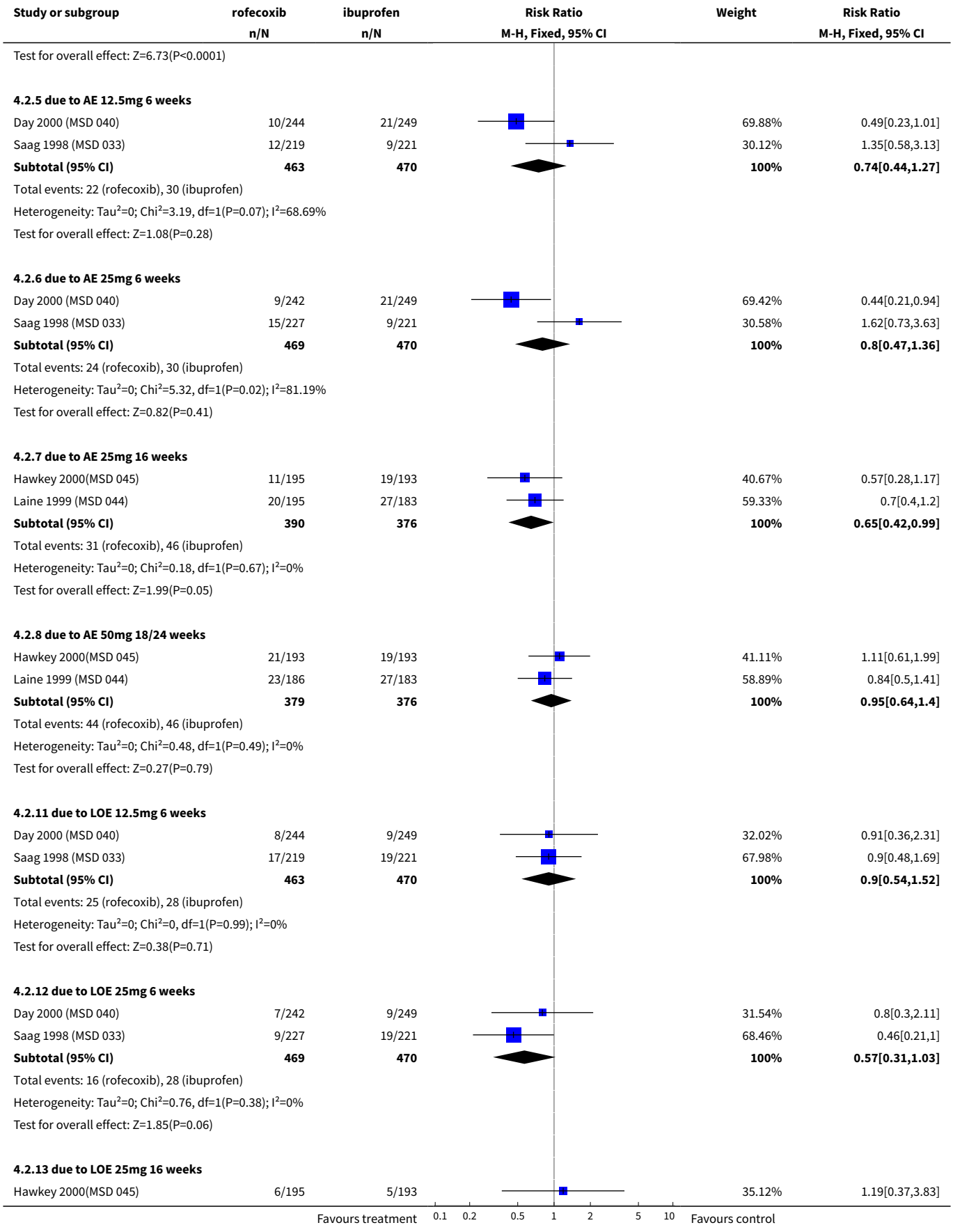


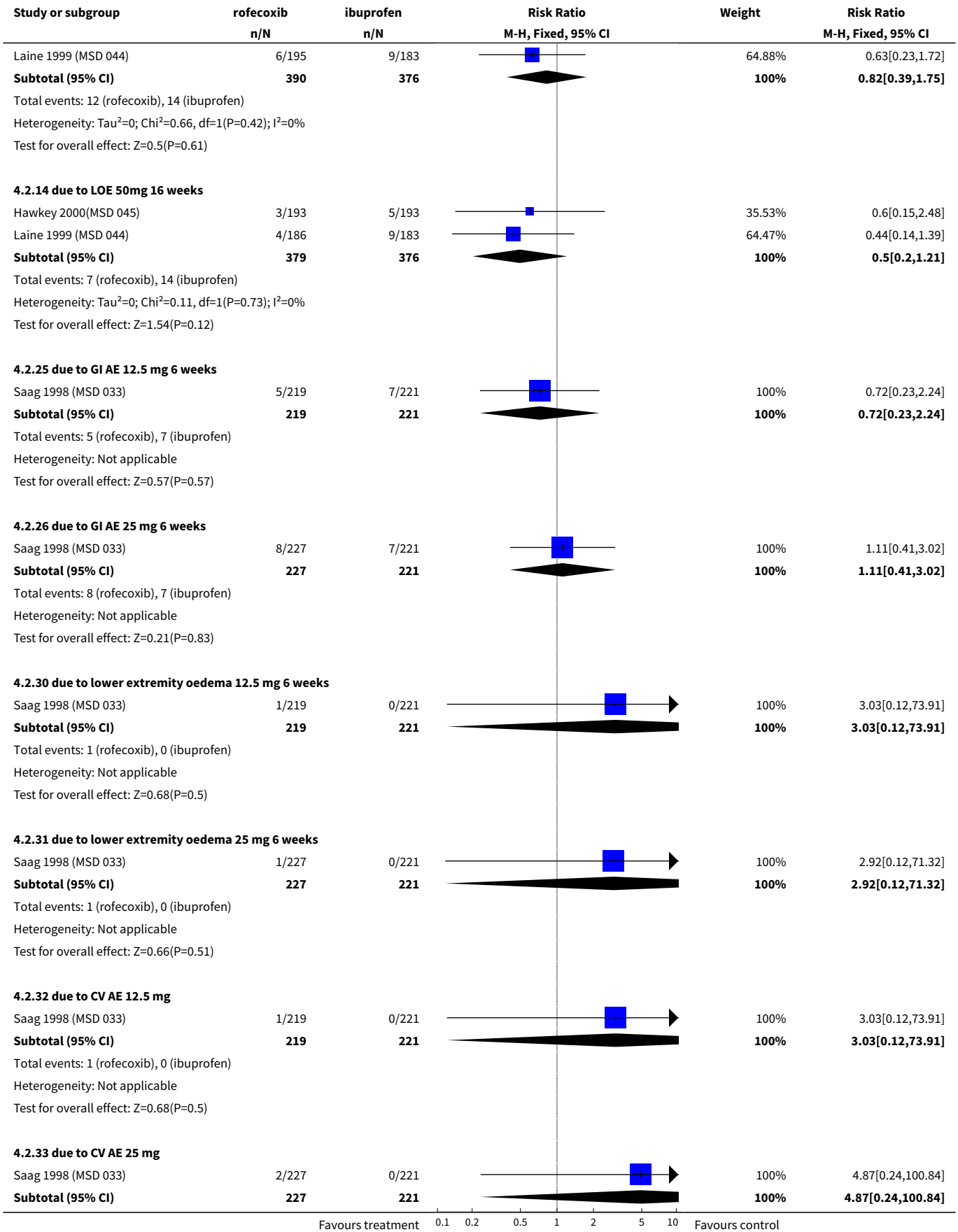




Analysis 4.2. Comparison 4 rofecoxib versus ibuprofen, Outcome 2 WITHDRAWALS*.







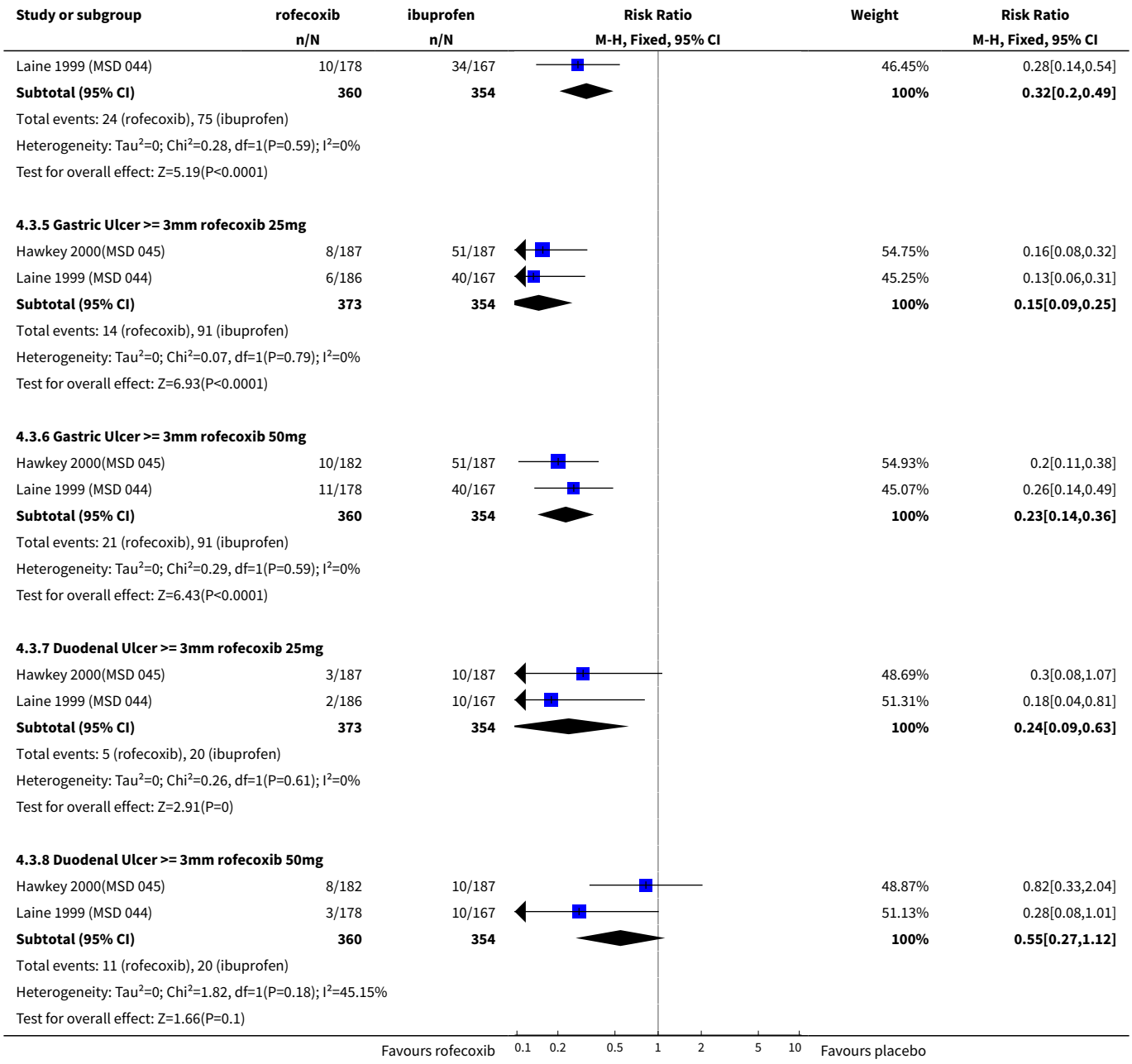
Study or subgroup	rofecoxib n/N	ibuprofen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 2 (rofecoxib), 0 (ibuprofen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.02(P=0.31)					
4.2.34 due to diarrhoea 12.5 mg 6 weeks					
Saag 1998 (MSD 033)	0/219	0/221			Not estimable
Subtotal (95% CI)	**219**	**221**			**Not estimable**
Total events: 0 (rofecoxib), 0 (ibuprofen)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.2.35 due to diarrhoea 25 mg 6 weeks					
Saag 1998 (MSD 033)	0/227	0/221			Not estimable
Subtotal (95% CI)	**227**	**221**			**Not estimable**
Total events: 0 (rofecoxib), 0 (ibuprofen)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

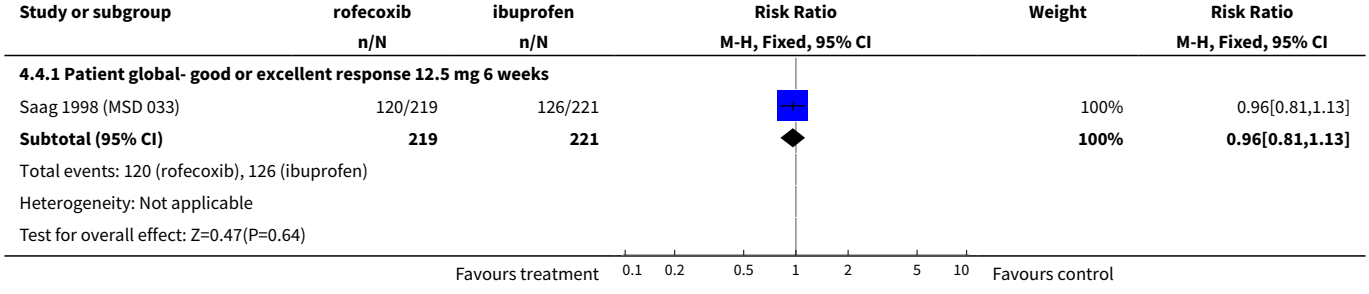
Analysis 4.3. Comparison 4 rofecoxib versus ibuprofen, Outcome 3 Ulcer 12 weeks (endoscoped).

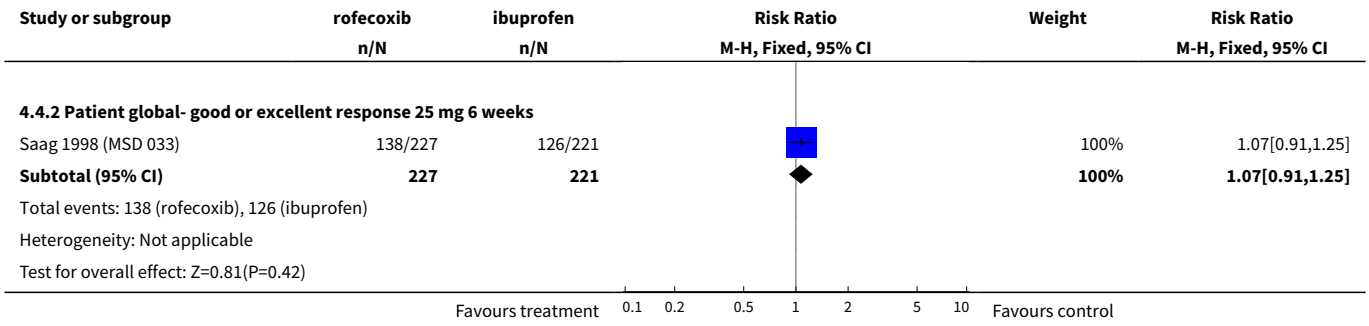
Study or subgroup	rofecoxib n/N	ibuprofen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 Ulcer >= 3mm rofecoxib 25mg					
Hawkey 2000(MSD 045)	10/187	55/187		53.15%	0.18[0.1,0.35]
Laine 1999 (MSD 044)	8/186	46/167		46.85%	0.16[0.08,0.32]
Subtotal (95% CI)	**373**	**354**		**100%**	**0.17[0.11,0.27]**
Total events: 18 (rofecoxib), 101 (ibuprofen)					
Heterogeneity: Tau^2=0; Chi^2=0.1, df=1(P=0.76); I^2=0%					
Test for overall effect: Z=7.25(P<0.0001)					
4.3.2 Ulcer >= 3mm rofecoxib 50mg					
Hawkey 2000(MSD 045)	16/182	55/187		53.34%	0.3[0.18,0.5]
Laine 1999 (MSD 044)	13/178	46/167		46.66%	0.27[0.15,0.47]
Subtotal (95% CI)	**360**	**354**		**100%**	**0.28[0.19,0.42]**
Total events: 29 (rofecoxib), 101 (ibuprofen)					
Heterogeneity: Tau^2=0; Chi^2=0.09, df=1(P=0.76); I^2=0%					
Test for overall effect: Z=6.41(P<0.0001)					
4.3.3 Ulcer >= 5mm rofecoxib 25mg					
Hawkey 2000(MSD 045)	7/187	41/187		53.36%	0.17[0.08,0.37]
Laine 1999 (MSD 044)	3/186	34/167		46.64%	0.08[0.02,0.25]
Subtotal (95% CI)	**373**	**354**		**100%**	**0.13[0.07,0.24]**
Total events: 10 (rofecoxib), 75 (ibuprofen)					
Heterogeneity: Tau^2=0; Chi^2=1.18, df=1(P=0.28); I^2=15.59%					
Test for overall effect: Z=6.29(P<0.0001)					
4.3.4 Ulcer >=5mm rofecoxib 50mg					
Hawkey 2000(MSD 045)	14/182	41/187		53.55%	0.35[0.2,0.62]

Favours rofecoxib 0.1 0.2 0.5 1 2 5 10 Favours placebo

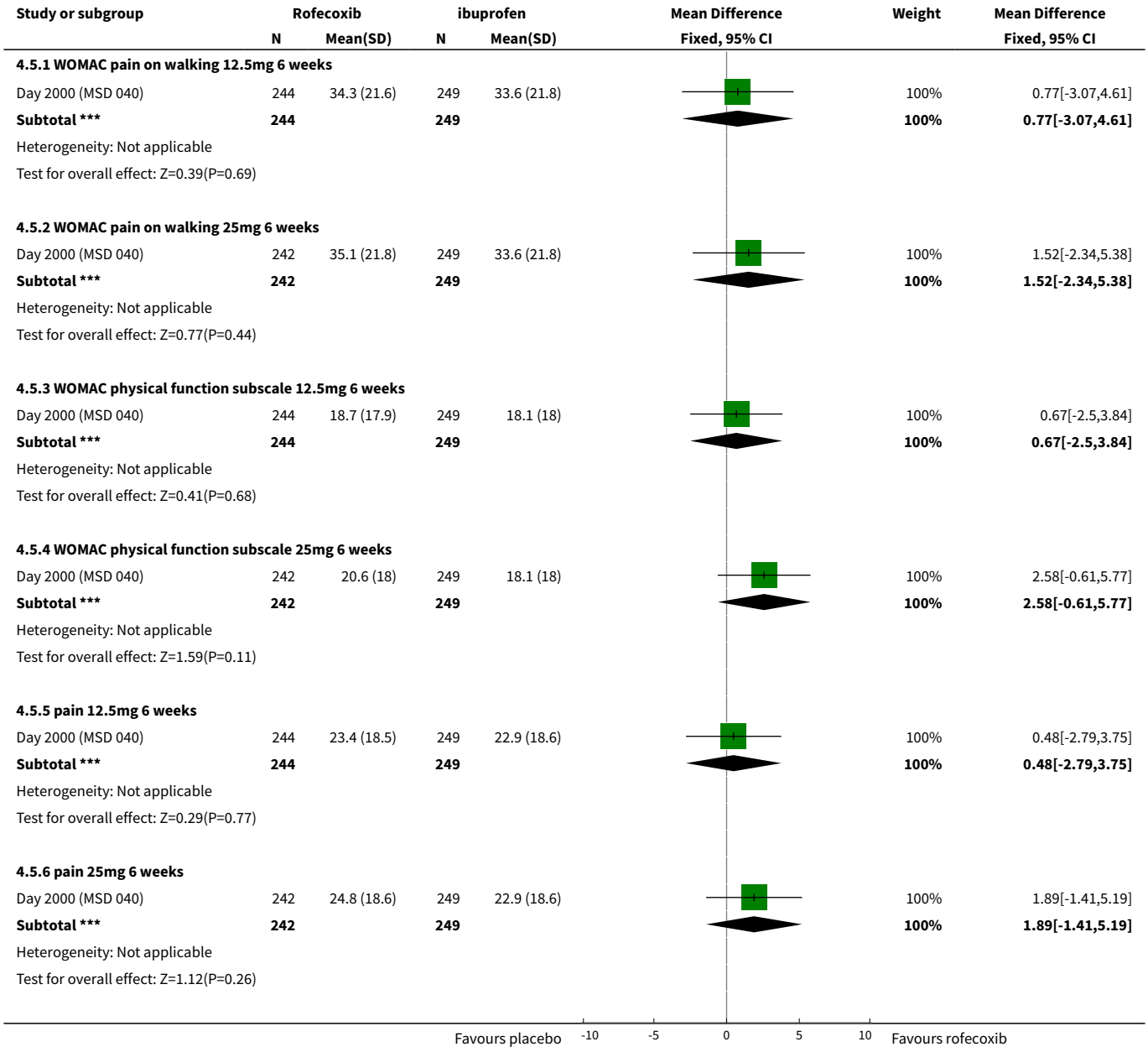


Analysis 4.4. Comparison 4 rofecoxib versus ibuprofen, Outcome 4 EFFICACY- patient/investigator- dicotomous.

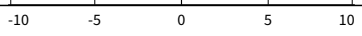




Analysis 4.5. Comparison 4 rofecoxib versus ibuprofen, Outcome 5 EFFICACY-WOMAC.

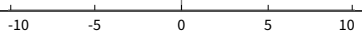


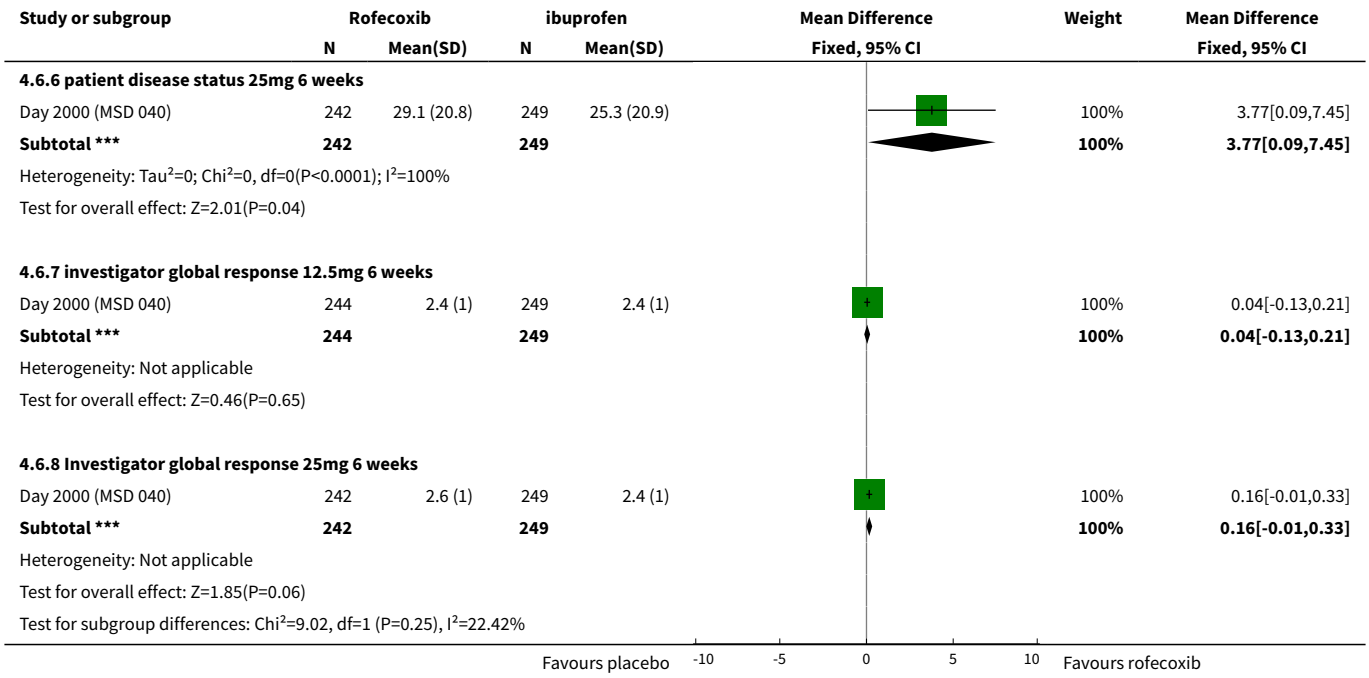
Study or subgroup	Rofecoxib N	Rofecoxib Mean(SD)	ibuprofen N	ibuprofen Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.5.7 stiffness 12.5mg 6 weeks							
Day 2000 (MSD 040)	244	21.2 (20.2)	249	20.2 (20.3)		100%	1.07[-2.5,4.64]
Subtotal ***	**244**		**249**			**100%**	**1.07[-2.5,4.64]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.59(P=0.56)							
4.5.8 stiffness 25mg 6 weeks							
Day 2000 (MSD 040)	242	20.8 (20.2)	249	20.2 (20.3)		100%	0.62[-2.96,4.2]
Subtotal ***	**242**		**249**			**100%**	**0.62[-2.96,4.2]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.34(P=0.73)							
Test for subgroup differences: Chi^2=1.36, df=1 (P=0.99), I^2=0%							



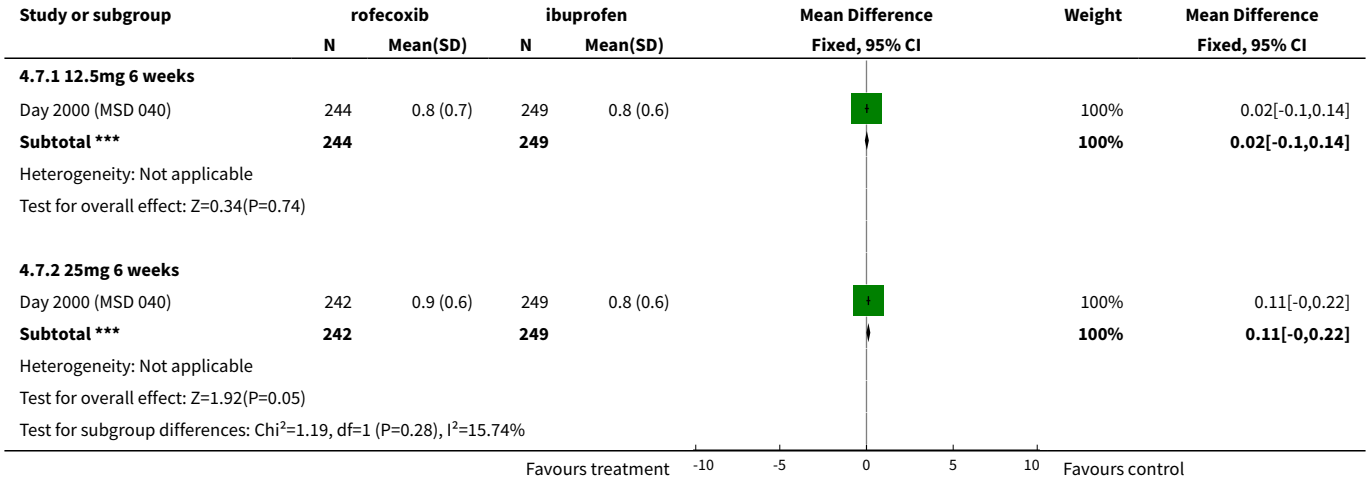
Analysis 4.6. Comparison 4 rofecoxib versus ibuprofen, Outcome 6 EFFICACY- patient/investigator measured- continuous.

Study or subgroup	Rofecoxib N	Rofecoxib Mean(SD)	ibuprofen N	ibuprofen Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.6.1 Patient Global Response 12.5mg 6 weeks							
Day 2000 (MSD 040)	244	2.3 (0.9)	249	2.2 (0.9)		100%	0.06[-0.1,0.22]
Subtotal ***	**244**		**249**			**100%**	**0.06[-0.1,0.22]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0.72(P=0.47)							
4.6.2 Patient Global Response 25mg 6 weeks							
Day 2000 (MSD 040)	242	2.4 (0.9)	249	2.2 (0.9)		100%	0.22[0.06,0.38]
Subtotal ***	**242**		**249**			**100%**	**0.22[0.06,0.38]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.65(P=0.01)							
4.6.3 Investigator Global Disease Status 12.5mg 6 weeks							
Day 2000 (MSD 040)	244	1.5 (0.8)	249	1.4 (0.8)		100%	0.07[-0.06,0.2]
Subtotal ***	**244**		**249**			**100%**	**0.07[-0.06,0.2]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.02(P=0.31)							
4.6.4 Investigator Global Disease Status 25mg 6 weeks							
Day 2000 (MSD 040)	242	1.6 (0.8)	249	1.4 (0.8)		100%	0.19[0.06,0.32]
Subtotal ***	**242**		**249**			**100%**	**0.19[0.06,0.32]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.79(P=0.01)							
4.6.5 patient disease status 12.5mg 6 weeks							
Day 2000 (MSD 040)	244	26.9 (20.6)	249	25.3 (20.9)		100%	1.65[-2.01,5.31]
Subtotal ***	**244**		**249**			**100%**	**1.65[-2.01,5.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.88(P=0.38)							

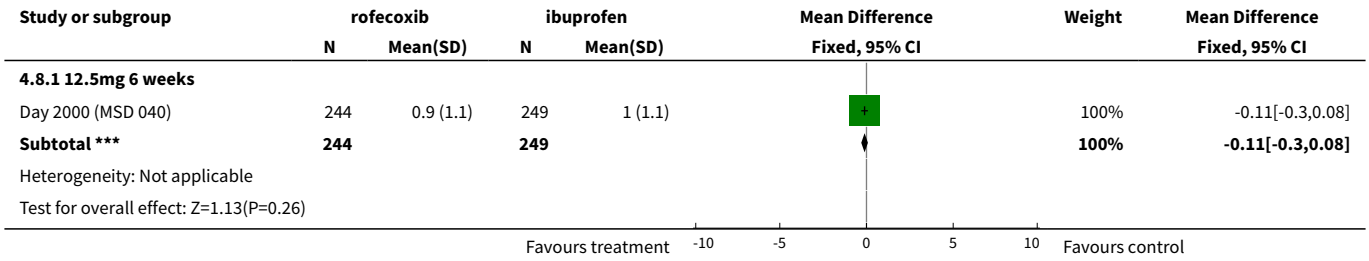




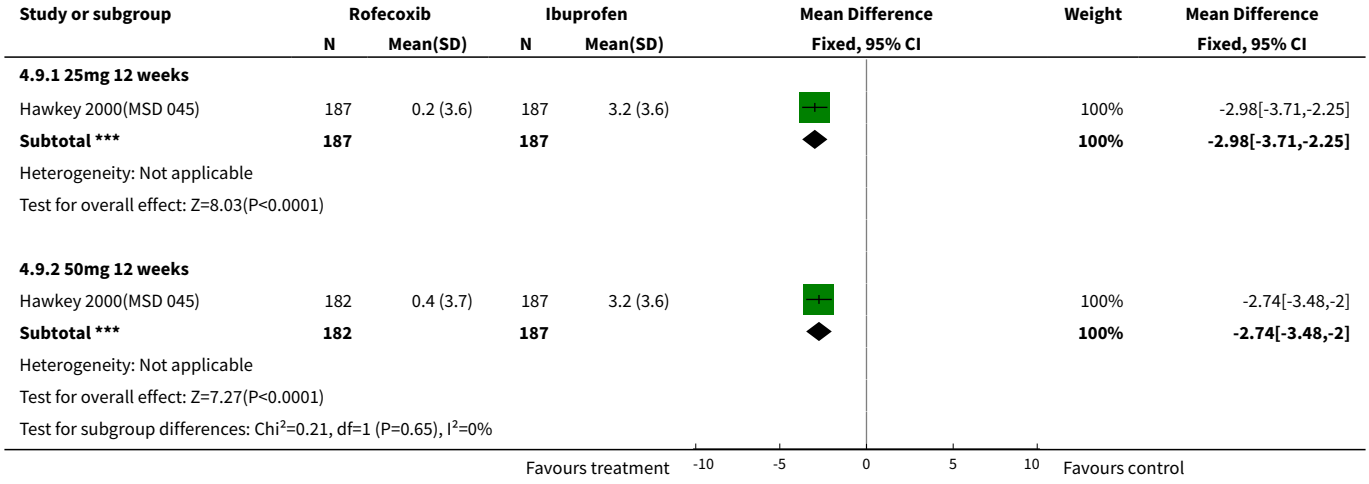
Analysis 4.7. Comparison 4 rofecoxib versus ibuprofen, Outcome 7 Sudy joint tenderness (0-3).



Analysis 4.8. Comparison 4 rofecoxib versus ibuprofen, Outcome 8 Paracetamol use- tablets per day.



Analysis 4.9. Comparison 4 rofecoxib versus ibuprofen, Outcome 9 Erosions (endoscoped)-change from baseline.



Comparison 5. rofecoxib versus naproxen

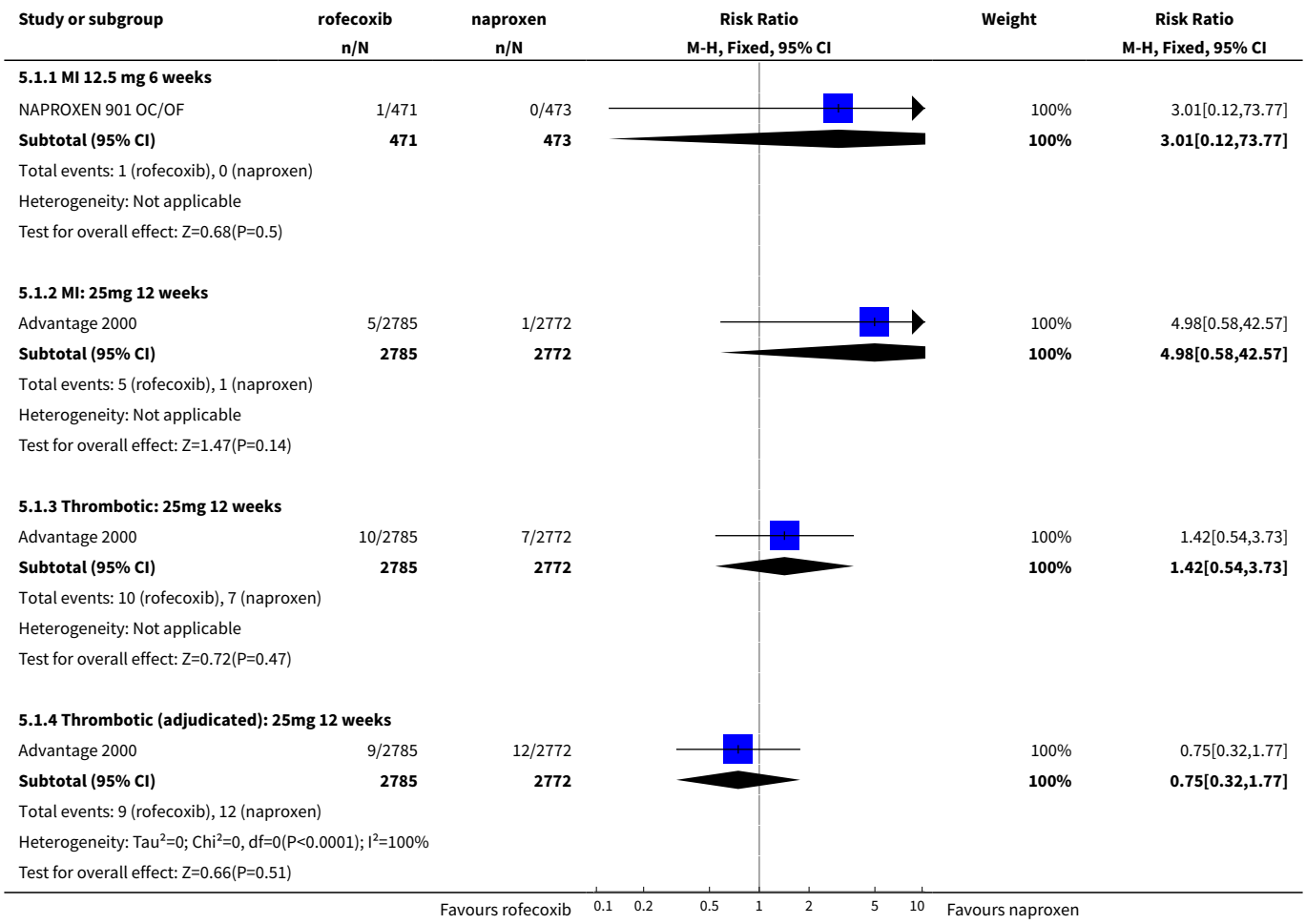
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 MI 12.5 mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	3.01 [0.12, 73.77]
1.2 MI: 25mg 12 weeks	1	5557	Risk Ratio (M-H, Fixed, 95% CI)	4.98 [0.58, 42.57]
1.3 Thrombotic: 25mg 12 weeks	1	5557	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.54, 3.73]
1.4 Thrombotic (adjudicated): 25mg 12 weeks	1	5557	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.32, 1.77]
1.5 Stroke: 25mg 12 weeks	1	5557	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.36]

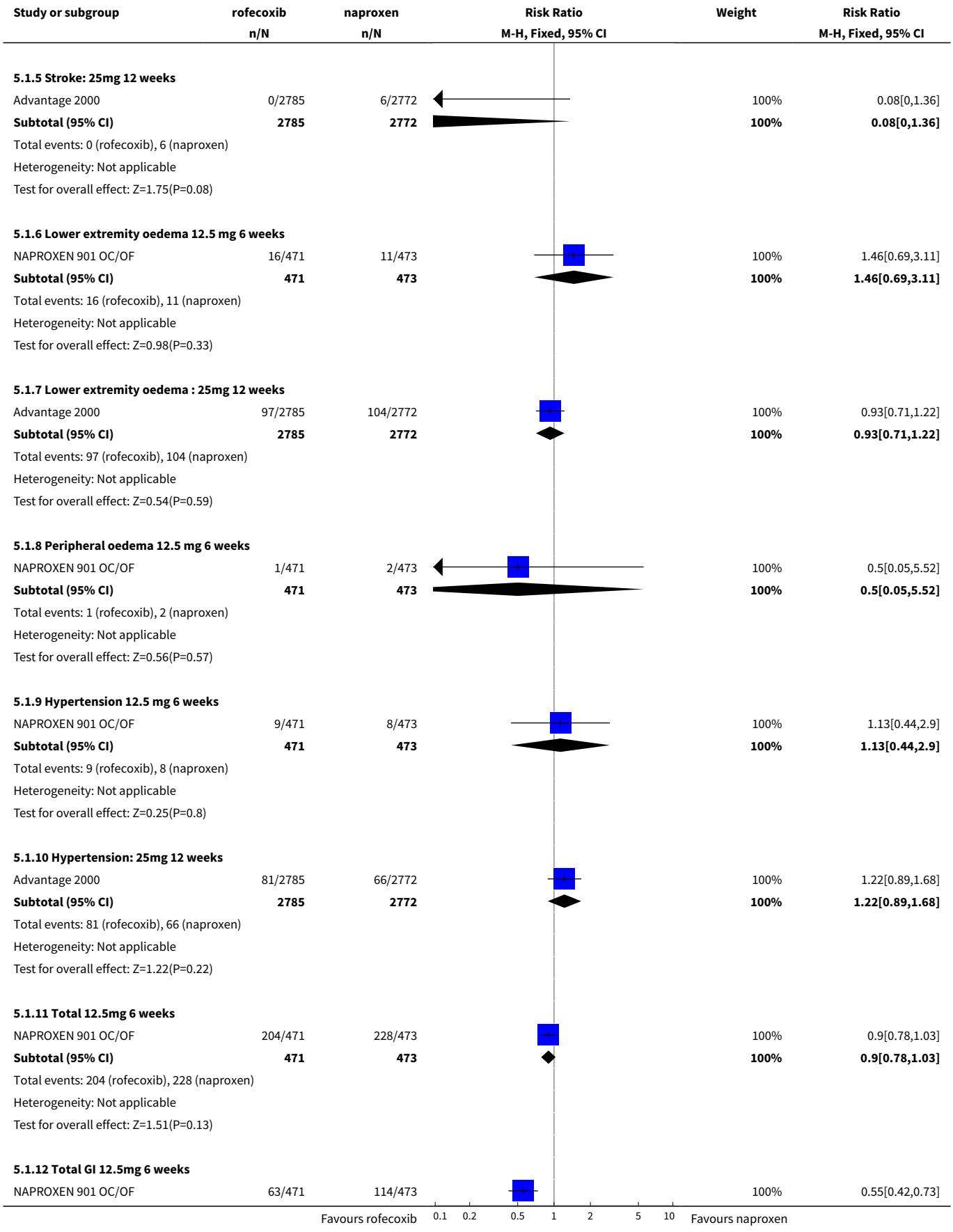
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Lower extremity oedema 12.5 mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.69, 3.11]
1.7 Lower extremity oedema : 25mg 12 weeks	1	5557	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.71, 1.22]
1.8 Peripheral oedema 12.5 mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.52]
1.9 Hypertension 12.5 mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.44, 2.90]
1.10 Hypertension: 25mg 12 weeks	1	5557	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.89, 1.68]
1.11 Total 12.5mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.78, 1.03]
1.12 Total GI 12.5mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.42, 0.73]
1.13 PUB 12.5mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.77]
1.14 Exceeding predefined limits of change diastolic : 25mg 12 weeks	1	5308	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.84, 1.51]
1.15 Exceeding predefined limits of change systolic : 25mg 12 weeks	1	5308	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.98, 1.35]
1.16 PUB 25mg 12 weeks	1	5557	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.05, 1.02]
1.17 Pre study hypertensive sub group: Hypertension: 25mg 12 weeks	1	2714	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.75, 1.70]
1.18 Pre study hypertensive sub group: Lower extremity oedema 25mg 12 weeks	1	2714	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.68, 1.37]
1.19 Pre-study hypertensive group: Exceeding predefined limits of change diastolic : 25mg 12 weeks	1	2605	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.88, 1.88]
1.20 Pre-study hypertensive group: Exceeding predefined limits of change systolic : 25mg 12 weeks	1	2605	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.88, 1.32]
1.21 laboratory 12.5 mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.57, 1.31]
1.22 Serious AEs 12.5 mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.27, 1.83]

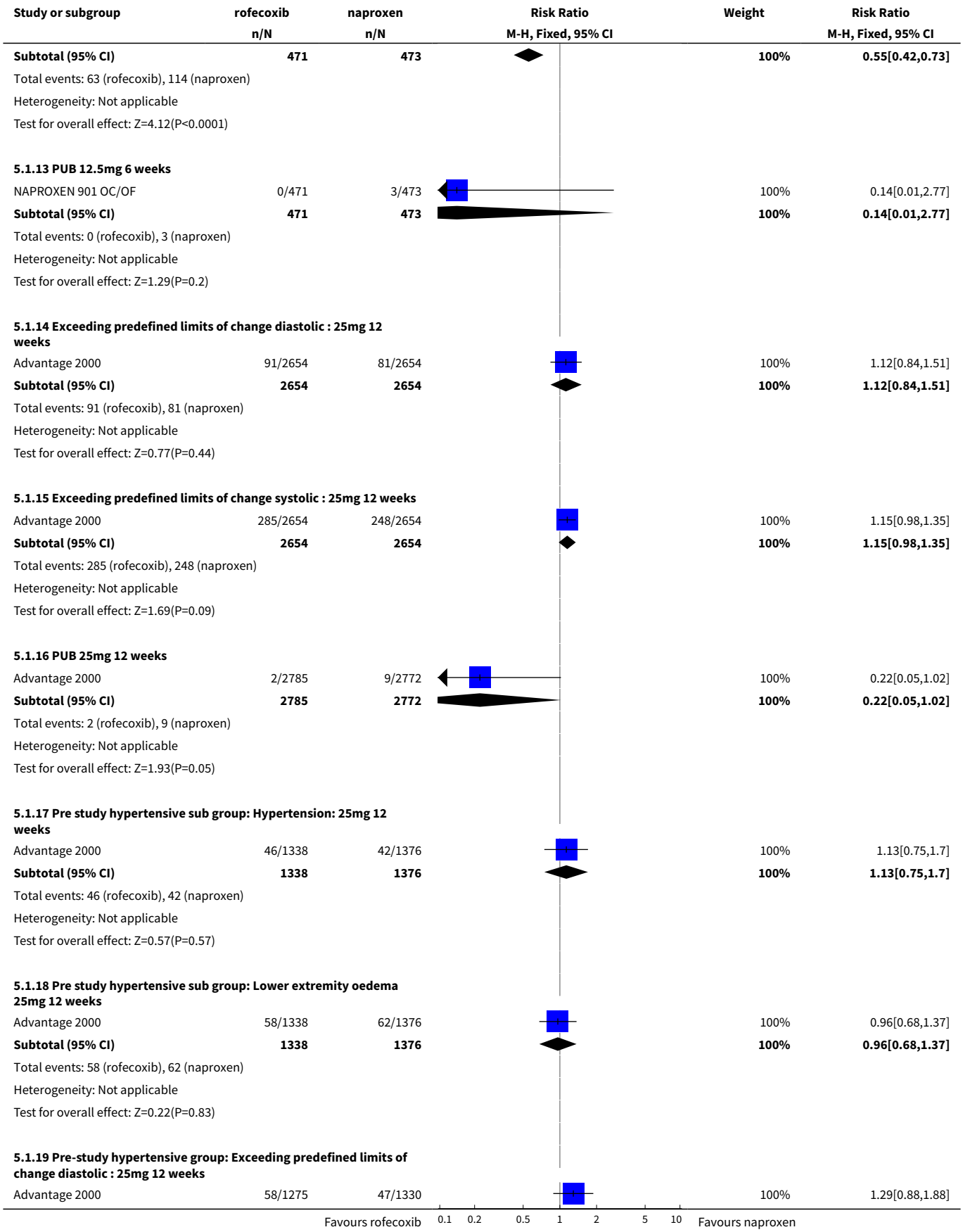
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Withdrawals	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Total 12.5mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.62, 1.23]
2.2 Total 25mg 12 weeks	1	5557	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.88, 1.04]
2.3 due to LOE 12.5mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.19, 2.36]
2.4 due to LOE 25mg 12 weeks	1	5557	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.82, 1.22]
2.5 due to AEs 12.5mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.47, 1.26]
2.6 due to AEs 25mg 12 weeks	1	5557	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.85, 1.10]
2.7 due to GI AEs 12.5mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.10, 0.75]
2.8 due to GI AEs 25mg 12 weeks	1	5557	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.60, 0.88]
2.9 due to GI AEs with concomitant low dose aspirin 25mg 12 weeks	1	719	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.32, 1.01]
2.11 due to laboratory test adverse event 25mg 12 weeks	1	5557	Risk Ratio (M-H, Fixed, 95% CI)	2.19 [0.76, 6.29]
2.12 due to hypertension : 12.5mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	5.02 [0.24, 104.31]
2.13 due to hypertension: 25mg 12 weeks	1	5557	Risk Ratio (M-H, Fixed, 95% CI)	2.49 [0.97, 6.40]
2.14 due to peripheral/lower extremity oedema : 12.5mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	7.03 [0.36, 135.72]
2.15 due to lower extremity oedema : 25mg 12 weeks	1	5557	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.67, 3.90]
2.16 Pre study hypertensive sub group: due to Hypertension: 25mg 12 weeks	1	2714	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [0.53, 6.13]
2.17 Pre study hypertensive sub group: due to lower extremity oedema: 25mg 12 weeks	1	2714	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.43, 3.23]
2.18 due to laboratory test adverse event 12.5mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 16.01]

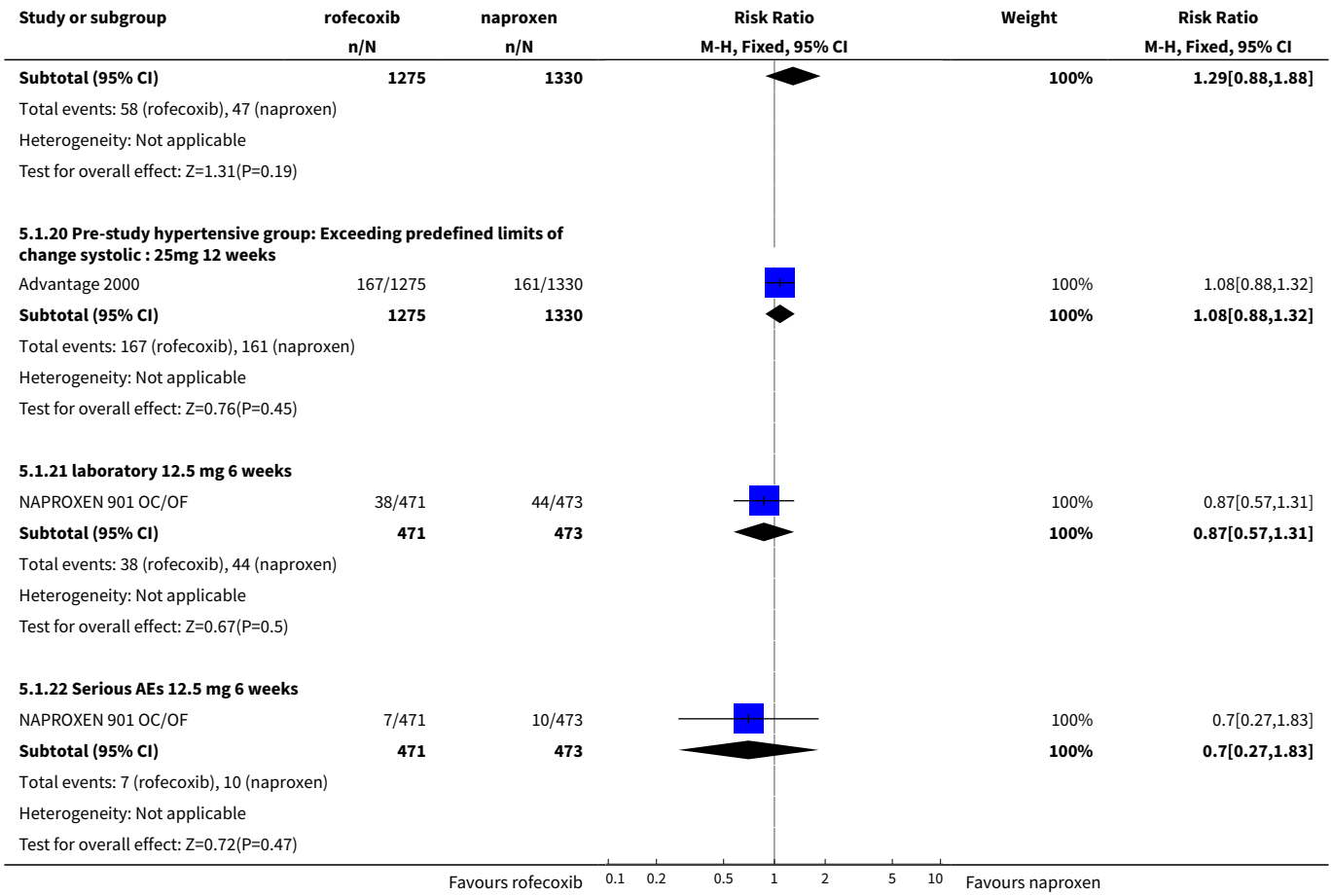
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Concomitant GI medication use	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 25mg 6 weeks	1	5557	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.66, 0.97]
3.2 25mg 12 weeks	1	5557	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.69, 0.95]
3.3 25mg 12 weeks:concomitant low dose aspirin	1	719	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.57, 1.18]
4 Use of rescue medication	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 12.5mg 6 weeks	1	944	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.93, 1.18]

Analysis 5.1. Comparison 5 rofecoxib versus naproxen, Outcome 1 Adverse events.

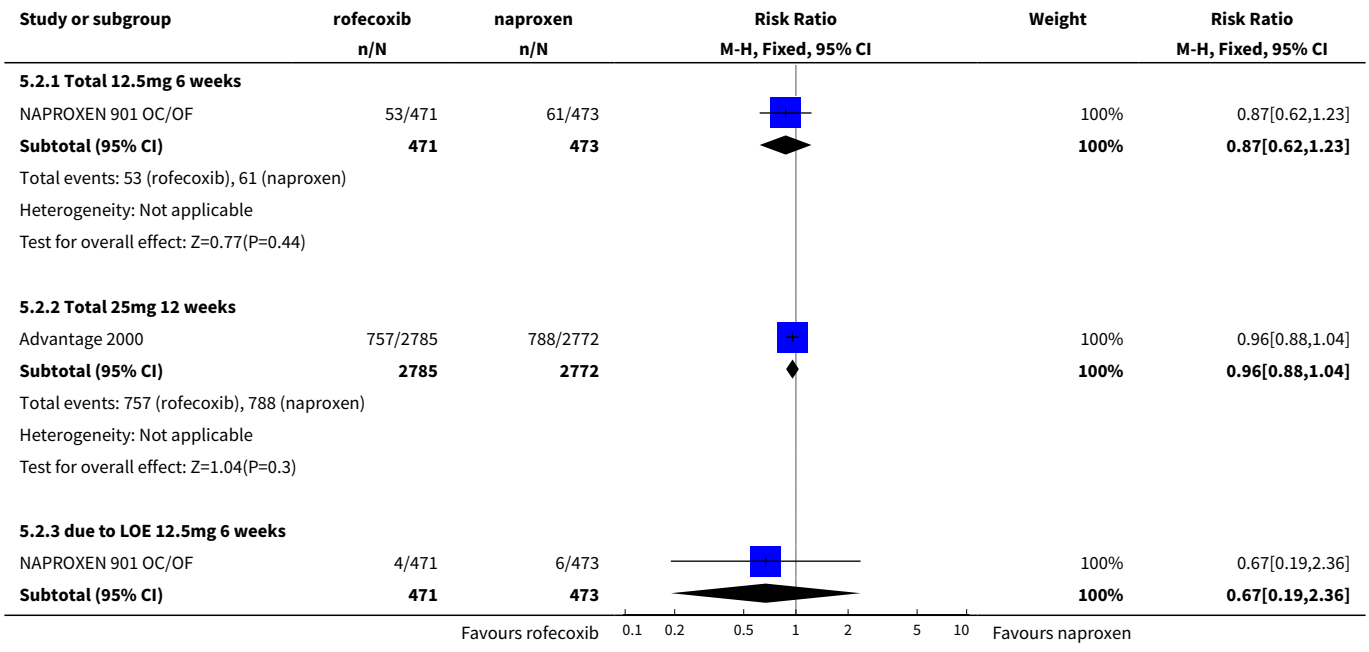


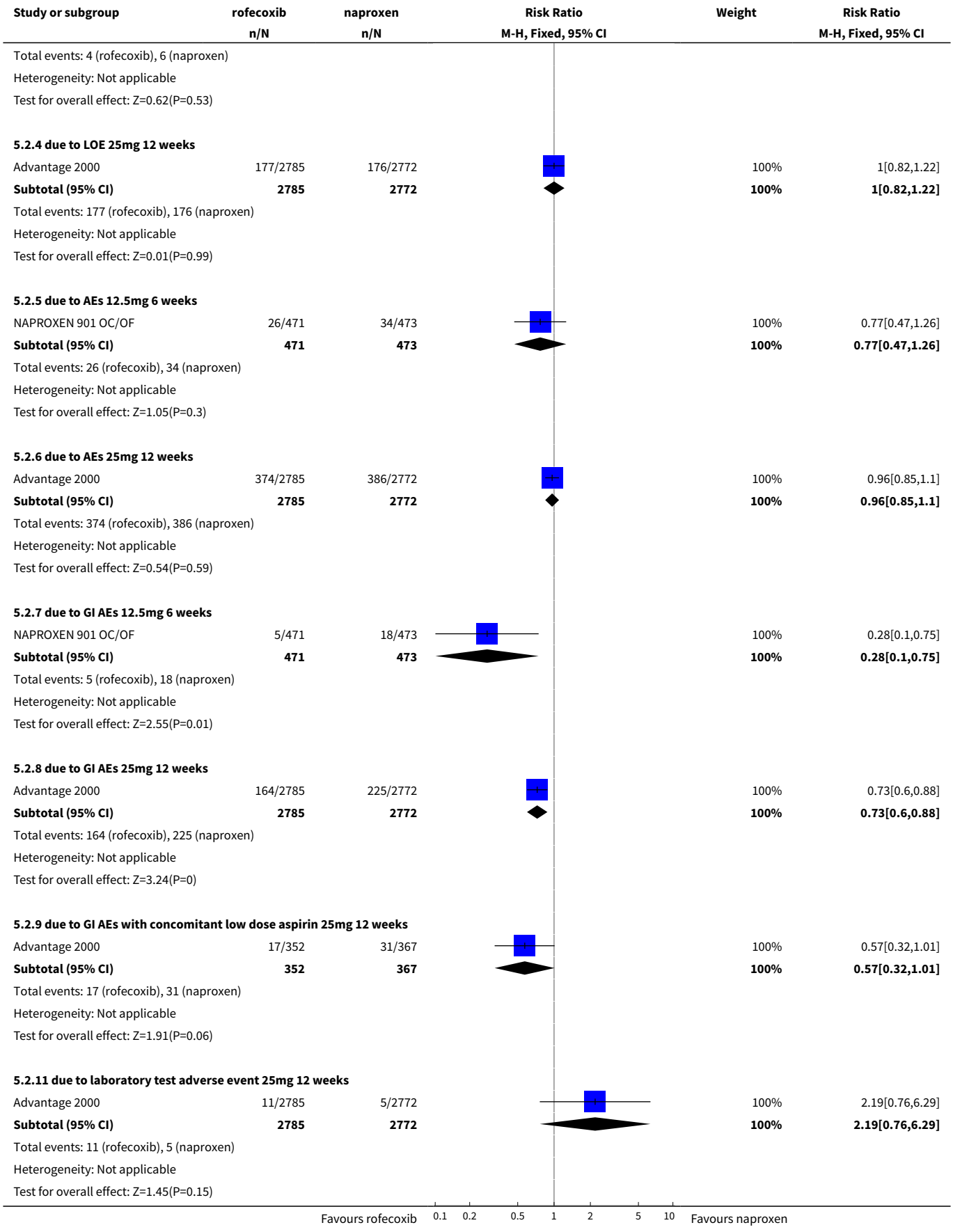


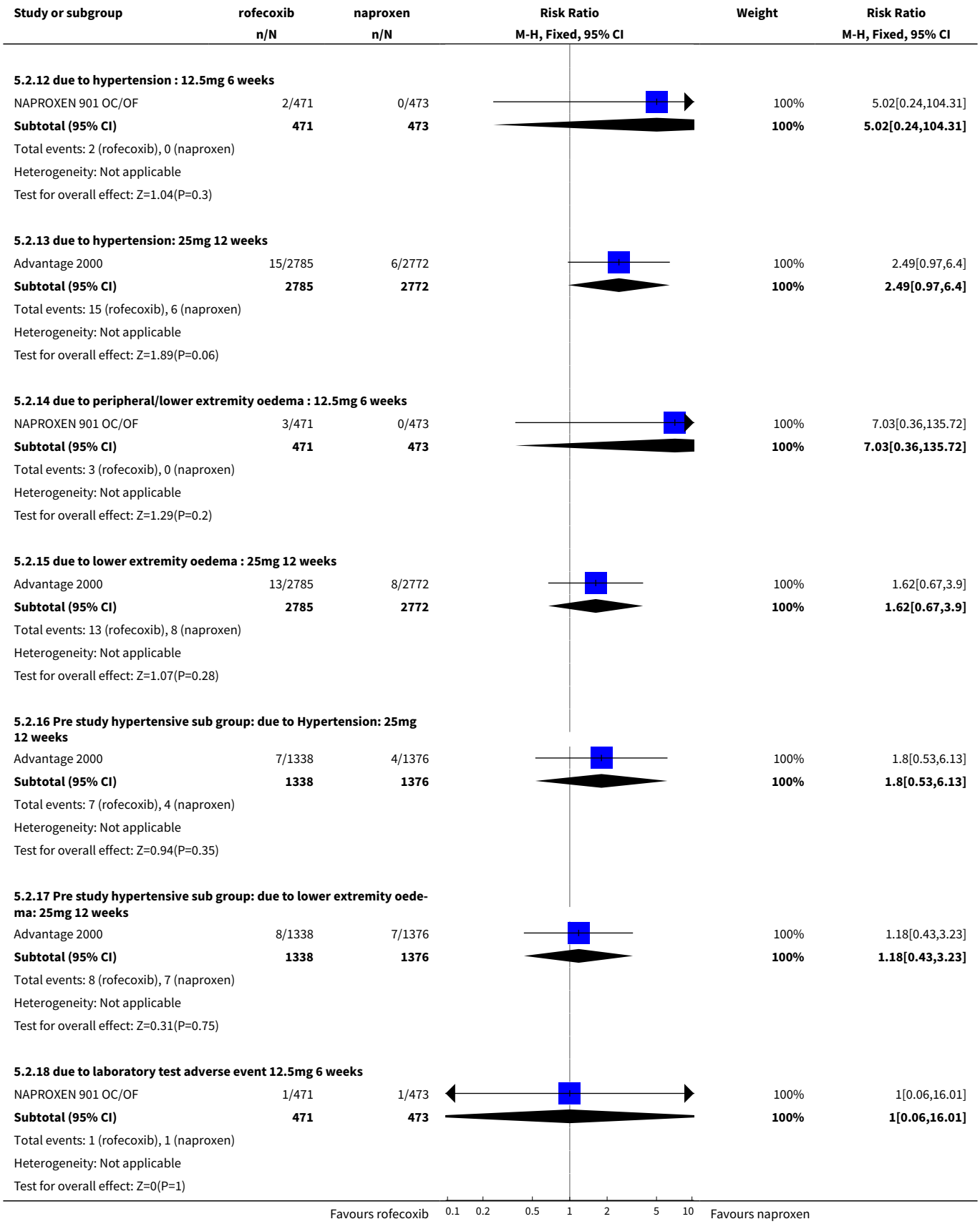




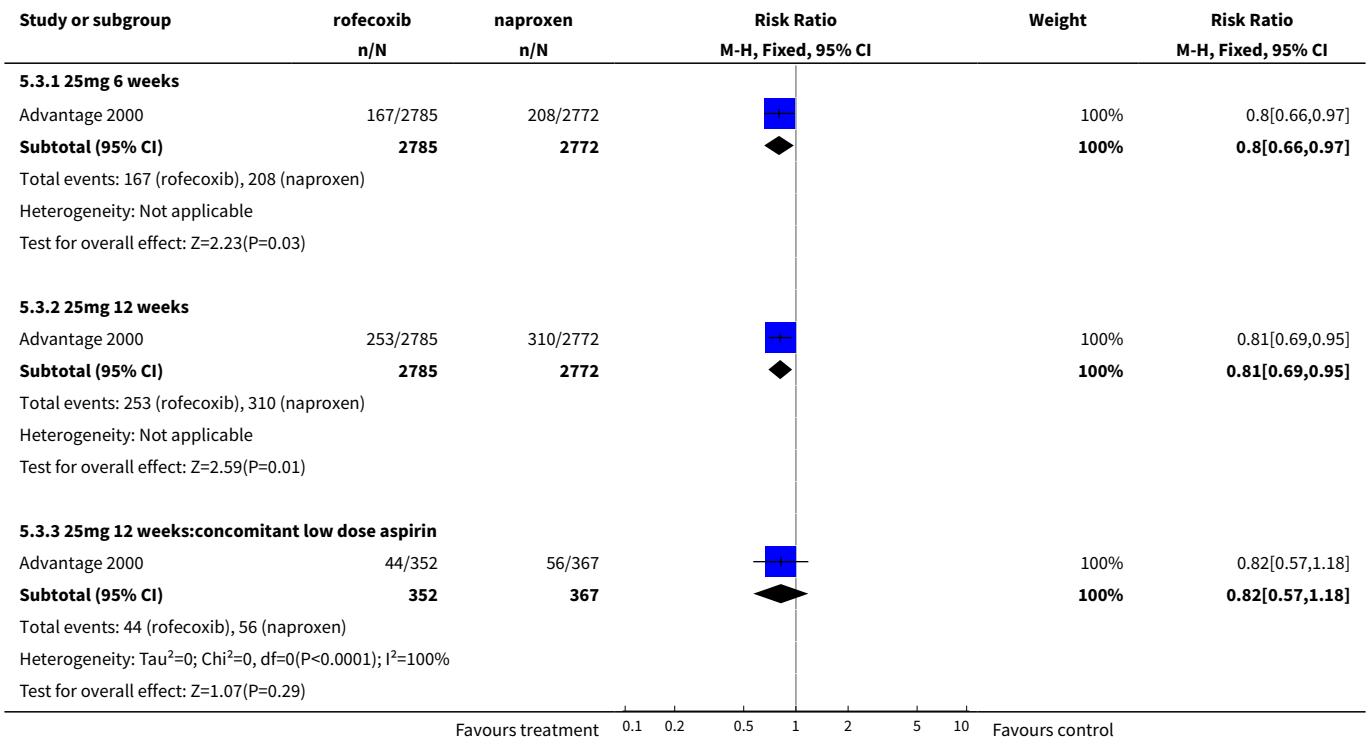
Analysis 5.2. Comparison 5 rofecoxib versus naproxen, Outcome 2 Withdrawals.



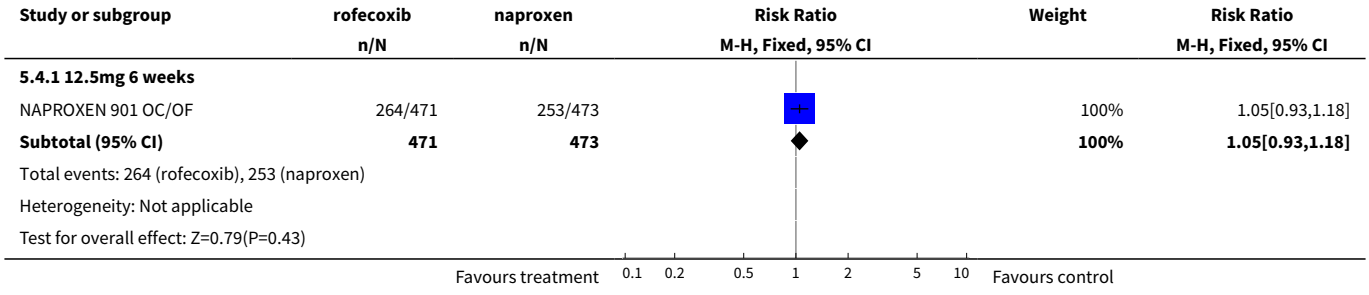




Analysis 5.3. Comparison 5 rofecoxib versus naproxen, Outcome 3 Concomitant GI medication use.



Analysis 5.4. Comparison 5 rofecoxib versus naproxen, Outcome 4 Use of rescue medication.

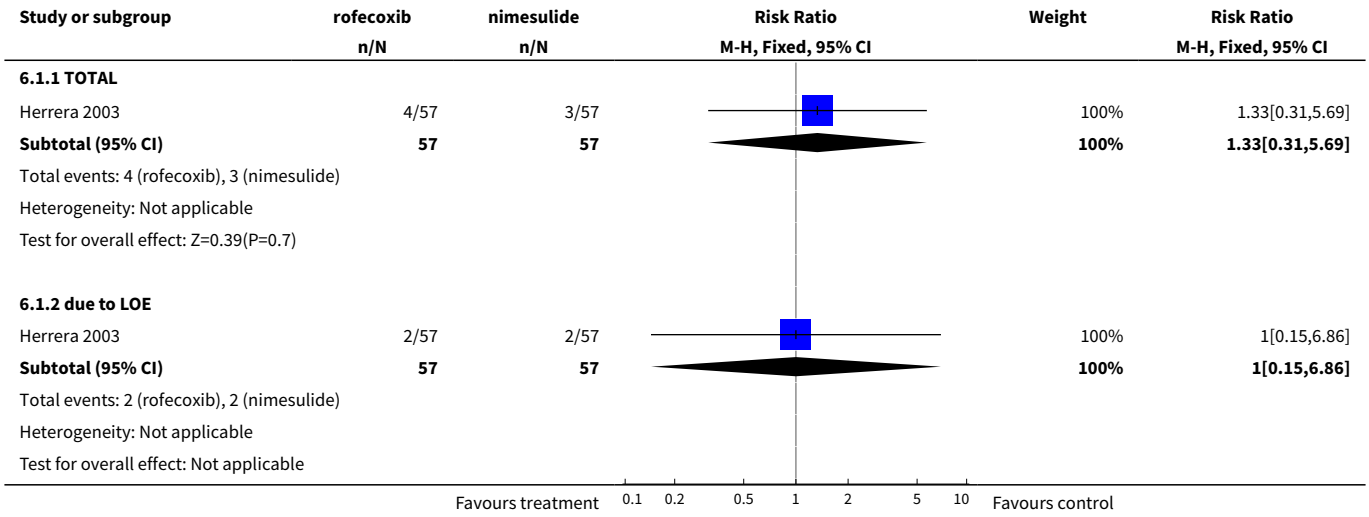


Comparison 6. rofecoxib versus nimesulide

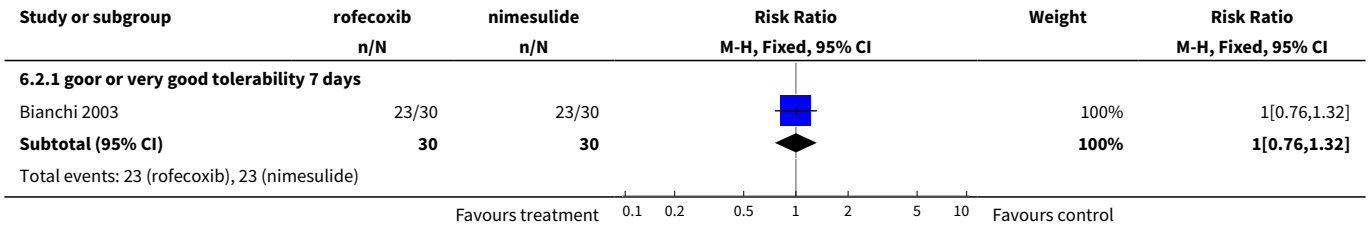
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawals	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 TOTAL	1	114	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.31, 5.69]
1.2 due to LOE	1	114	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.15, 6.86]

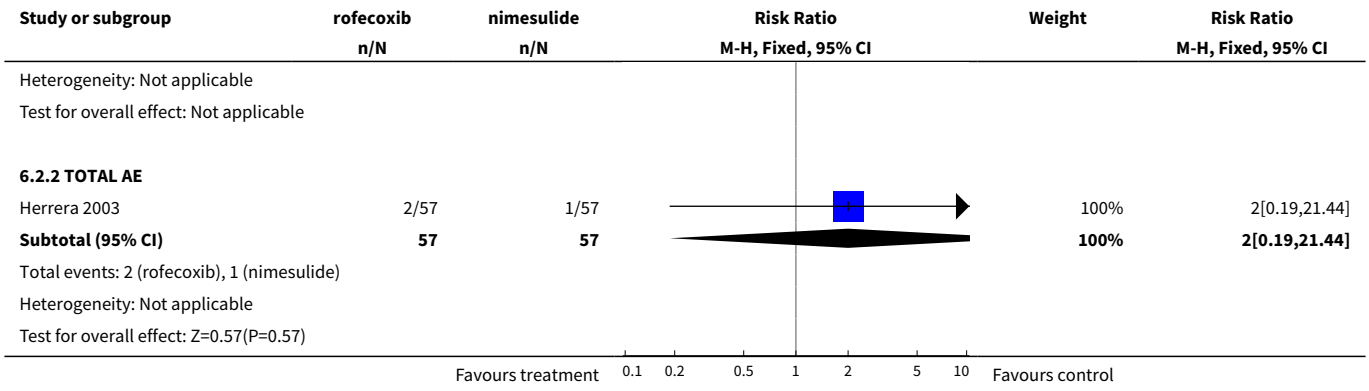
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Adverse Events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 goor or very good tolerability 7 days	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.76, 1.32]
2.2 TOTAL AE	1	114	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 21.44]
3 EFFICACY	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 goor or very good analgesic efficacy 7 days	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.57, 1.53]
3.2 Investigator assessment improved 30 days	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.61, 0.97]
3.3 Patient assessment improved 30 days	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.67, 1.03]
4 Use of paracetamol rescue	2	174	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.54, 1.68]

Analysis 6.1. Comparison 6 rofecoxib versus nimesulide, Outcome 1 Withdrawals.

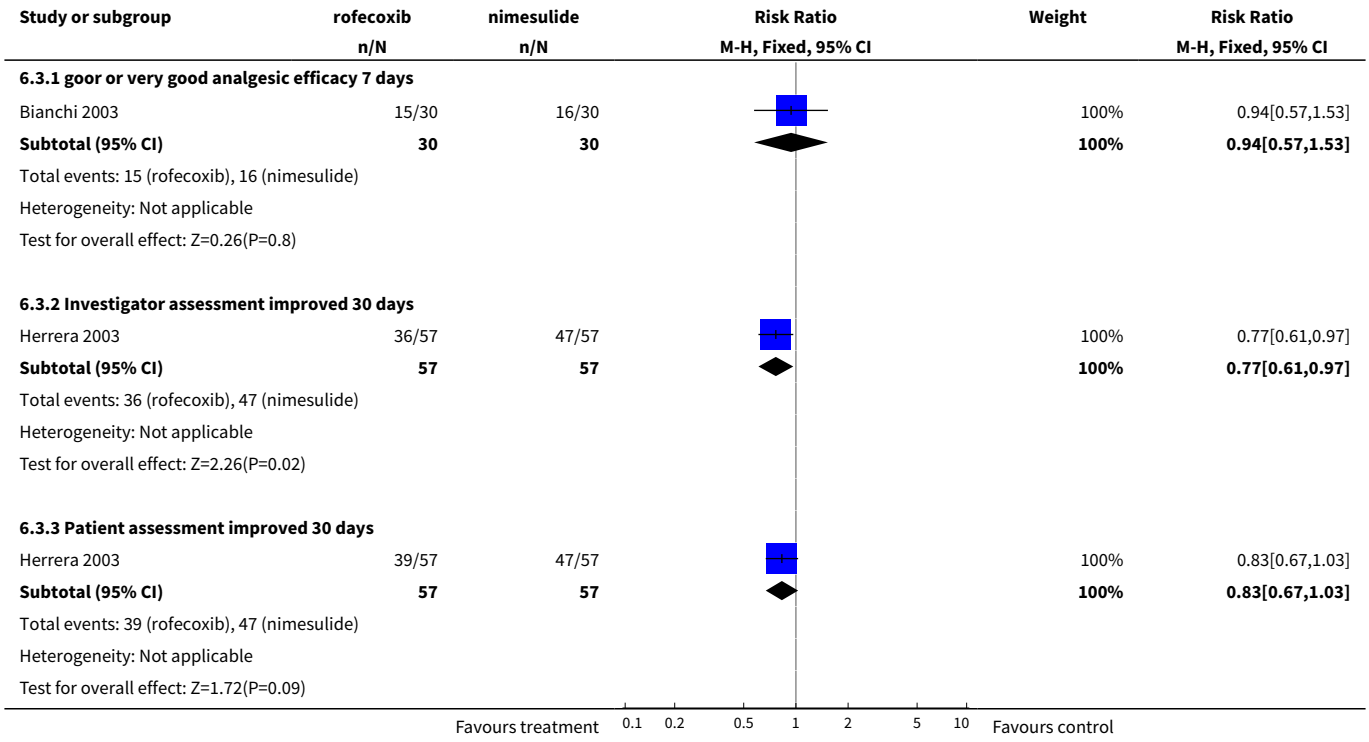


Analysis 6.2. Comparison 6 rofecoxib versus nimesulide, Outcome 2 Adverse Events.

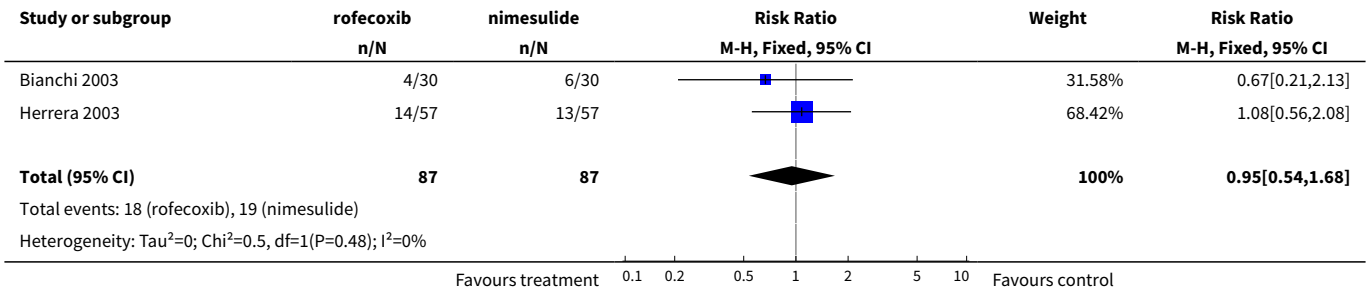


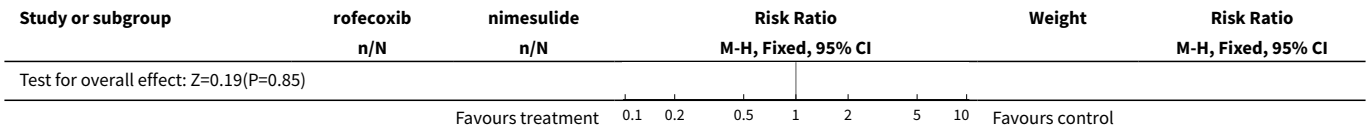


Analysis 6.3. Comparison 6 rofecoxib versus nimesulide, Outcome 3 EFFICACY.



Analysis 6.4. Comparison 6 rofecoxib versus nimesulide, Outcome 4 Use of paracetamol rescue.





Comparison 7. rofecoxib versus nabumetone

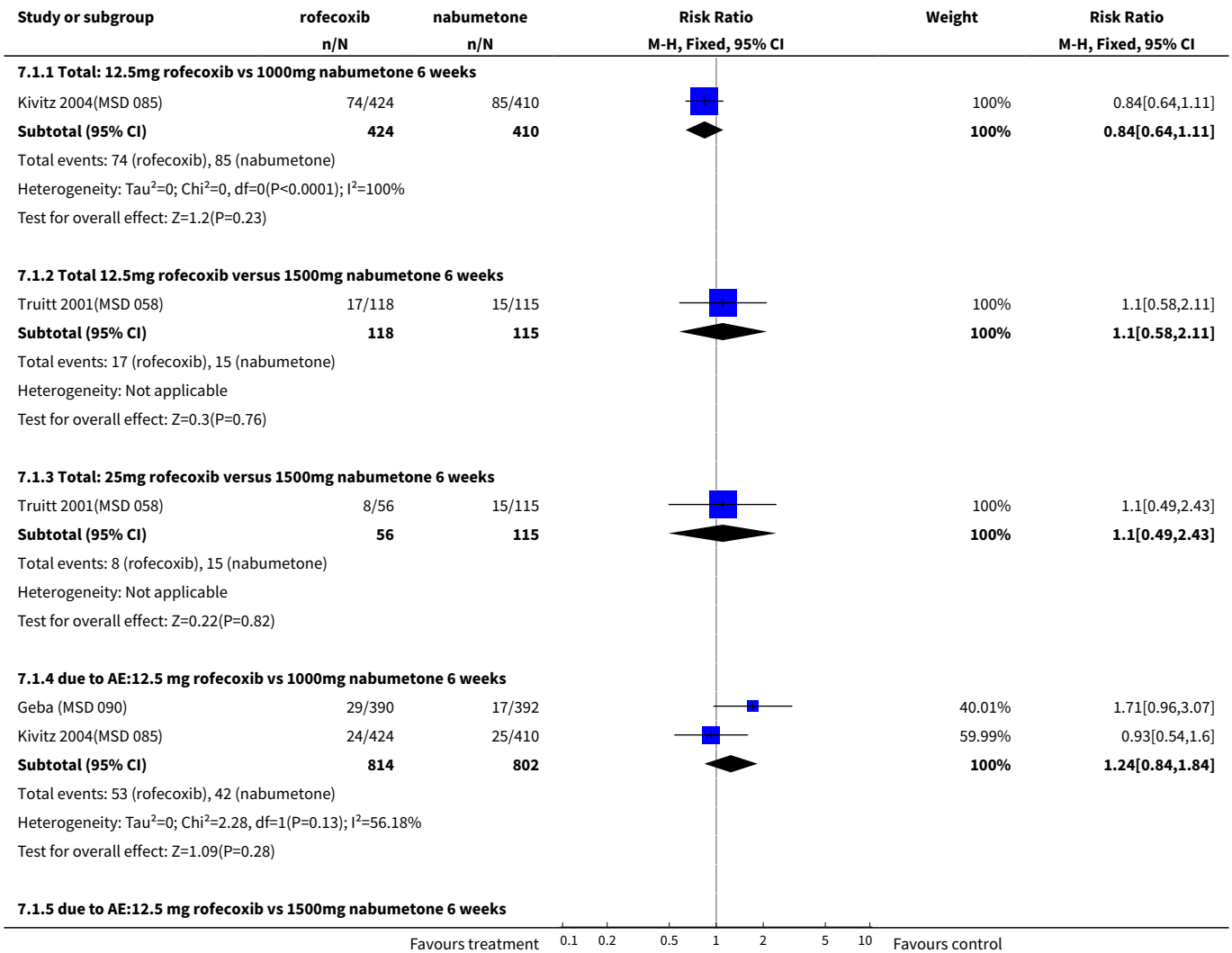
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 WITHDRAWALS*	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Total: 12.5mg rofecoxib vs 1000mg nabumetone 6 weeks	1	834	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.64, 1.11]
1.2 Total 12.5mg rofecoxib versus 1500mg nabumetone 6 weeks	1	233	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.58, 2.11]
1.3 Total: 25mg rofecoxib versus 1500mg nabumetone 6 weeks	1	171	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.49, 2.43]
1.4 due to AE:12.5 mg rofecoxib vs 1000mg nabumetone 6 weeks	2	1616	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.84, 1.84]
1.5 due to AE:12.5 mg rofecoxib vs 1500mg nabumetone 6 weeks	1	233	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.44, 2.74]
1.6 due to AE: 25mg rofecoxib versus 1500mg nabumetone 6 weeks	1	171	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.44, 3.74]
1.7 due to LOE: 12.5mg rofecoxib vs 1000mg nabumetone 6 weeks	1	834	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.41, 0.98]
1.8 due to LOE: 12.5mg rofecoxib versus 1500mg nabumetone 6 weeks	1	233	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.14, 6.80]
1.9 due to LOE: 25mg rofecoxib versus 1500mg nabumetone 6 weeks	1	171	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.02, 8.34]
2 ADVERSE EVENTS*	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 TOTAL 12.5mg rofecoxib vs 1000mg nabumetone 6 weeks	2	1616	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.99, 1.20]
2.2 TOTAL GI 12.5mg rofecoxib vs 1000mg nabumetone 6 weeks	1	834	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.77, 2.30]
2.3 Serious 12.5mg rofecoxib versus 1000mg nabumetone 6 weeks	2	1616	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.57, 2.89]
2.4 Serious 12.5mg rofecoxib versus 1500mg nabumetone 6 weeks	1	233	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.45, 4.18]

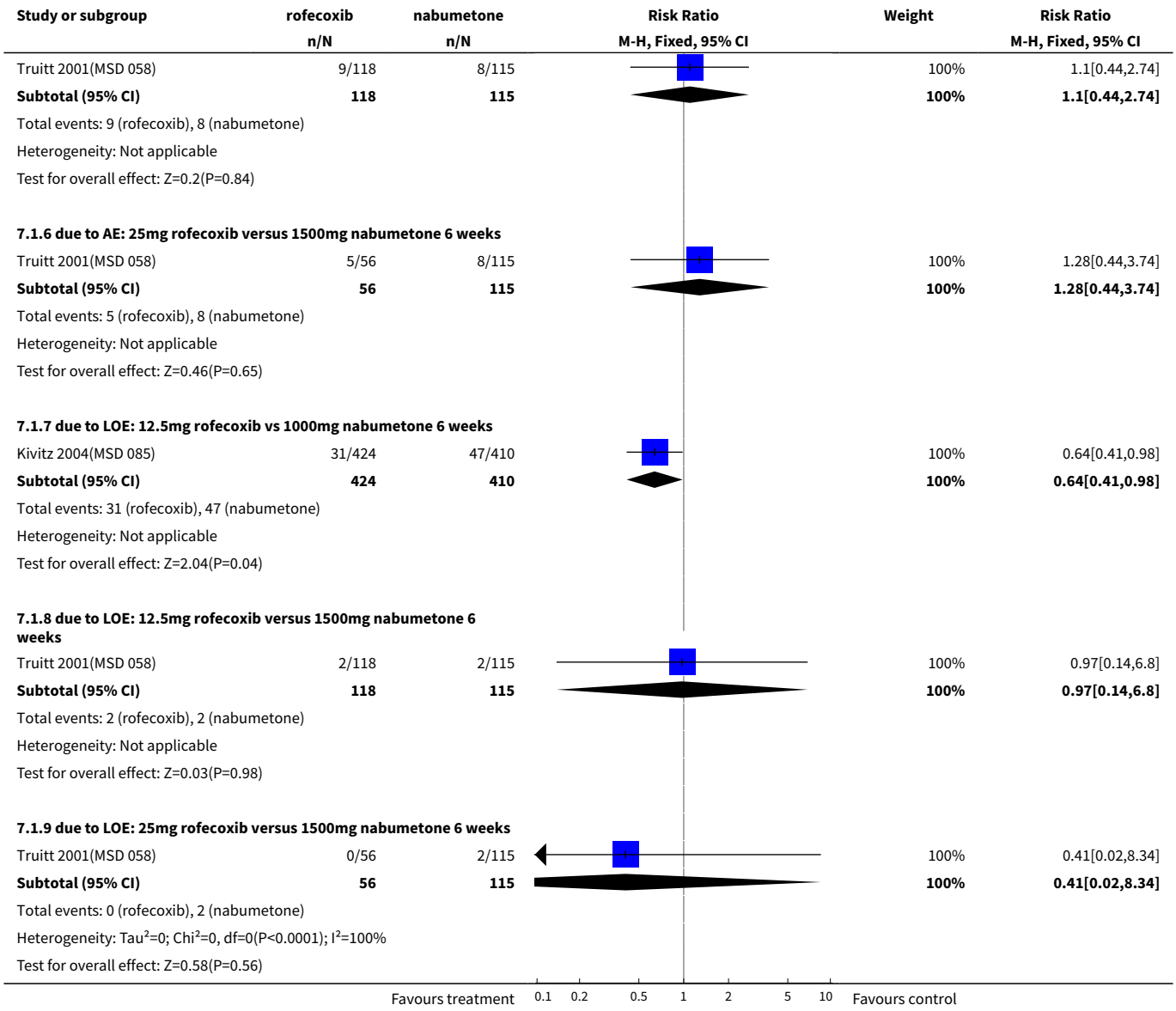
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5 Serious: 25mg rofecoxib versus 1500mg nabumetone 6 weeks	1	171	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.05, 3.43]
2.6 LOWER EXTREMITY OEDEMA: rofecoxib 12.5mg vs nabumetone 1000mg 6 weeks	2	1616	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.72, 2.77]
2.7 LOWER EXTREMITY OEDEMA: rofecoxib 12.5mg vs nabumetone 1500mg 6 weeks	1	233	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.61, 5.08]
2.8 LOWER EXTREMITY OEDEMA: rofecoxib 25mg vs nabumetone 1500mg 6 weeks	1	171	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.31, 4.97]
2.9 Drug related lower extremity oedema: rofecoxib 12.5mg vs nabumetone 1500mg 6 weeks	1	233	Risk Ratio (M-H, Fixed, 95% CI)	2.44 [0.48, 12.31]
2.10 Drug related lower extremity oedema: rofecoxib 25mg vs nabumetone 1500mg 6 weeks	1	171	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.30, 14.20]
2.11 OEDEMA: rofecoxib 12.5mg vs nabumetone 25mg 6 weeks	1	233	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.12 OEDEMA: rofecoxib 25mg vs nabumetone 1500mg 6 weeks	1	171	Risk Ratio (M-H, Fixed, 95% CI)	6.11 [0.25, 147.53]
2.13 Diarrhoea 12.5mg rofecoxib vs 1000 mg nabumetone 6 weeks	1	834	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.67, 2.58]
2.14 Diarrhoea 12.5mg rofecoxib vs 1500 mg nabumetone 6 weeks	1	233	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.24, 1.77]
2.15 Diarrhoea 25mg rofecoxib vs 1500 mg nabumetone 6 weeks	1	171	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.10, 2.04]
2.16 HYPERTENSION: rofecoxib 12.5mg vs nabumetone 1000mg 6 weeks	2	1616	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.53, 4.12]
2.17 Blood pressure increase: rofecoxib 12.5mg vs nabumetone 1500mg 6 weeks	1	233	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 4.02]
2.18 Blood pressure increase: rofecoxib 25mg vs nabumetone 1500mg 6 weeks	1	171	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.10, 11.08]
2.19 aged >65: TOTAL 12.5mg rofecoxib vs 1000mg nabumetone 6 weeks	1	834	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.86, 1.15]
2.23 CV 12.5mg mg rofecoxib 1000mg nabumetone 6 weeks	1	834	Risk Ratio (M-H, Fixed, 95% CI)	2.90 [0.12, 71.01]
2.24 CV 25mg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 EFFICACY-WOMAC	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 physical function 12.5mg 6 weeks	1	233	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-7.56, 6.58]
4.2 physical function 25mg 6 weeks	1	171	Mean Difference (IV, Fixed, 95% CI)	-0.81 [-9.05, 7.43]
4.3 pain 12.5mg 6 weeks	1	233	Mean Difference (IV, Fixed, 95% CI)	0.42 [-7.41, 8.25]
4.4 pain 25mg 6 weeks	1	171	Mean Difference (IV, Fixed, 95% CI)	1.71 [-7.42, 10.84]
4.5 stiffness 12.5mg 6 weeks	1	233	Mean Difference (IV, Fixed, 95% CI)	-0.72 [-9.24, 7.80]
4.6 stiffness 25mg 6 weeks	1	171	Mean Difference (IV, Fixed, 95% CI)	1.20 [-8.73, 11.13]
5 EFFICACY - patient/investigator measured - dicotomous	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Response- patient measured good/ excellent 12.5mg rofecoxib vs 1000mg nabumetone 6 weeks: average of 6 weeks	2	1616	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.05, 1.29]
5.2 response- investigator measured good/excellent 12.5mg rofecoxib vs 1000mg nabumetone 6 weeks: average of 6 wee	1	834	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.02, 1.32]
6 EFFICACY- patient/investigator measured - continuous	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 patient- global disease status 12.5mg 6 weeks	1	233	Mean Difference (IV, Fixed, 95% CI)	-0.61 [-9.73, 8.51]
6.2 patient- global disease status 25mg 6 weeks	1	171	Mean Difference (IV, Fixed, 95% CI)	-0.55 [-11.23, 10.13]
6.3 study joint tenderness 12.5mg 6 weeks	1	233	Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.14, 0.42]
6.4 study joint tenderness 25mg 6 weeks	1	171	Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.16, 0.48]
6.5 investigator- global disease status- 12.5mg 6 weeks	1	233	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.32, 0.34]
6.6 investigator-global disease status- 25mg 6 weeks	1	171	Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.23, 0.55]

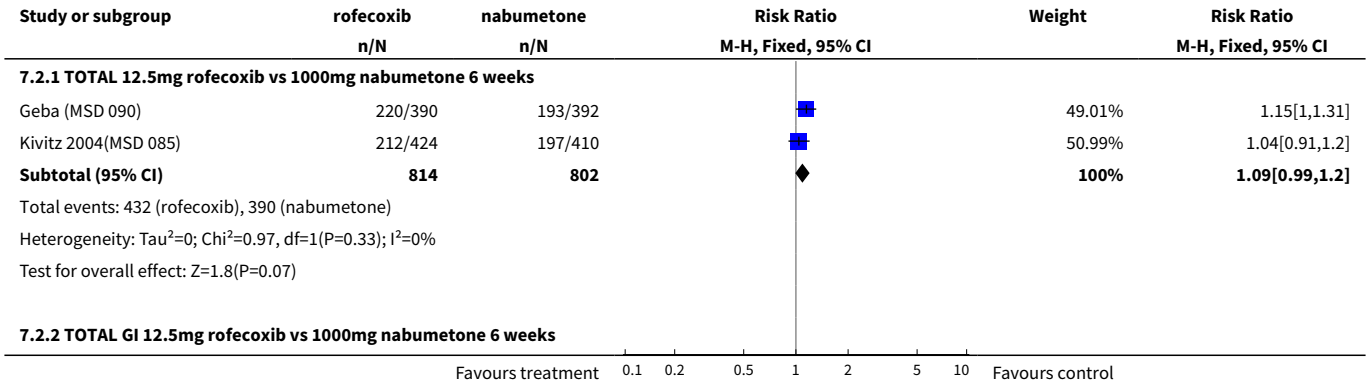
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Paracetamol use- tablets per day	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 12.5mg 6 weeks	1	233	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.40, 0.30]
7.2 25mg 6 weeks	1	171	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.45, 0.37]
8 Paracetamol use- number of patients	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 12.5mg rofecoxib vs 1000mg nabumetone 6 weeks: average of 6 weeks	1	834	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.93, 1.09]

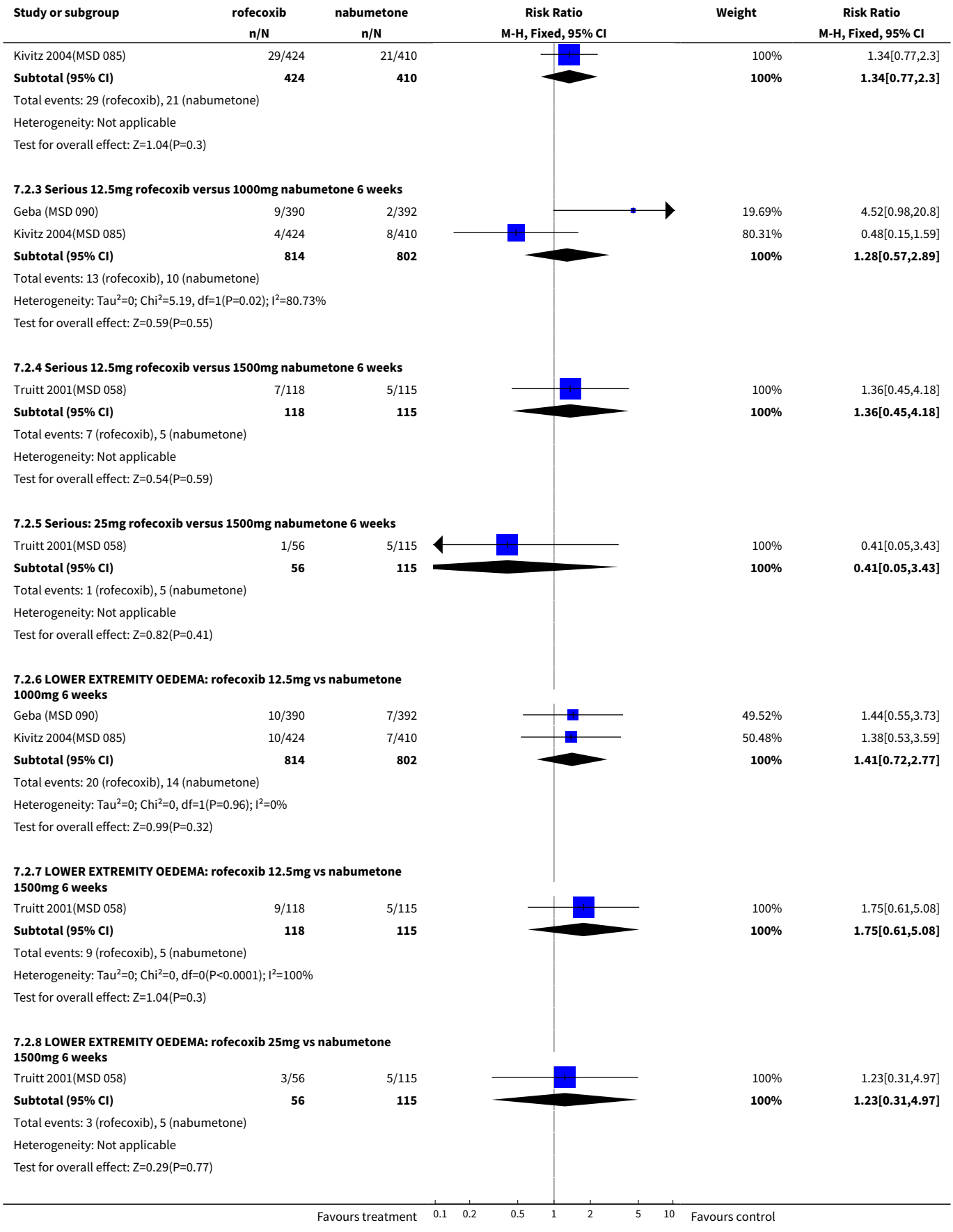
Analysis 7.1. Comparison 7 rofecoxib versus nabumetone, Outcome 1 WITHDRAWALS*.

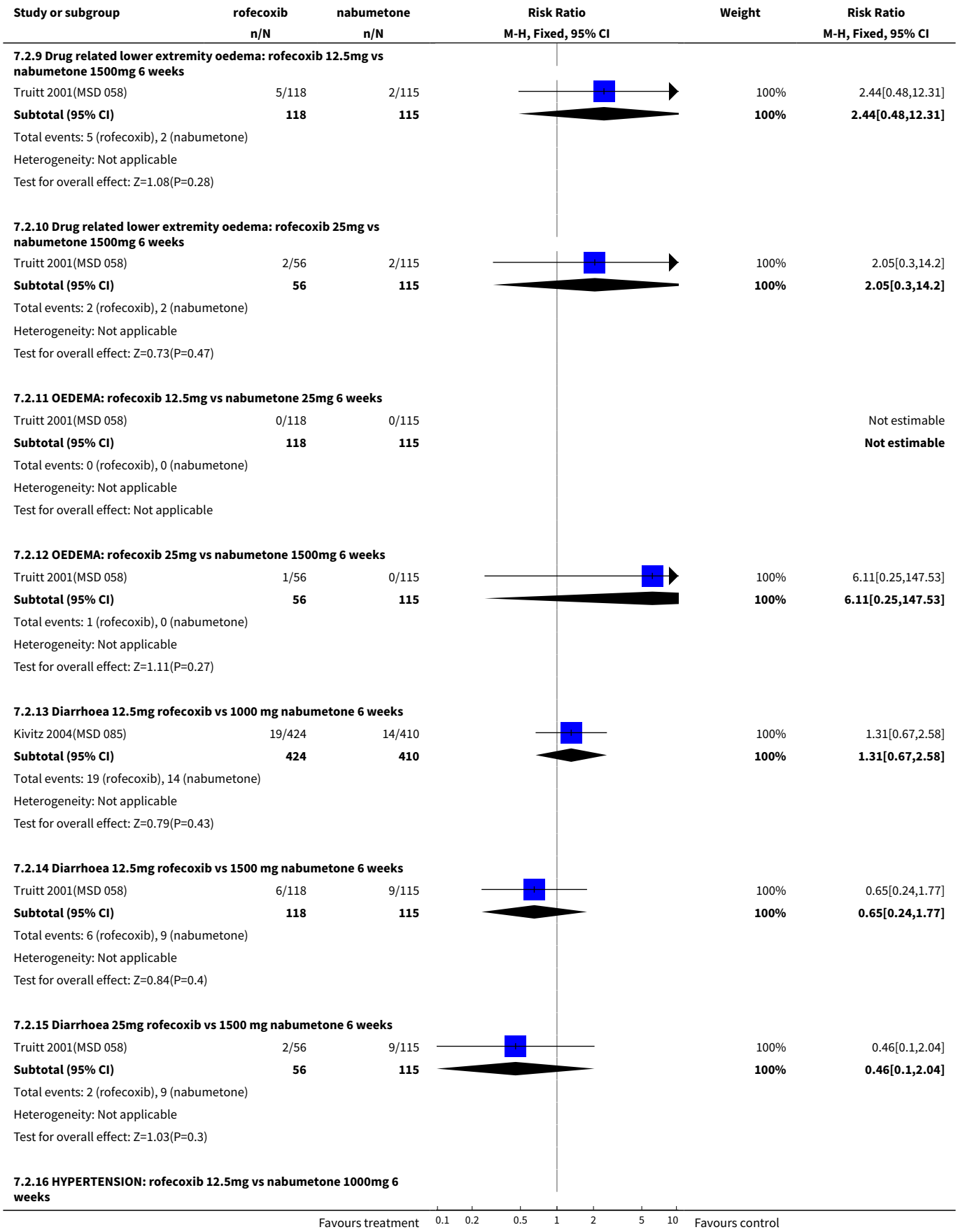


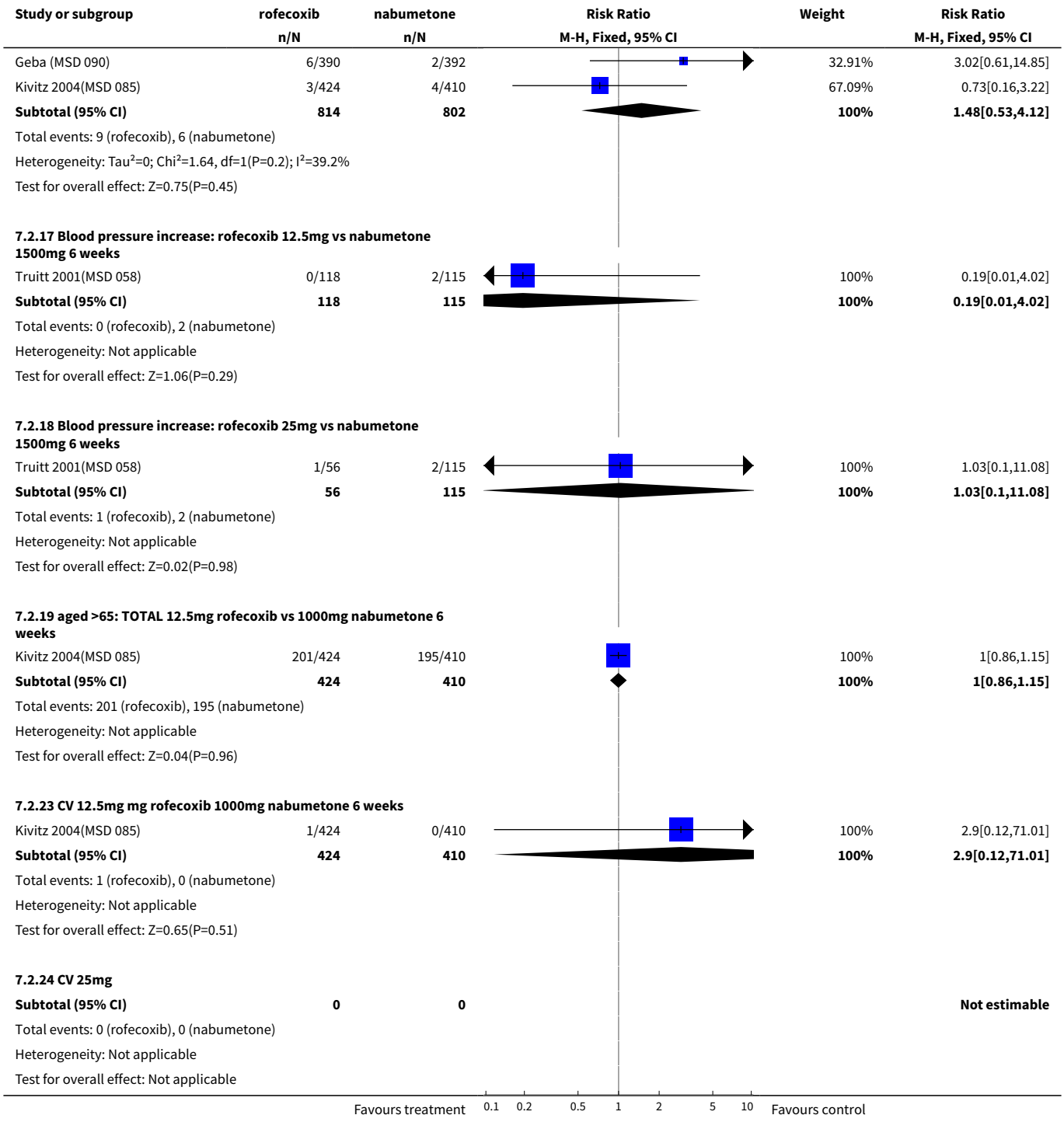


Analysis 7.2. Comparison 7 rofecoxib versus nabumetone, Outcome 2 ADVERSE EVENTS*.

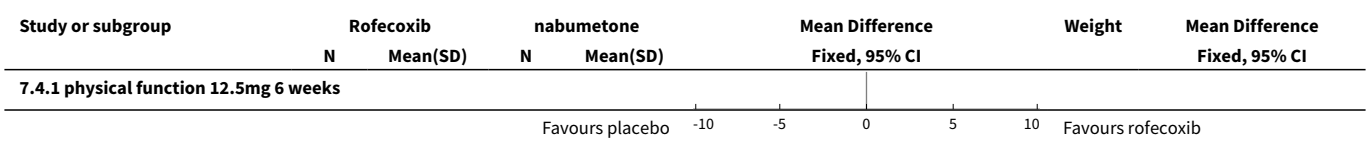


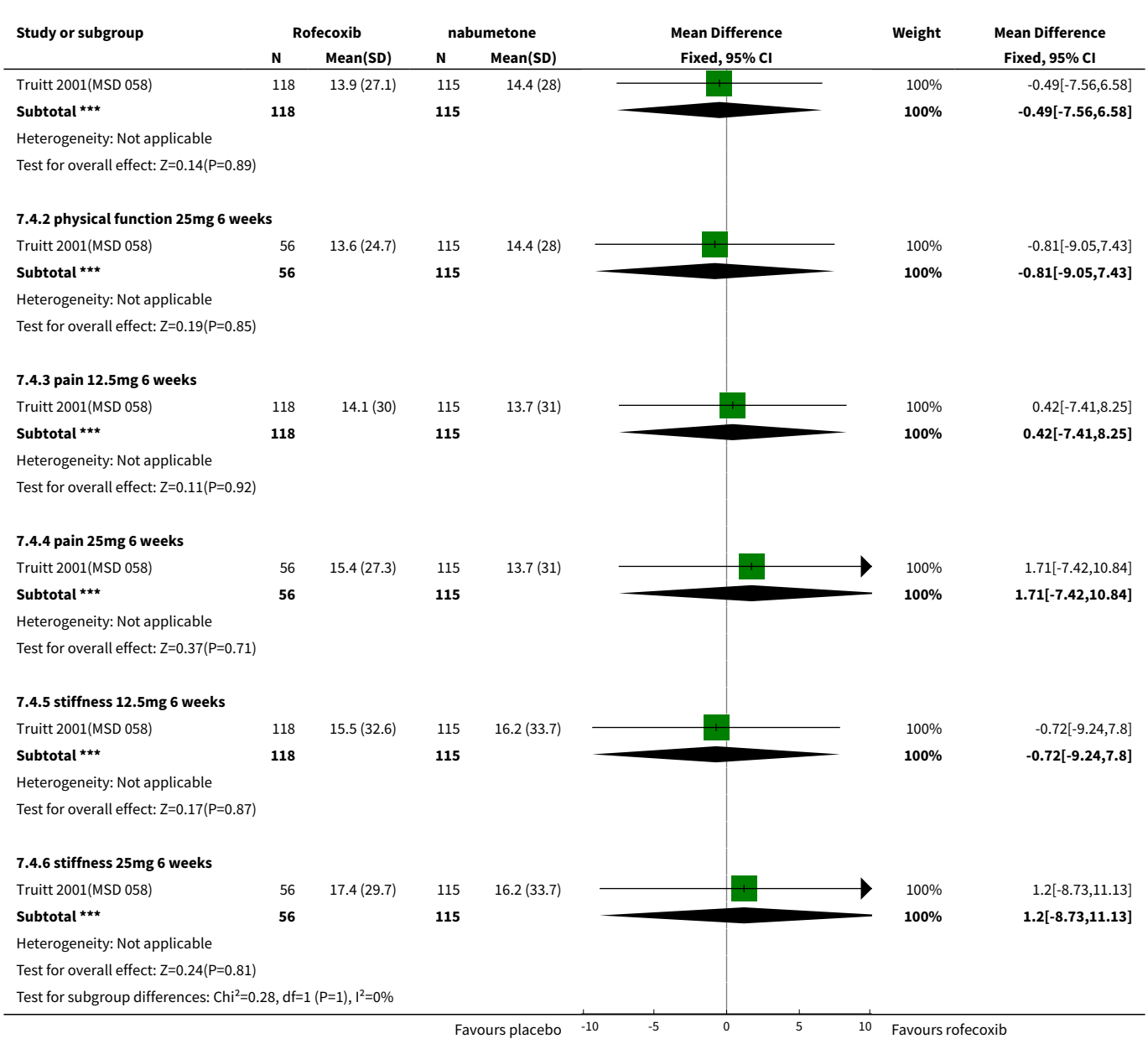




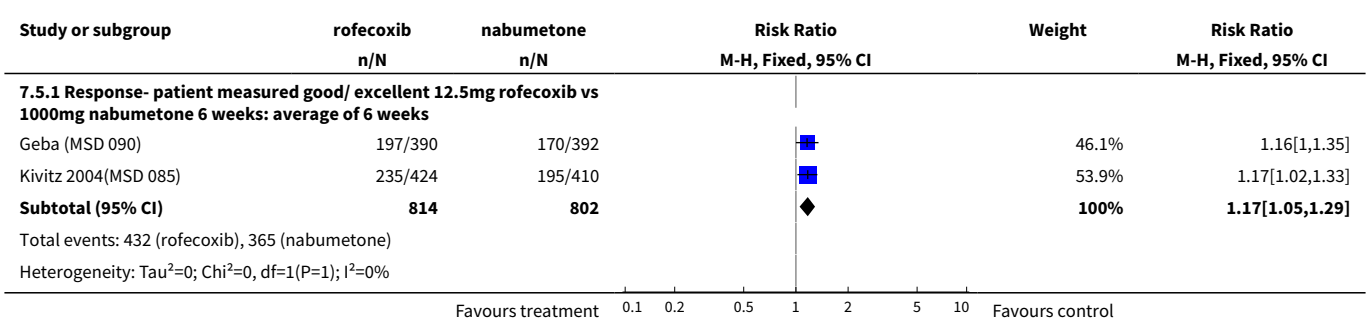


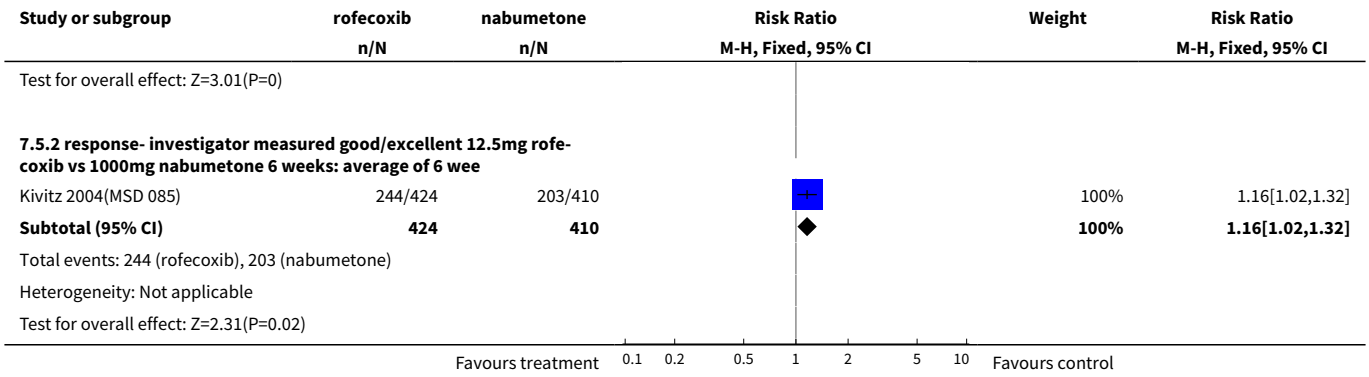
Analysis 7.4. Comparison 7 rofecoxib versus nabumetone, Outcome 4 EFFICACY-WOMAC.



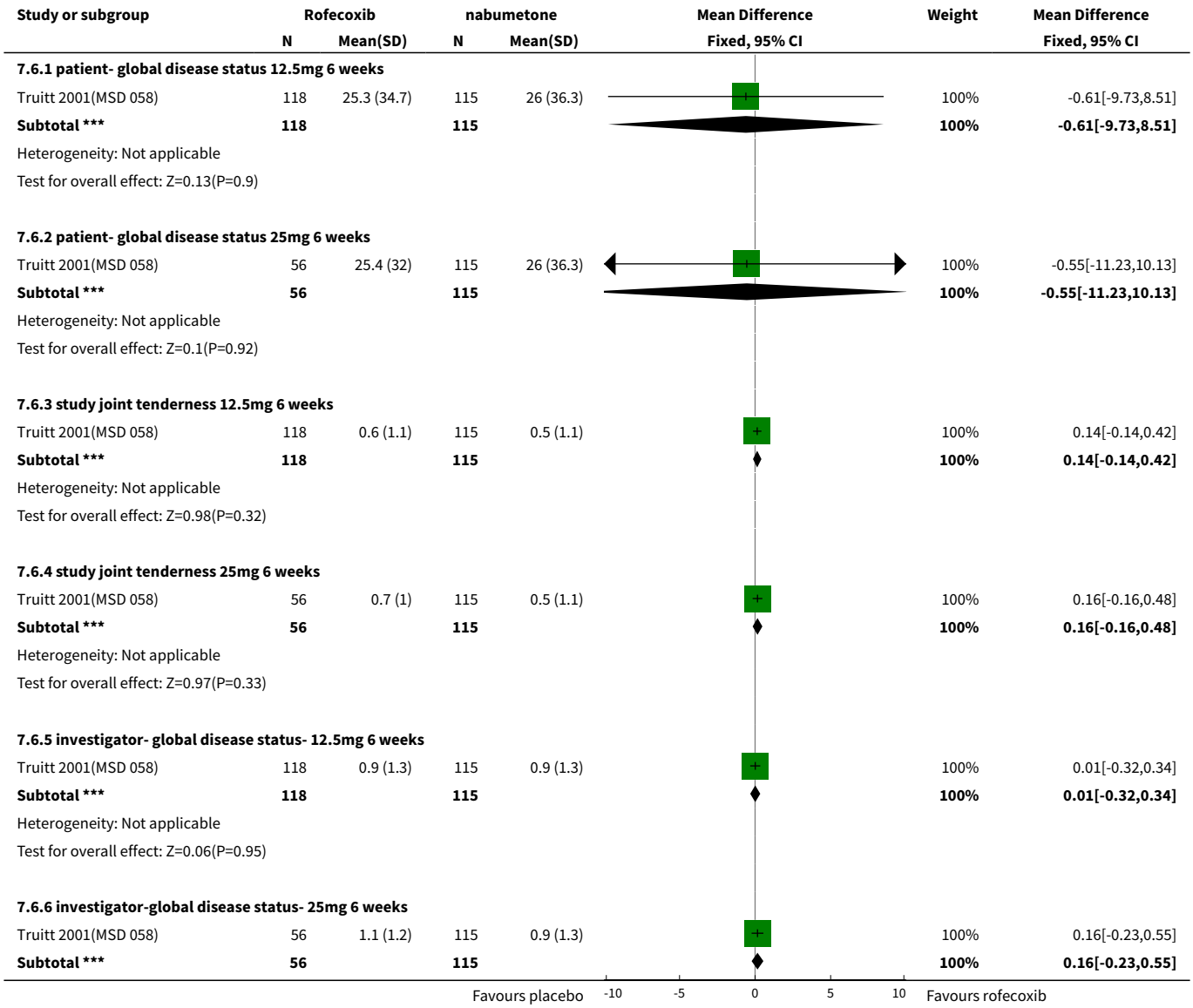


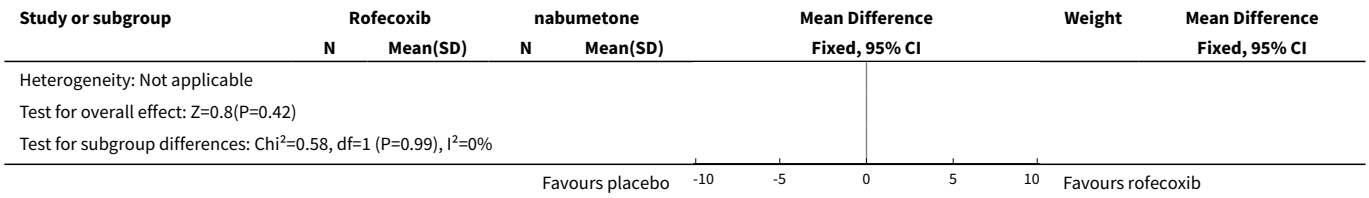
Analysis 7.5. Comparison 7 rofecoxib versus nabumetone, Outcome 5 EFFICACY - patient/investigator measured - dicotomous.



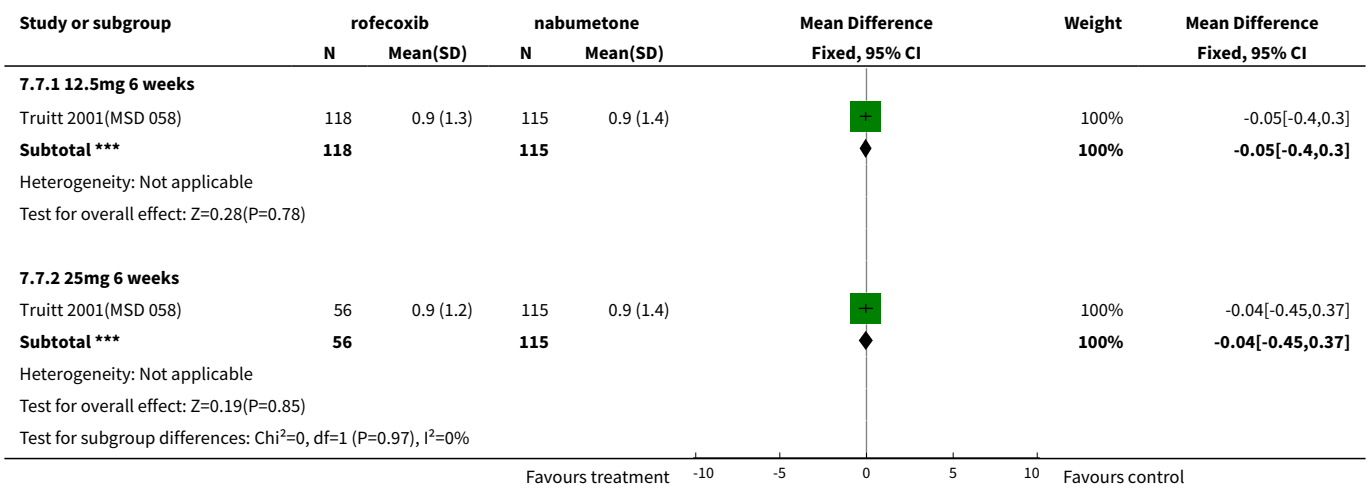


Analysis 7.6. Comparison 7 rofecoxib versus nabumetone, Outcome 6 EFFICACY- patient/investigator measured - continuous.

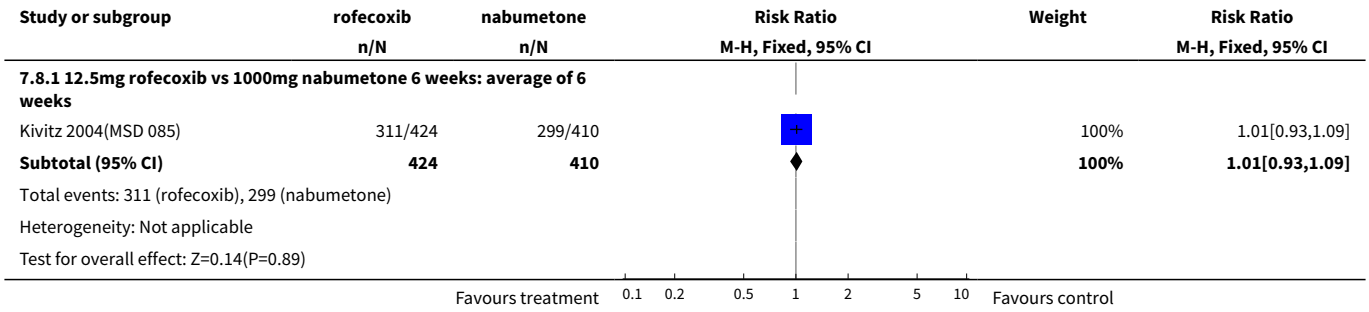




Analysis 7.7. Comparison 7 rofecoxib versus nabumetone, Outcome 7 Paracetamol use- tablets per day.



Analysis 7.8. Comparison 7 rofecoxib versus nabumetone, Outcome 8 Paracetamol use- number of patients.



Comparison 8. rofecoxib versus paracetamol

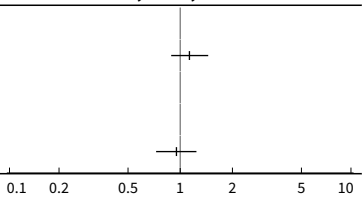
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 TOTAL 12.5mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

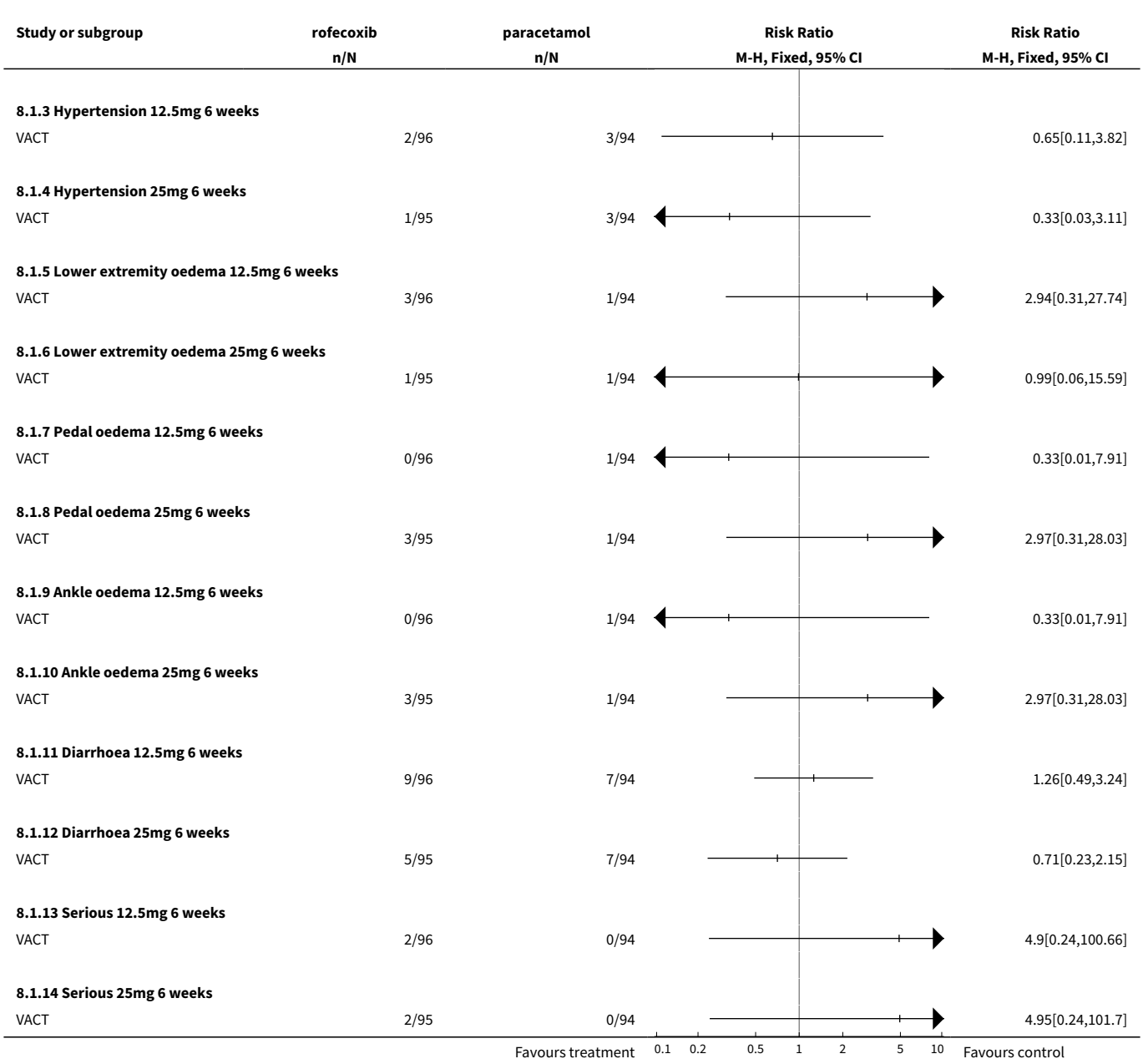
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 TOTAL 25mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Hypertension 12.5mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Hypertension 25mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Lower extremity oedema 12.5mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 Lower extremity oedema 25mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.7 Pedal oedema 12.5mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.8 Pedal oedema 25mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.9 Ankle oedema 12.5mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.10 Ankle oedema 25mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.11 Diarrhoea 12.5mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.12 Diarrhoea 25mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.13 Serious 12.5mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.14 Serious 25mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Withdrawals	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 TOTAL 12.5mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 TOTAL 25mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 due to AE 12.5mg 6 weels	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 due to AE 25mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 due to LOE 12.5mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 due to LOE 25mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Efficacy	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Walking Pain 12.5mg 6 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Walking Pain 25mg 6 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 Rest Pain 12.5mg 6 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 Rest Pain 25mg 6 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.5 Morning Stiffness 12.5mg 6 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.6 Morning Stiffness 25mg 6 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.7 Night Pain 12.5mg 6 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.8 Night Pain 25mg 6 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.9 Pain Subscale 12.5mg 6 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.10 Pain Subscale 25mg 6 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.11 Stiffness Subscale 12.5mg 6 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.12 Stiffness Subscale 25mg 6 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.13 Function Subscale 12.5mg 6 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.14 Function Subscale 25mg 6 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 EFFICACY- patient/investigator assessed dicotomous	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Patient global response to therapy 12.5 mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 patient global response to therapy 25 mg 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

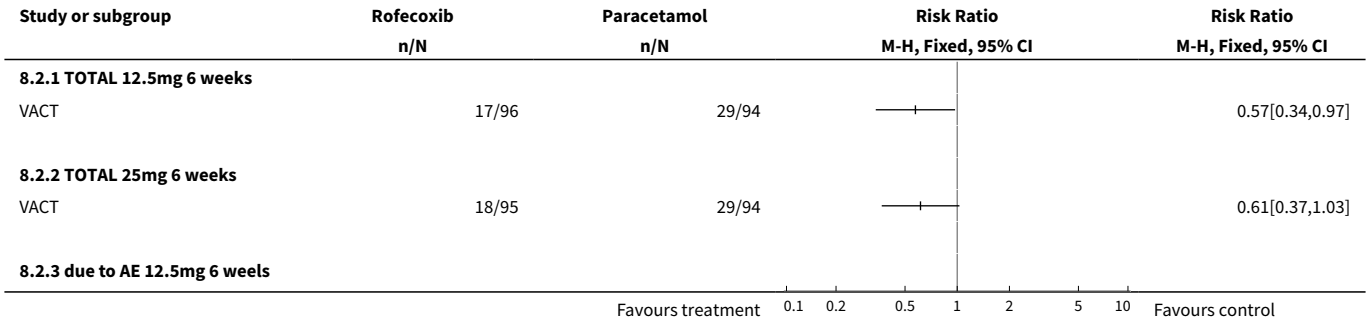
Analysis 8.1. Comparison 8 rofecoxib versus paracetamol, Outcome 1 Adverse events.

Study or subgroup	rofecoxib n/N	paracetamol n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
8.1.1 TOTAL 12.5mg 6 weeks				
VACT	59/96	51/94		1.13[0.89,1.45]
8.1.2 TOTAL 25mg 6 weeks				
VACT	49/95	51/94		0.95[0.73,1.24]





Analysis 8.2. Comparison 8 rofecoxib versus paracetamol, Outcome 2 Withdrawals.



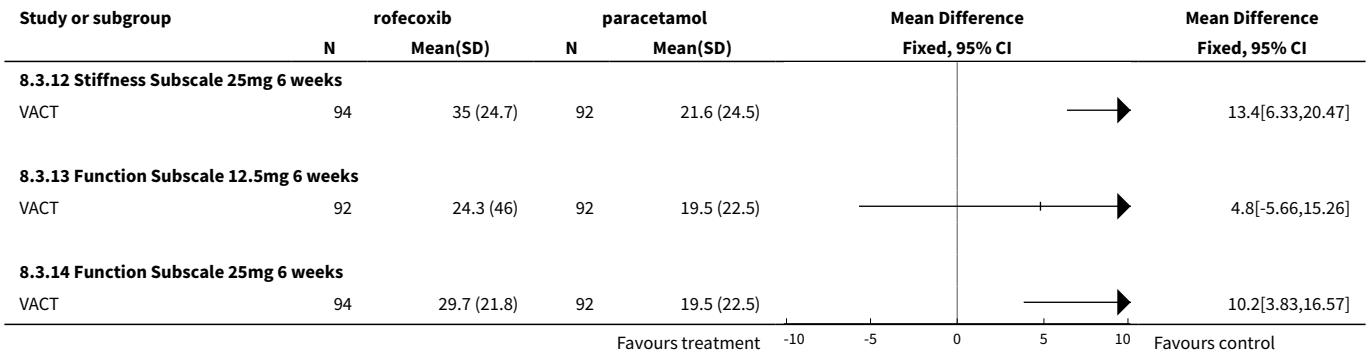
Study or subgroup	Rofecoxib n/N	Paracetamol n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
VACT	7/96	6/94		1.14[0.4,3.27]
8.2.4 due to AE 25mg 6 weeks				
VACT	6/95	6/94		0.99[0.33,2.96]
8.2.5 due to LOE 12.5mg 6 weeks				
VACT	8/96	16/94		0.49[0.22,1.09]
8.2.6 due to LOE 25mg 6 weeks				
VACT	8/95	16/94		0.49[0.22,1.1]

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

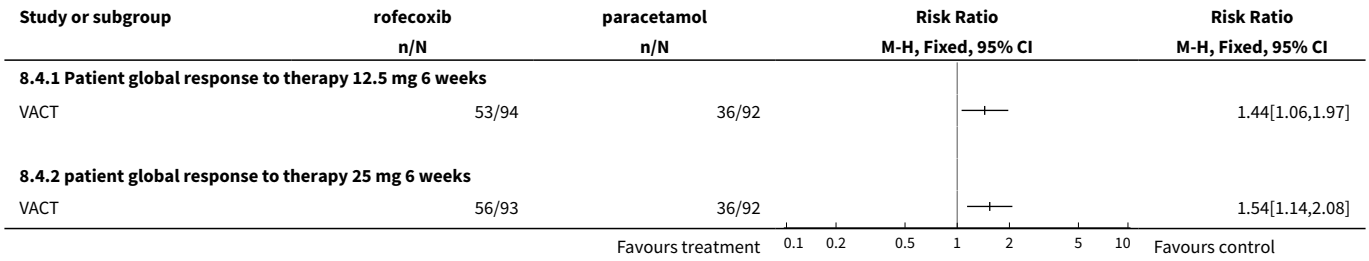
Analysis 8.3. Comparison 8 rofecoxib versus paracetamol, Outcome 3 Efficacy.

Study or subgroup	rofecoxib N	rofecoxib Mean(SD)	paracetamol N	paracetamol Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
8.3.1 Walking Pain 12.5mg 6 weeks						
VACT	92	35.1 (24.5)	92	30.3 (25.5)		4.8[-2.41,12.01]
8.3.2 Walking Pain 25mg 6 weeks						
VACT	94	42 (24.7)	92	30.3 (25.5)		11.7[4.49,18.91]
8.3.3 Rest Pain 12.5mg 6 weeks						
VACT	92	24.8 (22.5)	92	21.7 (22.5)		3.1[-3.4,9.6]
8.3.4 Rest Pain 25mg 6 weeks						
VACT	94	31.1 (22.8)	92	21.7 (22.5)		9.4[2.9,15.9]
8.3.5 Morning Stiffness 12.5mg 6 weeks						
VACT	92	29 (25.5)	92	22.3 (25.5)		6.7[-0.65,14.05]
8.3.6 Morning Stiffness 25mg 6 weeks						
VACT	94	36.2 (24.7)	92	22.3 (25.5)		13.9[6.69,21.11]
8.3.7 Night Pain 12.5mg 6 weeks						
VACT	92	25.2 (22.5)	92	23.6 (23.5)		1.6[-5.05,8.25]
8.3.8 Night Pain 25mg 6 weeks						
VACT	94	32.7 (22.8)	92	23.6 (23.5)		9.1[2.45,15.75]
8.3.9 Pain Subscale 12.5mg 6 weeks						
VACT	92	28 (22.5)	92	24.9 (22.5)		3.1[-3.4,9.6]
8.3.10 Pain Subscale 25mg 6 weeks						
VACT	94	35.4 (22.8)	92	24.9 (22.5)		10.5[4,17]
8.3.11 Stiffness Subscale 12.5mg 6 weeks						
VACT	92	28.2 (24.5)	92	21.6 (24.5)		6.6[-0.47,13.67]

Favours treatment -10 -5 0 5 10 Favours control



Analysis 8.4. Comparison 8 rofecoxib versus paracetamol, Outcome 4 EFFICACY- patient/investigator assessed dicotomous.



Comparison 9. rofecoxib versus celecoxib

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawals	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 due to AE 12.5mg 6 weeks	1	193	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [0.53, 5.85]
1.2 due to AE 25mg 6 weeks	5	2595	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.77, 1.39]
1.3 due to LOE 12.5mg 6 weeks	1	193	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.36, 2.23]
1.4 due to LOE 25mg 6 weeks	5	2595	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.47, 1.24]
1.5 Total 12.5mg 6 weeks	1	193	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.55, 1.86]
1.6 Total 25mg 6 weeks	5	2595	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.76, 1.14]
1.7 due to cardiorenal AE 25mg 6 weeks	2	1471	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.58, 3.07]
1.8 due to GI AE 25mg 6 weeks	1	122	Risk Ratio (M-H, Fixed, 95% CI)	4.27 [0.49, 37.12]
1.9 due to aggrevated hypertension 25mg 6 weeks	1	810	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [0.63, 15.22]

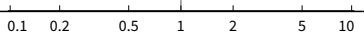
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.10 due to peripheral oedema 25mg 6 weeks	1	810	Risk Ratio (M-H, Fixed, 95% CI)	2.58 [0.50, 13.20]
1.11 due to hypertension	1	931	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.12, 71.74]
1.12 due to oedema 25mg 6 weeks	1	192	Risk Ratio (M-H, Fixed, 95% CI)	5.10 [0.25, 104.94]
2 Adverse events	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 TOTAL 12.5mg 6 weeks	1	193	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.93, 1.53]
2.2 TOTAL 25mg 6 weeks	4	1503	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.95, 1.14]
2.3 Total GI AE 25mg 6 weeks	1	122	Risk Ratio (M-H, Fixed, 95% CI)	3.05 [1.39, 6.68]
2.4 Oedema 25mg 6 weeks	4	2473	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.27, 2.47]
2.5 Systolic BP increase 25mg 6 weeks	3	2833	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.24, 1.90]
2.6 Diastolic BP increase 25mg 6 weeks	3	2833	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.91, 2.63]
2.7 CHF 12.5mg 6 weeks	1	193	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.8 CHF 25mg 6 weeks	3	2094	Risk Ratio (M-H, Fixed, 95% CI)	3.06 [0.73, 12.72]
2.9 Laboratory renal 25mg 6 weeks	1	810	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.34, 3.17]
2.10 Serious 12.5mg 6 weeks	1	193	Risk Ratio (M-H, Fixed, 95% CI)	5.05 [0.25, 103.86]
2.11 Serious 25mg 6 weeks	3	1381	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.79, 2.93]
2.12 Hypertension 25mg 6 weeks	2	571	Risk Ratio (M-H, Fixed, 95% CI)	3.51 [0.73, 16.84]
2.13 Diarrhoea 25mg 6 weeks	3	693	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.40, 1.57]
2.14 Dyspepsia 25mg 6 weeks	4	1503	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.82, 1.89]
2.15 Headache 25mg 6 weeks	3	693	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.64, 1.08]
2.16 PUBS 25mg 6 weeks	2	570	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.17 Upper GI distress	1	122	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.33, 6.10]
2.18 Hypertension 12.5mg 6 weeks	1	193	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [0.19, 21.92]
2.19 PUBS 12.5mg 6 weeks	1	192	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.20 Diarrhoea 12.5mg 6 weeks	1	193	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.50, 3.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.21 Dyspepsia 12.5mg 6 weeks	1	193	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.94]
2.22 Headache 12.5mg 6 weeks	1	193	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.12, 1.11]
2.23 Lower extremity oedema 12.5mg 6 weeks	1	193	Risk Ratio (M-H, Fixed, 95% CI)	7.07 [0.37, 135.10]
2.24 goor or very good tolerability 7 days	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.81, 1.49]
2.25 Systolic BP increase 25mg 6 weeks: older hypertensives only	2	1902	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.40, 2.33]
2.26 Oedema 25mg 6 weeks (standard population)	2	571	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.61, 4.85]
2.27 Systolic BP increase 25mg 6 weeks (standard population)	1	931	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.69, 1.52]
3 Mean Systolic BP change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Overall	1	1092	Mean Difference (IV, Fixed, 95% CI)	3.3 [1.89, 4.71]
4 EFFICACY-WOMAC	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Walking Pain 12.5mg 6 weeks	1	186	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-8.17, 5.97]
4.2 Walking Pain 25mg 6 weeks	1	188	Mean Difference (IV, Fixed, 95% CI)	5.80 [-1.27, 12.87]
4.3 Rest Pain 12.5mg 6 weeks	1	186	Mean Difference (IV, Fixed, 95% CI)	1.40 [-5.10, 7.90]
4.4 Rest Pain 25mg 6 weeks	1	188	Mean Difference (IV, Fixed, 95% CI)	7.70 [1.20, 14.20]
4.5 Morning Stiffness 12.5mg 6 weeks	1	186	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-7.46, 7.26]
4.6 Morning Stiffness 25mg 6 weeks	1	188	Mean Difference (IV, Fixed, 95% CI)	7.10 [-0.11, 14.31]
4.7 Night Pain 12.5mg 6 weeks	1	186	Mean Difference (IV, Fixed, 95% CI)	2.60 [-3.90, 9.10]
4.8 Night Pain 25mg 6 weeks	1	188	Mean Difference (IV, Fixed, 95% CI)	10.10 [3.60, 16.60]
4.9 Pain Subscale 12.5mg 6 weeks	1	186	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-7.10, 5.90]

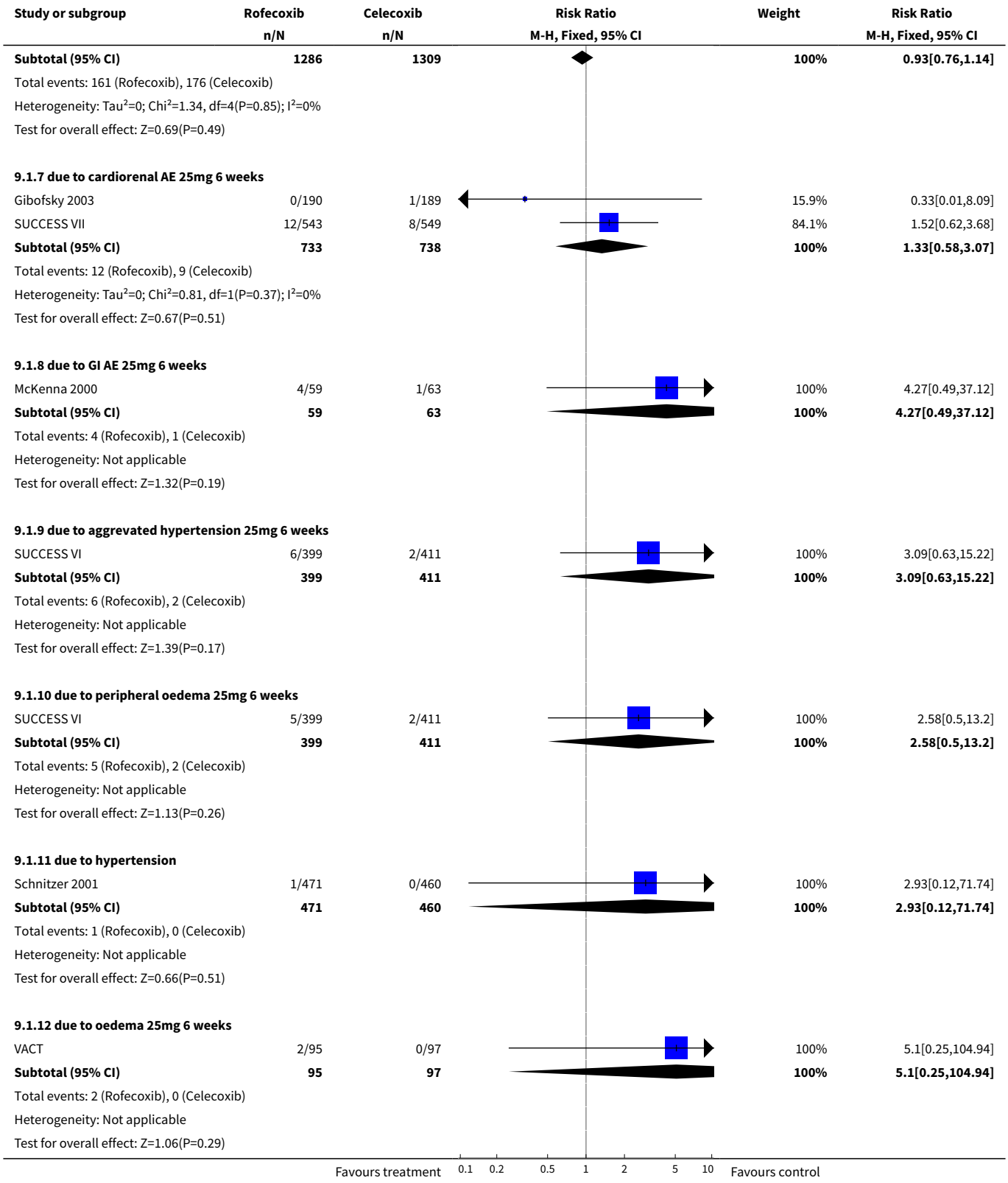
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.10 Pain Subscale 25mg 6 weeks	2	567	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.81, 0.84]
4.11 Stiffness Subscale 12.5mg 6 weeks	1	186	Mean Difference (IV, Fixed, 95% CI)	0.30 [-6.77, 7.37]
4.12 Stiffness Subscale 25mg 6 weeks	2	567	Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.17, 0.39]
4.13 Function Subscale 12.5mg 6 weeks	1	186	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-10.98, 9.78]
4.14 Function Subscale 25mg 6 weeks	2	567	Mean Difference (IV, Fixed, 95% CI)	0.12 [-2.41, 2.66]
5 EFFICACY -patient/investigator measures- dicotomous	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 goor or very good analgesic efficacy 7 days	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.63, 1.81]
5.2 patient improved pain 25mg 6 weeks	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.82, 1.18]
5.3 patient improved arthritis 25mg 6 weeks	1	379	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.72, 1.12]
5.4 physician improved arthritis 25mg 6 weeks	1	379	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.71, 1.10]
5.5 patient global response to therapy - good or excellent 12.5 mg 6 weeks	1	188	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.93, 1.64]
5.6 patient global response to therapy- good or excellent 25 mg 6 weeks	3	2168	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.05, 1.24]
6 EFFICACY- patient/investigator measures- continuous	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 patient- pain on walking 25mg 6 weeks	1	379	Mean Difference (IV, Fixed, 95% CI)	-2.30 [-7.84, 3.24]
7 Adjustment of medication	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 to manage hypertension 25mg 6 weeks	1	1092	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.64, 2.82]
7.2 to manage oedema 25mg 6 weeks	1	1092	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.53, 2.78]
8 Use of paracetamol rescue	3	818	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.65, 1.75]

Analysis 9.1. Comparison 9 rofecoxib versus celecoxib, Outcome 1 Withdrawals.

Study or subgroup	Rofecoxib n/N	Celecoxib n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
9.1.1 due to AE 12.5mg 6 weeks					
VACT	7/96	4/97		100%	1.77[0.53,5.85]
Subtotal (95% CI)	**96**	**97**		**100%**	**1.77[0.53,5.85]**
Total events: 7 (Rofecoxib), 4 (Celecoxib)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.93(P=0.35)					
9.1.2 due to AE 25mg 6 weeks					
Gibofsky 2003	10/190	11/189		13.59%	0.9[0.39,2.08]
McKenna 2000	4/59	4/63		4.77%	1.07[0.28,4.08]
SUCCESS VI	36/399	37/411		44.91%	1[0.65,1.55]
SUCCESS VII	27/543	26/549		31.86%	1.05[0.62,1.78]
VACT	6/95	4/97		4.88%	1.53[0.45,5.26]
Subtotal (95% CI)	**1286**	**1309**		**100%**	**1.03[0.77,1.39]**
Total events: 83 (Rofecoxib), 82 (Celecoxib)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.51$, df=4(P=0.97); $I^2=0\%$					
Test for overall effect: Z=0.22(P=0.83)					
9.1.3 due to LOE 12.5mg 6 weeks					
VACT	8/96	9/97		100%	0.9[0.36,2.23]
Subtotal (95% CI)	**96**	**97**		**100%**	**0.9[0.36,2.23]**
Total events: 8 (Rofecoxib), 9 (Celecoxib)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.23(P=0.82)					
9.1.4 due to LOE 25mg 6 weeks					
Gibofsky 2003	10/190	10/189		28.14%	0.99[0.42,2.33]
McKenna 2000	2/59	5/63		13.57%	0.43[0.09,2.12]
SUCCESS VI	4/399	8/411		22.12%	0.52[0.16,1.7]
SUCCESS VII	3/543	4/549		11.17%	0.76[0.17,3.37]
VACT	8/95	9/97		25%	0.91[0.37,2.25]
Subtotal (95% CI)	**1286**	**1309**		**100%**	**0.76[0.47,1.24]**
Total events: 27 (Rofecoxib), 36 (Celecoxib)					
Heterogeneity: $Tau^2=0$; $Chi^2=1.43$, df=4(P=0.84); $I^2=0\%$					
Test for overall effect: Z=1.09(P=0.28)					
9.1.5 Total 12.5mg 6 weeks					
VACT	17/96	17/97		100%	1.01[0.55,1.86]
Subtotal (95% CI)	**96**	**97**		**100%**	**1.01[0.55,1.86]**
Total events: 17 (Rofecoxib), 17 (Celecoxib)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.03(P=0.97)					
9.1.6 Total 25mg 6 weeks					
Gibofsky 2003	29/190	31/189		17.84%	0.93[0.58,1.48]
McKenna 2000	10/59	14/63		7.77%	0.76[0.37,1.58]
SUCCESS VI	51/399	63/411		35.62%	0.83[0.59,1.17]
SUCCESS VII	53/543	51/549		29.11%	1.05[0.73,1.51]
VACT	18/95	17/97		9.66%	1.08[0.59,1.97]

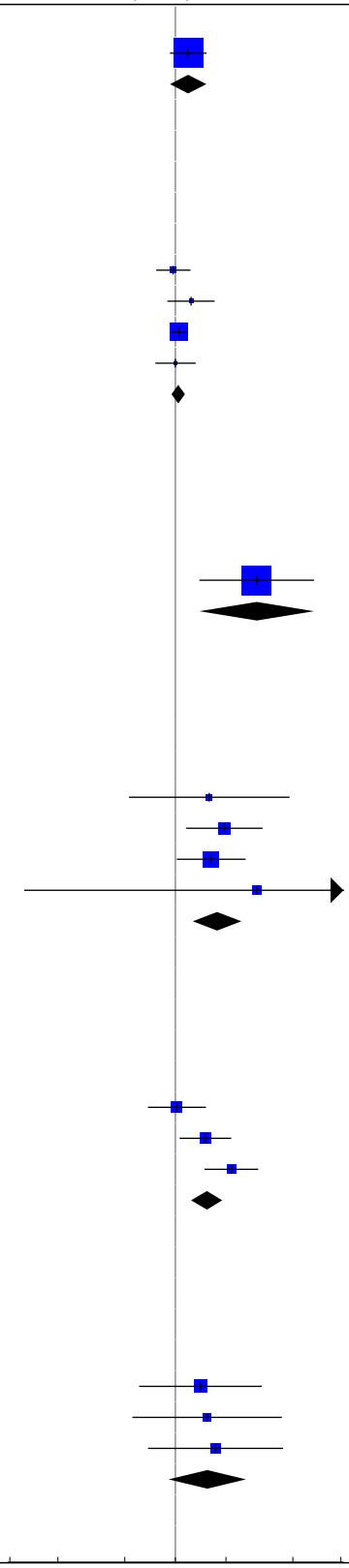


Favours treatment — Favours control

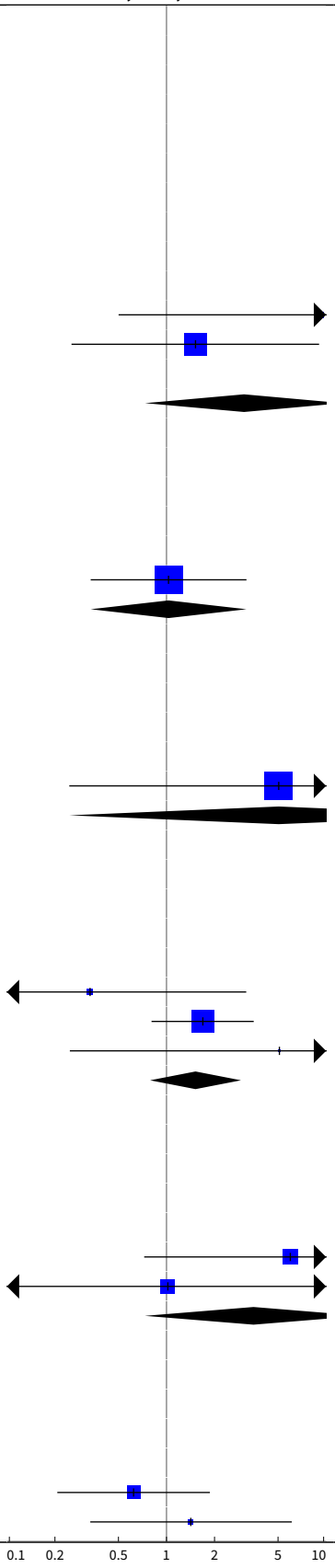


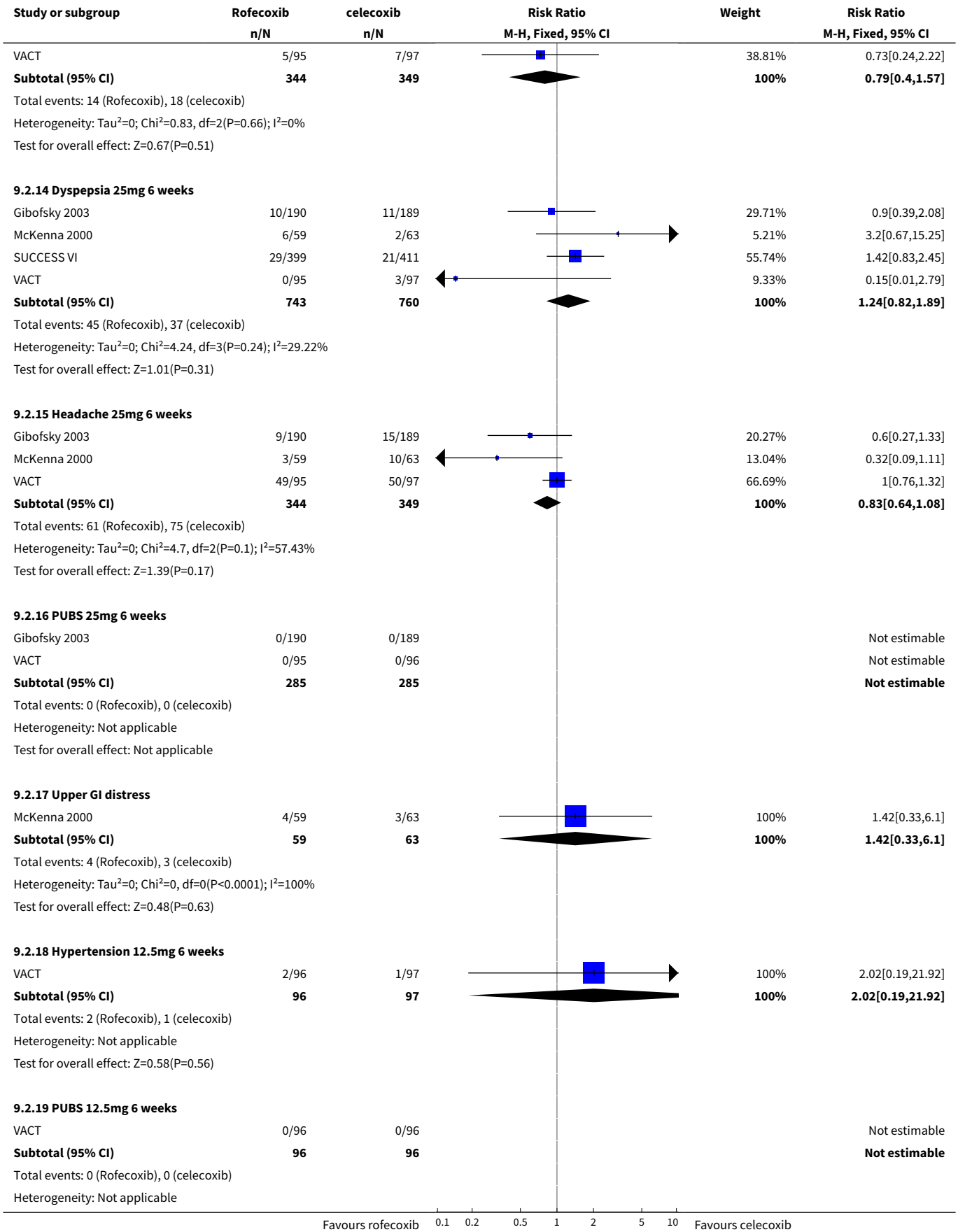
Analysis 9.2. Comparison 9 rofecoxib versus celecoxib, Outcome 2 Adverse events.

Study or subgroup	Rofecoxib n/N	celecoxib n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
9.2.1 TOTAL 12.5mg 6 weeks					
VACT	59/96	50/97		100%	1.19[0.93,1.53]
Subtotal (95% CI)	**96**	**97**		**100%**	**1.19[0.93,1.53]**
Total events: 59 (Rofecoxib), 50 (celecoxib)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.38(P=0.17)					
9.2.2 TOTAL 25mg 6 weeks					
Gibofsky 2003	80/190	82/189		20.7%	0.97[0.77,1.23]
McKenna 2000	36/59	31/63		7.55%	1.24[0.9,1.71]
SUCCESS VI	243/399	239/411		59.29%	1.05[0.93,1.17]
VACT	49/95	50/97		12.46%	1[0.76,1.32]
Subtotal (95% CI)	**743**	**760**		**100%**	**1.04[0.95,1.14]**
Total events: 408 (Rofecoxib), 402 (celecoxib)					
Heterogeneity: Tau^2=0; Chi^2=1.57, df=3(P=0.67); I^2=0%					
Test for overall effect: Z=0.83(P=0.4)					
9.2.3 Total GI AE 25mg 6 weeks					
McKenna 2000	20/59	7/63		100%	3.05[1.39,6.68]
Subtotal (95% CI)	**59**	**63**		**100%**	**3.05[1.39,6.68]**
Total events: 20 (Rofecoxib), 7 (celecoxib)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.79(P=0.01)					
9.2.4 Oedema 25mg 6 weeks					
Gibofsky 2003	8/190	5/189		9.82%	1.59[0.53,4.78]
SUCCESS VI	38/399	20/411		38.58%	1.96[1.16,3.3]
SUCCESS VII	42/543	26/549		50.63%	1.63[1.02,2.62]
VACT	1/95	0/97		0.97%	3.06[0.13,74.25]
Subtotal (95% CI)	**1227**	**1246**		**100%**	**1.77[1.27,2.47]**
Total events: 89 (Rofecoxib), 51 (celecoxib)					
Heterogeneity: Tau^2=0; Chi^2=0.4, df=3(P=0.94); I^2=0%					
Test for overall effect: Z=3.36(P=0)					
9.2.5 Systolic BP increase 25mg 6 weeks					
Schnitzer 2001	45/471	43/460		34.63%	1.02[0.69,1.52]
SUCCESS VI	66/399	45/411		35.29%	1.51[1.06,2.15]
SUCCESS VII	81/543	38/549		30.08%	2.16[1.49,3.11]
Subtotal (95% CI)	**1413**	**1420**		**100%**	**1.54[1.24,1.9]**
Total events: 192 (Rofecoxib), 126 (celecoxib)					
Heterogeneity: Tau^2=0; Chi^2=7.31, df=2(P=0.03); I^2=72.66%					
Test for overall effect: Z=3.96(P<0.0001)					
9.2.6 Diastolic BP increase 25mg 6 weeks					
Schnitzer 2001	13/471	9/460		41.43%	1.41[0.61,3.27]
SUCCESS VI	9/399	6/411		26.89%	1.55[0.56,4.3]
SUCCESS VII	12/543	7/549		31.67%	1.73[0.69,4.37]
Subtotal (95% CI)	**1413**	**1420**		**100%**	**1.55[0.91,2.63]**
Total events: 34 (Rofecoxib), 22 (celecoxib)					
Heterogeneity: Tau^2=0; Chi^2=0.1, df=2(P=0.95); I^2=0%					

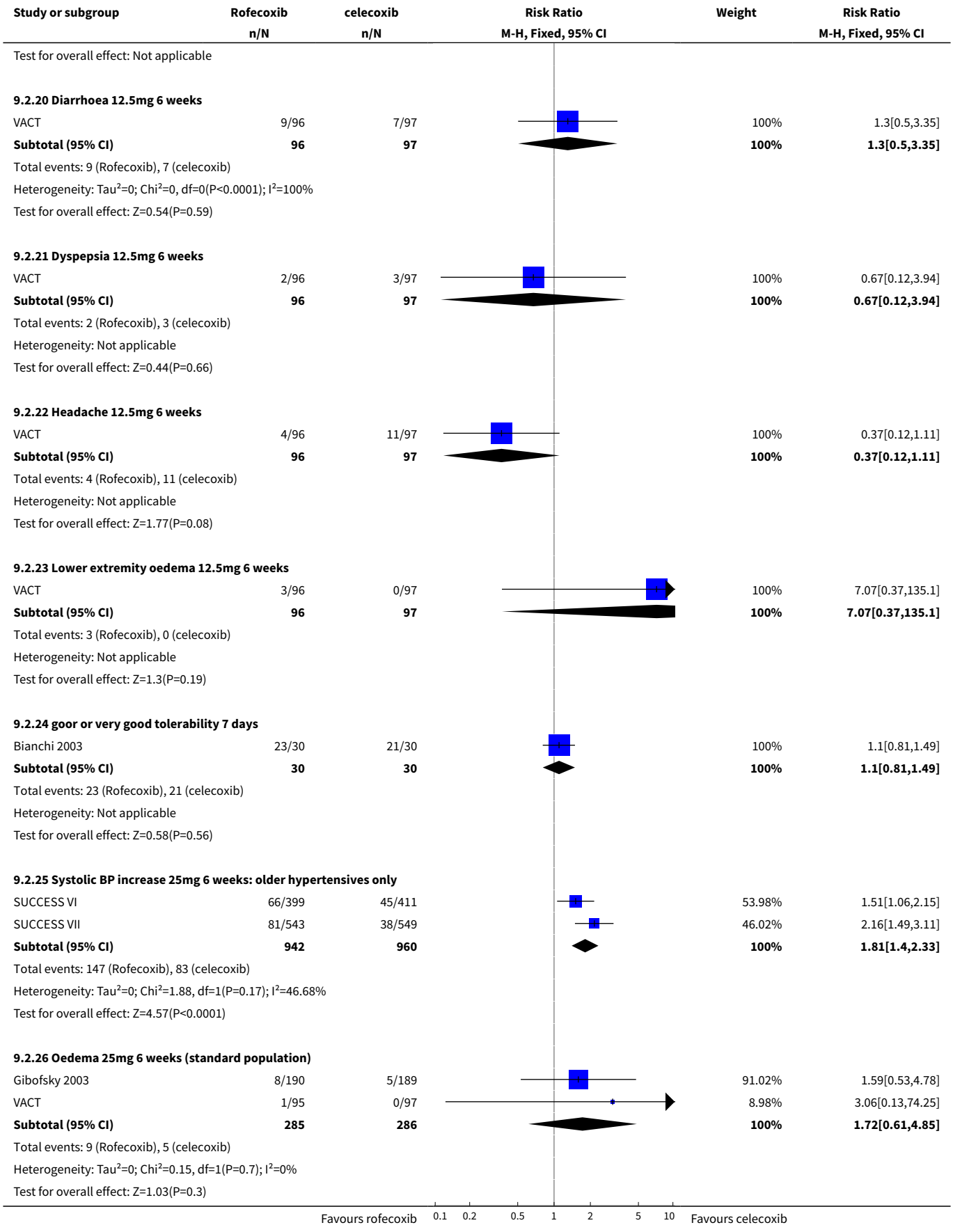


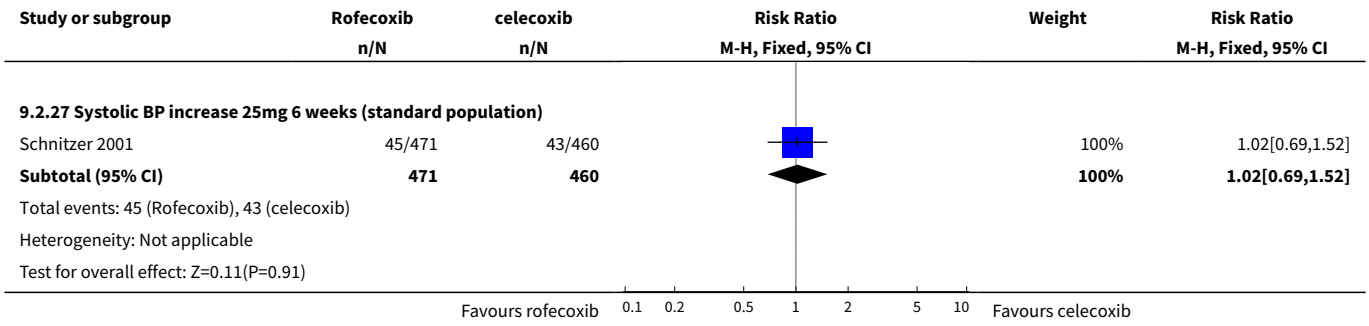
Study or subgroup	Rofecoxib n/N	celecoxib n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=1.62(P=0.11)					
9.2.7 CHF 12.5mg 6 weeks					
VACT	0/96	0/97			Not estimable
Subtotal (95% CI)	**96**	**97**			**Not estimable**
Total events: 0 (Rofecoxib), 0 (celecoxib)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
9.2.8 CHF 25mg 6 weeks					
SUCCESS VI	4/399	0/411		19.85%	9.27[0.5,171.62]
SUCCESS VII	3/543	2/549		80.15%	1.52[0.25,9.04]
VACT	0/95	0/97			Not estimable
Subtotal (95% CI)	**1037**	**1057**		**100%**	**3.06[0.73,12.72]**
Total events: 7 (Rofecoxib), 2 (celecoxib)					
Heterogeneity: Tau^2=0; Chi^2=1.15, df=1(P=0.28); I^2=12.81%					
Test for overall effect: Z=1.53(P=0.12)					
9.2.9 Laboratory renal 25mg 6 weeks					
SUCCESS VI	6/399	6/411		100%	1.03[0.34,3.17]
Subtotal (95% CI)	**399**	**411**		**100%**	**1.03[0.34,3.17]**
Total events: 6 (Rofecoxib), 6 (celecoxib)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.05(P=0.96)					
9.2.10 Serious 12.5mg 6 weeks					
VACT	2/96	0/97		100%	5.05[0.25,103.86]
Subtotal (95% CI)	**96**	**97**		**100%**	**5.05[0.25,103.86]**
Total events: 2 (Rofecoxib), 0 (celecoxib)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.29)					
9.2.11 Serious 25mg 6 weeks					
Gibofsky 2003	1/190	3/189		20.98%	0.33[0.03,3.16]
SUCCESS VI	18/399	11/411		75.57%	1.69[0.81,3.52]
VACT	2/95	0/97		3.45%	5.1[0.25,104.94]
Subtotal (95% CI)	**684**	**697**		**100%**	**1.52[0.79,2.93]**
Total events: 21 (Rofecoxib), 14 (celecoxib)					
Heterogeneity: Tau^2=0; Chi^2=2.44, df=2(P=0.29); I^2=18.2%					
Test for overall effect: Z=1.25(P=0.21)					
9.2.12 Hypertension 25mg 6 weeks					
Gibofsky 2003	6/190	1/189		50.33%	5.97[0.73,49.1]
VACT	1/95	1/97		49.67%	1.02[0.06,16.09]
Subtotal (95% CI)	**285**	**286**		**100%**	**3.51[0.73,16.84]**
Total events: 7 (Rofecoxib), 2 (celecoxib)					
Heterogeneity: Tau^2=0; Chi^2=1.01, df=1(P=0.31); I^2=1.4%					
Test for overall effect: Z=1.57(P=0.12)					
9.2.13 Diarrhoea 25mg 6 weeks					
Gibofsky 2003	5/190	8/189		44.94%	0.62[0.21,1.87]
McKenna 2000	4/59	3/63		16.26%	1.42[0.33,6.1]



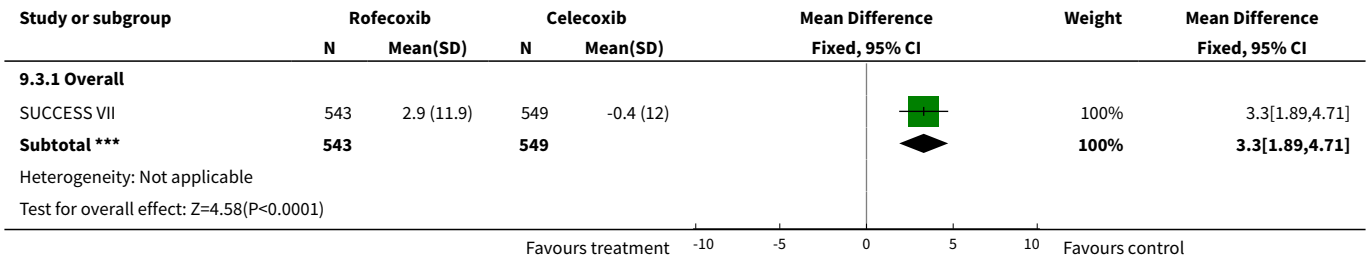


Study or subgroup	Rofecoxib n/N	celecoxib n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
VACT	5/95	7/97		38.81%	0.73[0.24,2.22]
Subtotal (95% CI)	**344**	**349**		**100%**	**0.79[0.4,1.57]**
Total events: 14 (Rofecoxib), 18 (celecoxib)					
Heterogeneity: Tau^2=0; Chi^2=0.83, df=2(P=0.66); I^2=0%					
Test for overall effect: Z=0.67(P=0.51)					
9.2.14 Dyspepsia 25mg 6 weeks					
Gibofsky 2003	10/190	11/189		29.71%	0.9[0.39,2.08]
McKenna 2000	6/59	2/63		5.21%	3.2[0.67,15.25]
SUCCESS VI	29/399	21/411		55.74%	1.42[0.83,2.45]
VACT	0/95	3/97		9.33%	0.15[0.01,2.79]
Subtotal (95% CI)	**743**	**760**		**100%**	**1.24[0.82,1.89]**
Total events: 45 (Rofecoxib), 37 (celecoxib)					
Heterogeneity: Tau^2=0; Chi^2=4.24, df=3(P=0.24); I^2=29.22%					
Test for overall effect: Z=1.01(P=0.31)					
9.2.15 Headache 25mg 6 weeks					
Gibofsky 2003	9/190	15/189		20.27%	0.6[0.27,1.33]
McKenna 2000	3/59	10/63		13.04%	0.32[0.09,1.11]
VACT	49/95	50/97		66.69%	1[0.76,1.32]
Subtotal (95% CI)	**344**	**349**		**100%**	**0.83[0.64,1.08]**
Total events: 61 (Rofecoxib), 75 (celecoxib)					
Heterogeneity: Tau^2=0; Chi^2=4.7, df=2(P=0.1); I^2=57.43%					
Test for overall effect: Z=1.39(P=0.17)					
9.2.16 PUBS 25mg 6 weeks					
Gibofsky 2003	0/190	0/189			Not estimable
VACT	0/95	0/96			Not estimable
Subtotal (95% CI)	**285**	**285**			**Not estimable**
Total events: 0 (Rofecoxib), 0 (celecoxib)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
9.2.17 Upper GI distress					
McKenna 2000	4/59	3/63		100%	1.42[0.33,6.1]
Subtotal (95% CI)	**59**	**63**		**100%**	**1.42[0.33,6.1]**
Total events: 4 (Rofecoxib), 3 (celecoxib)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.48(P=0.63)					
9.2.18 Hypertension 12.5mg 6 weeks					
VACT	2/96	1/97		100%	2.02[0.19,21.92]
Subtotal (95% CI)	**96**	**97**		**100%**	**2.02[0.19,21.92]**
Total events: 2 (Rofecoxib), 1 (celecoxib)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.58(P=0.56)					
9.2.19 PUBS 12.5mg 6 weeks					
VACT	0/96	0/96			Not estimable
Subtotal (95% CI)	**96**	**96**			**Not estimable**
Total events: 0 (Rofecoxib), 0 (celecoxib)					
Heterogeneity: Not applicable					

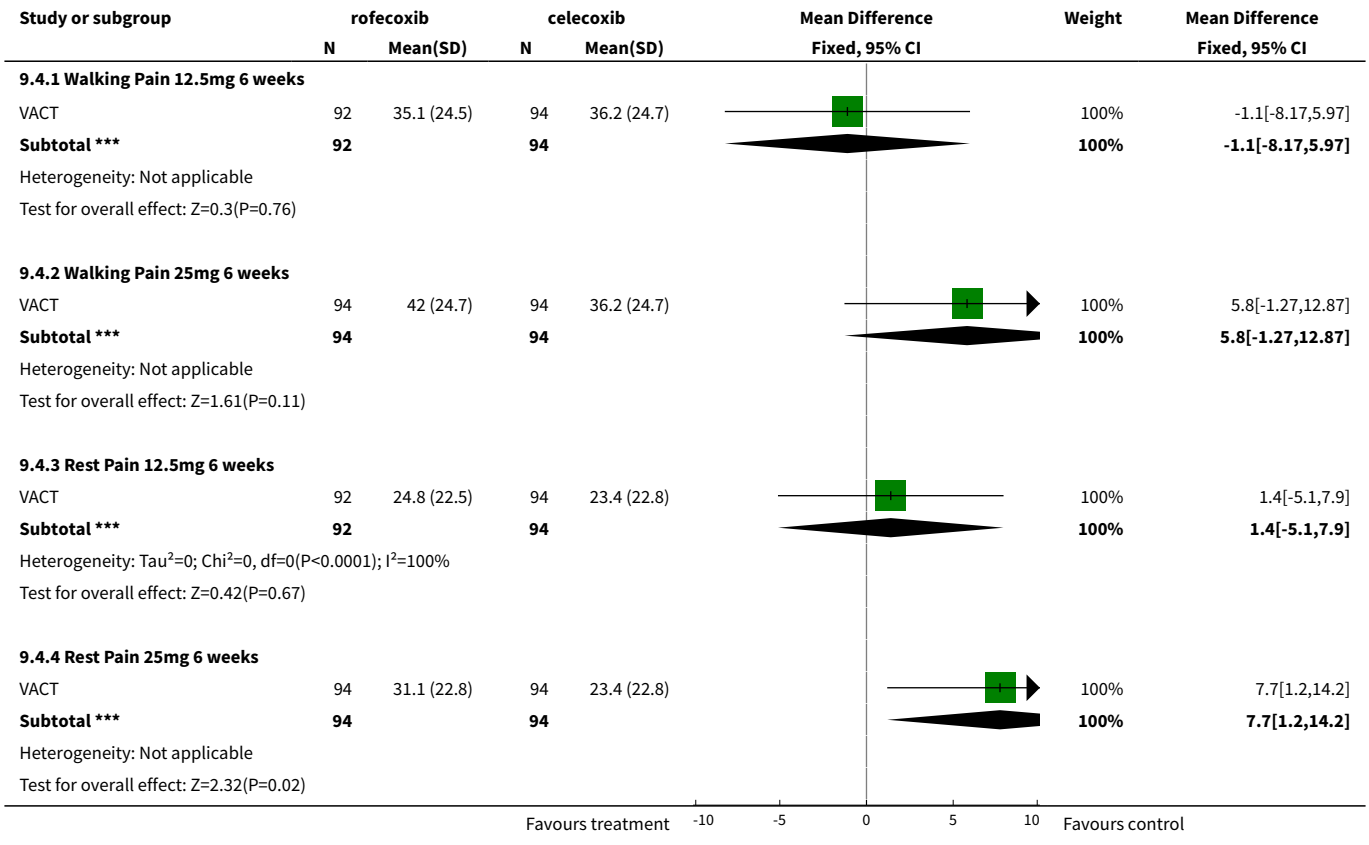


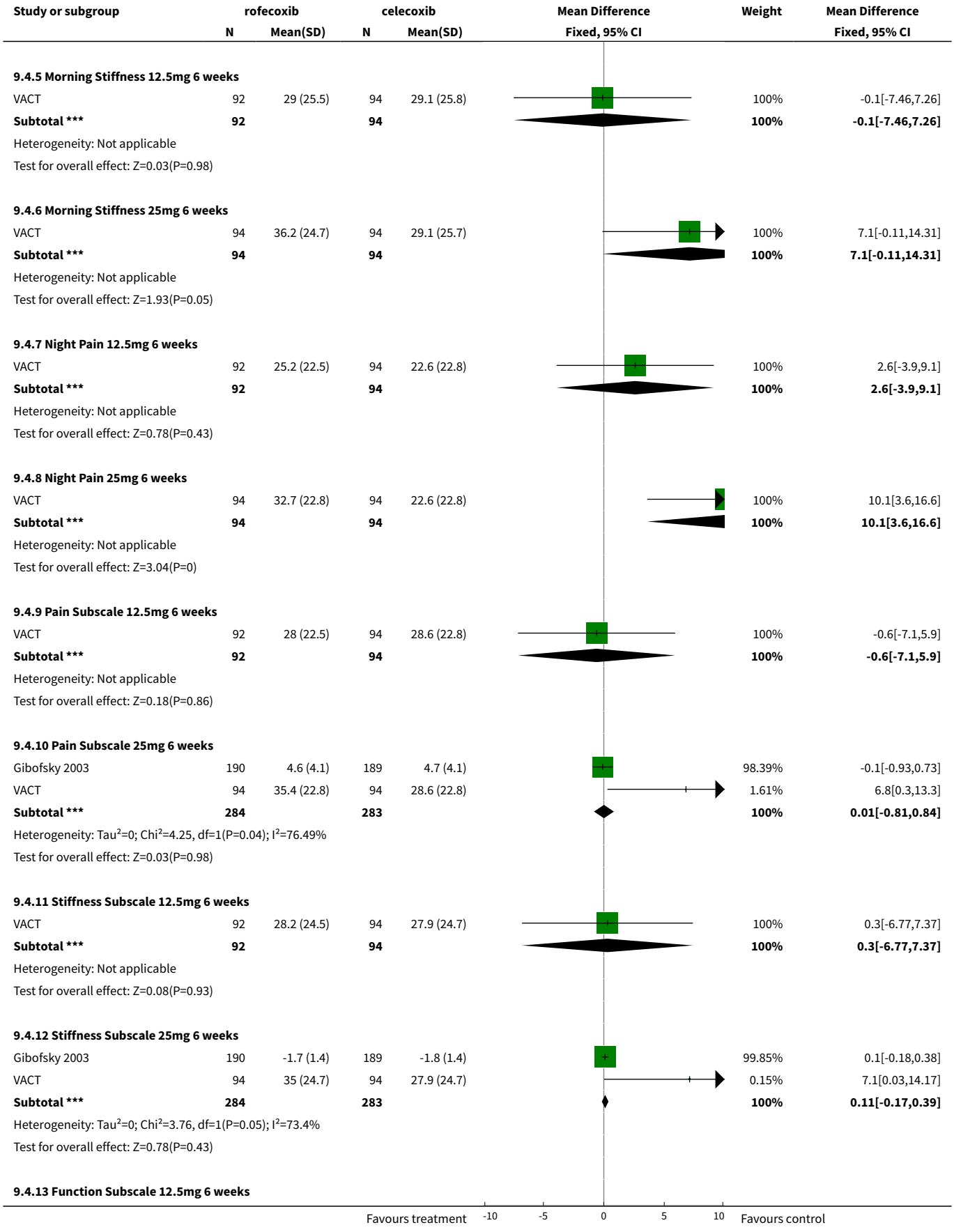


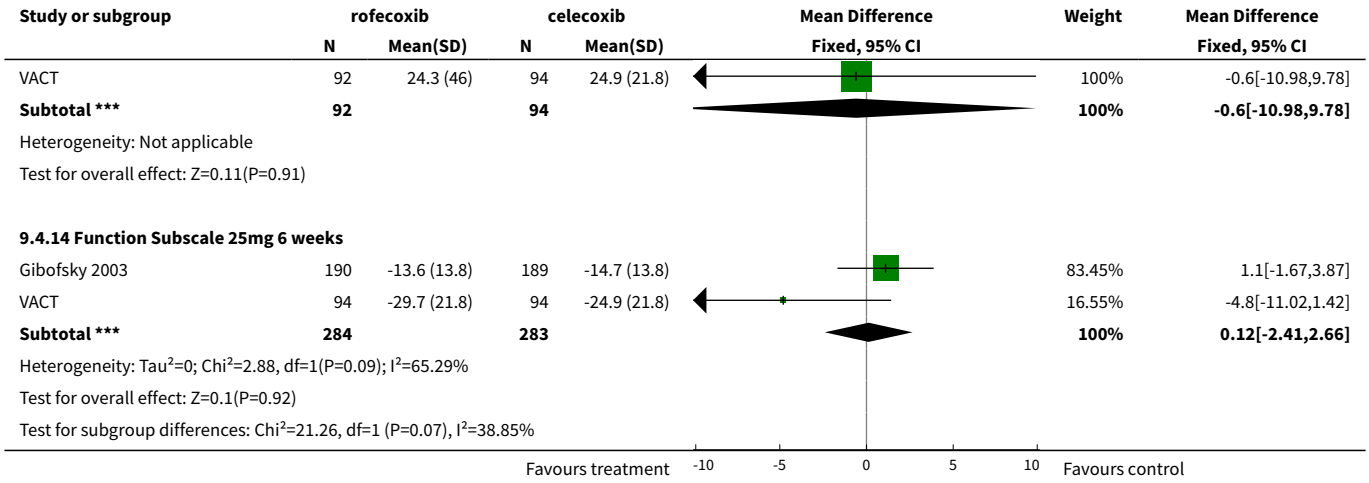
Analysis 9.3. Comparison 9 rofecoxib versus celecoxib, Outcome 3 Mean Systolic BP change from baseline.



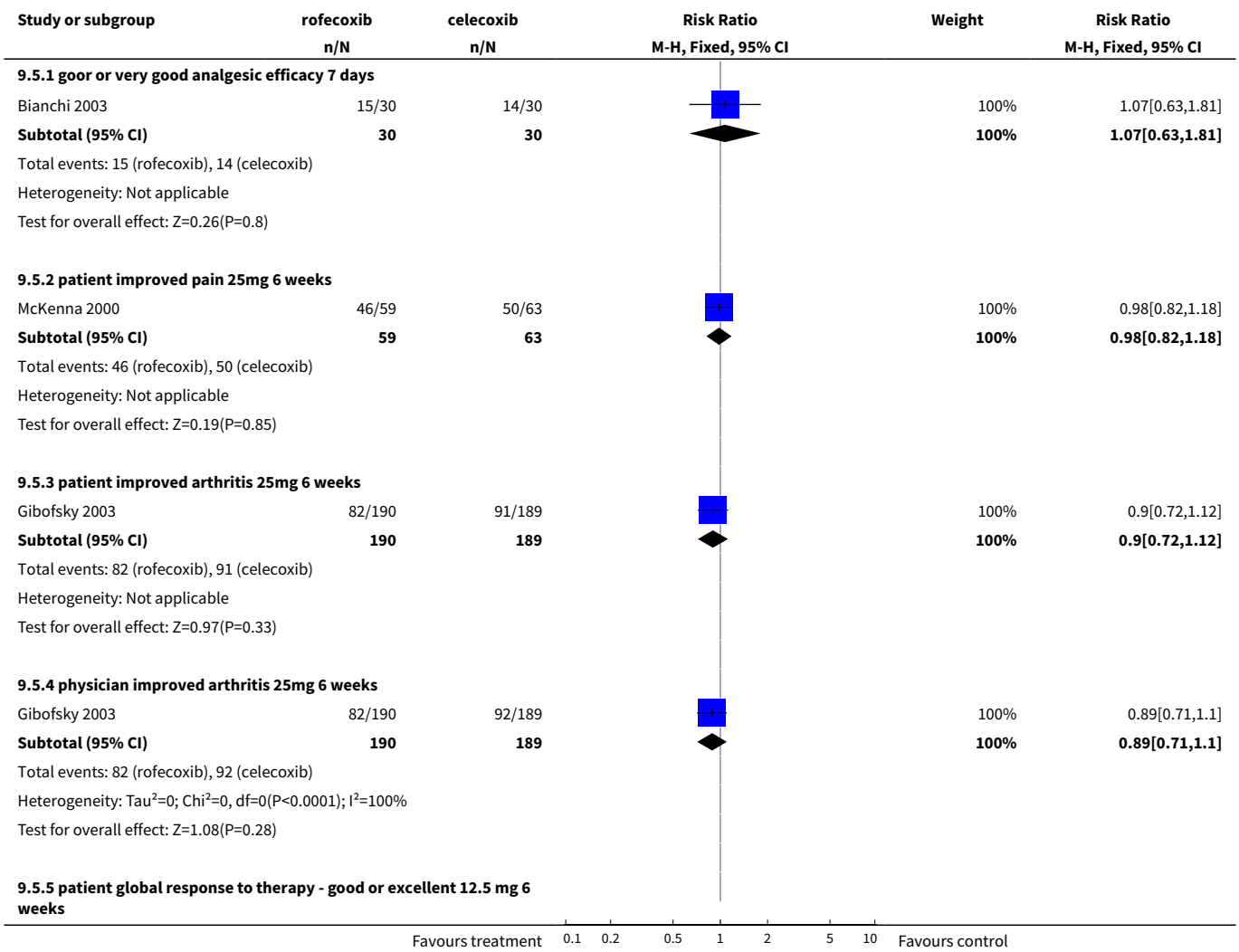
Analysis 9.4. Comparison 9 rofecoxib versus celecoxib, Outcome 4 EFFICACY-WOMAC.

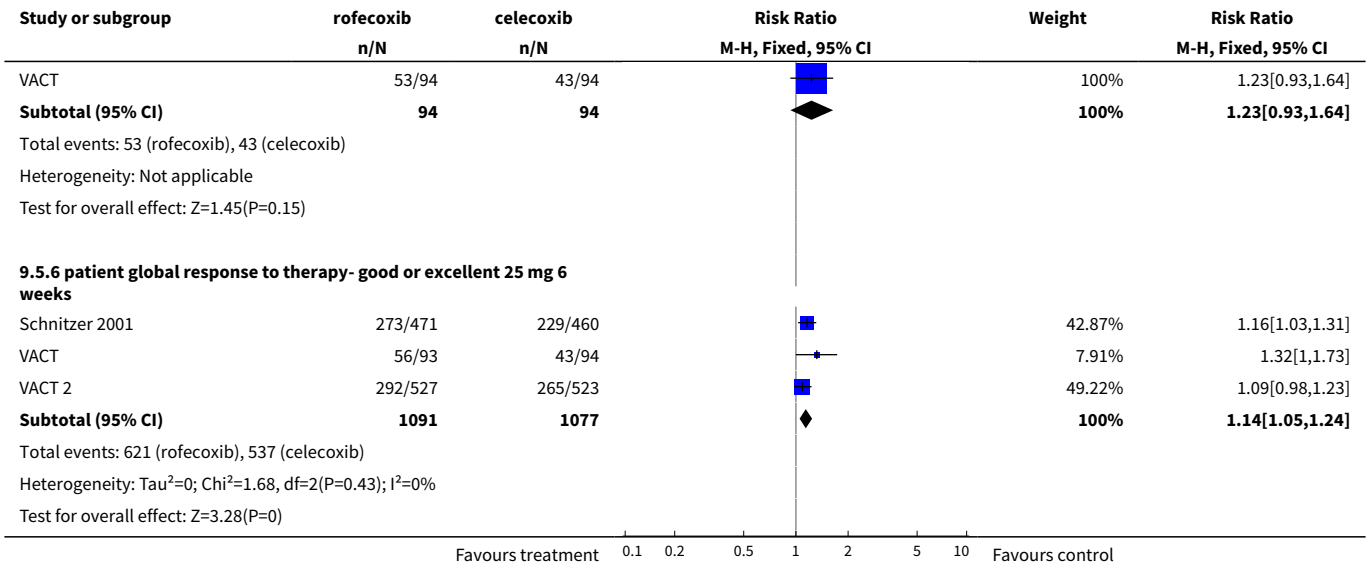




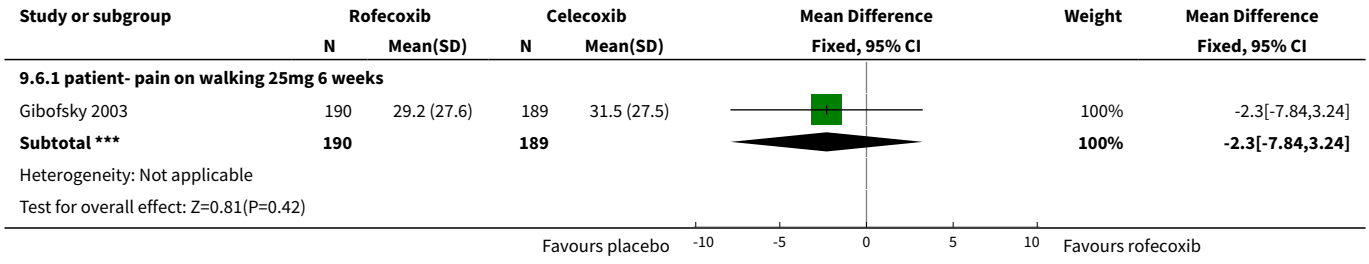


Analysis 9.5. Comparison 9 rofecoxib versus celecoxib, Outcome 5 EFFICACY -patient/investigator measures- dicotomous.

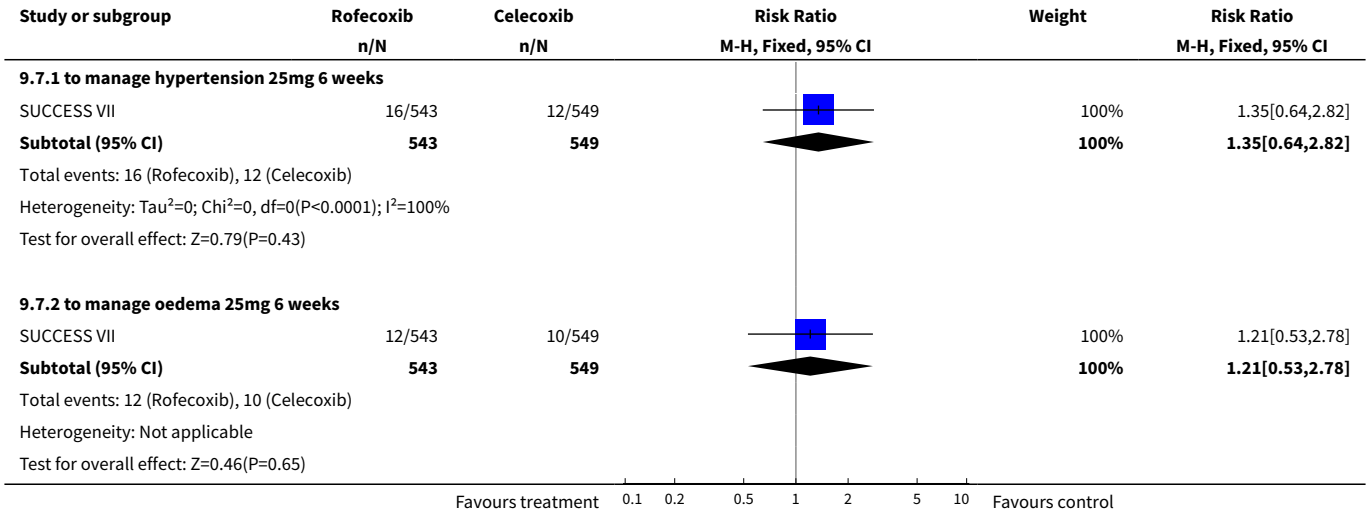




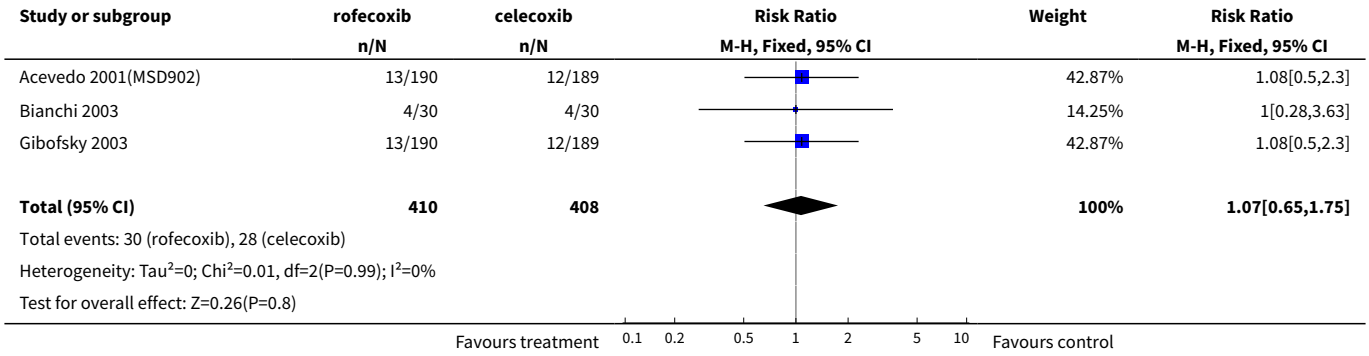
Analysis 9.6. Comparison 9 rofecoxib versus celecoxib, Outcome 6 EFFICACY- patient/investigator measures- continuous.



Analysis 9.7. Comparison 9 rofecoxib versus celecoxib, Outcome 7 Adjustment of medication.



Analysis 9.8. Comparison 9 rofecoxib versus celecoxib, Outcome 8 Use of paracetamol rescue.

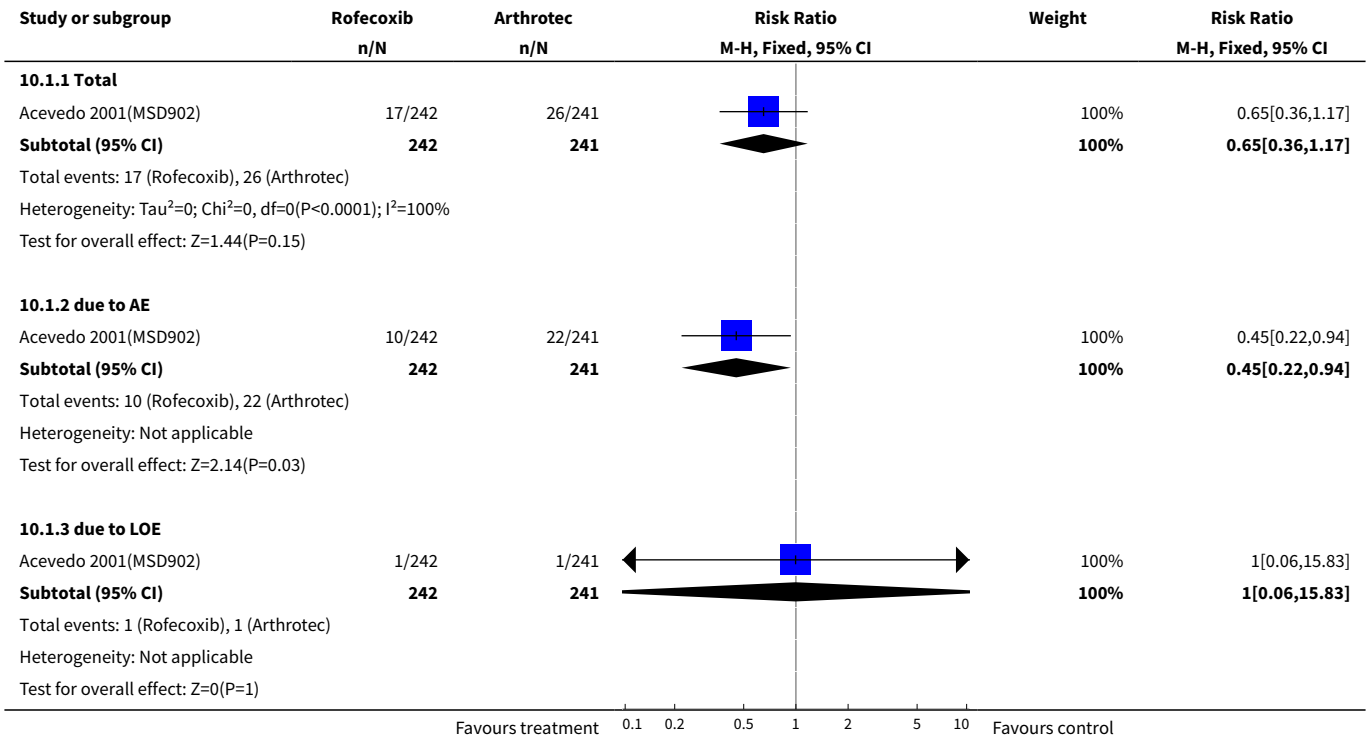


Comparison 10. rofecoxib versus arthrotec

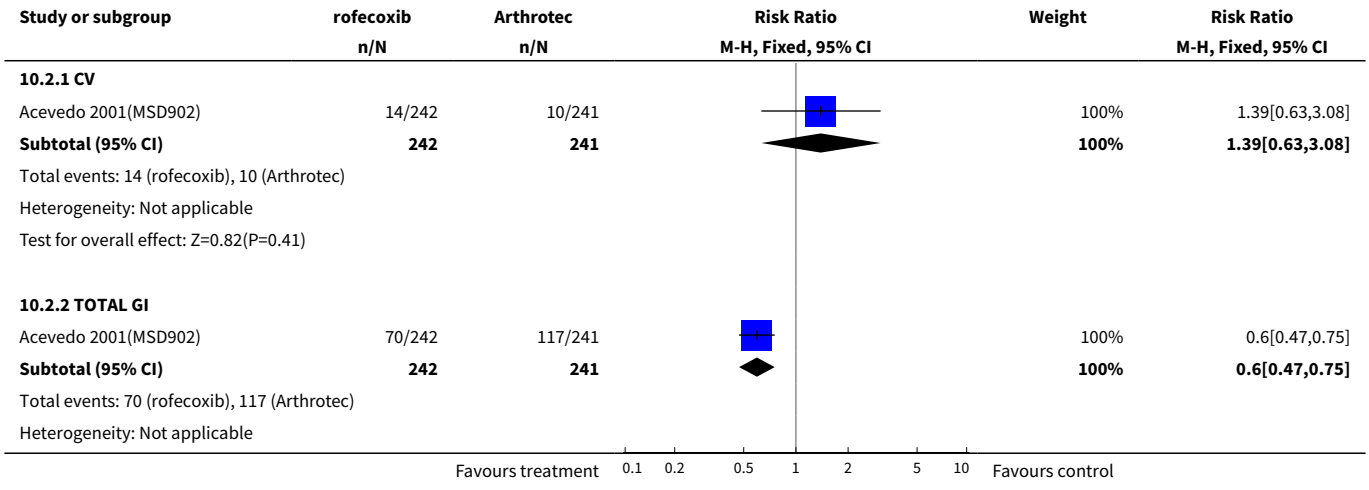
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 WITHDRAWALS 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Total	1	483	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.36, 1.17]
1.2 due to AE	1	483	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.22, 0.94]
1.3 due to LOE	1	483	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.83]
2 ADVERSE EVENTS 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 CV	1	483	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.63, 3.08]
2.2 TOTAL GI	1	483	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.47, 0.75]
2.3 TOTAL	1	483	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.63, 0.83]
2.4 Diarrhoea	1	483	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.18, 0.54]
2.5 Abdominal Pain	1	483	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.39, 1.10]
2.6 Lower extremity oedema	1	483	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.29, 3.40]
2.7 NSAID -type GI	1	483	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.41, 0.87]
2.8 SERIOUS	1	483	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.17, 3.30]
3 EFFICACY 6 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Patient Global (100mm VAS) change from baseline	1	483	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.30, 0.06]

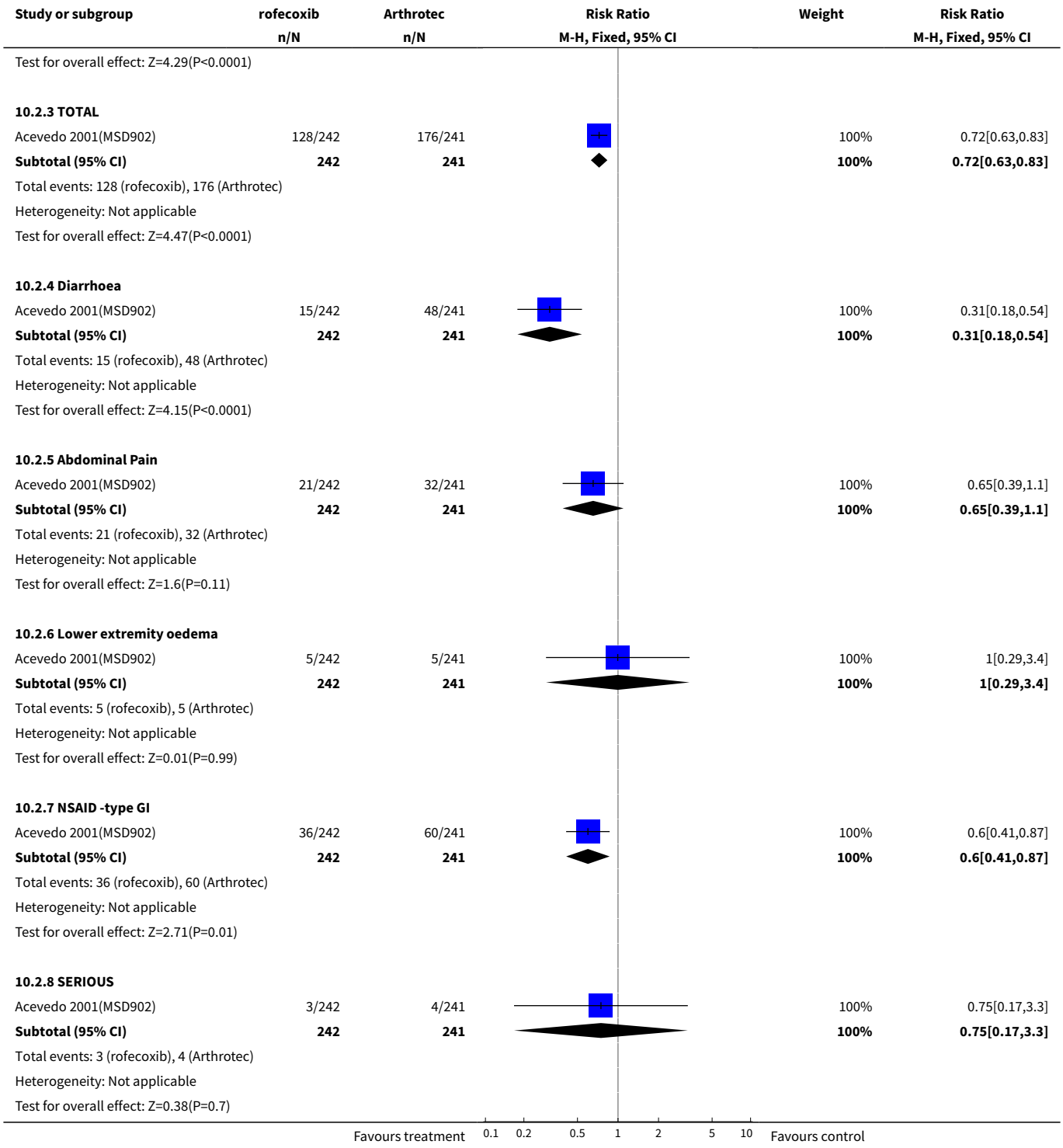
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Investigator Global (0-4 Likert) change from baseline	1	483	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.14, 0.22]

Analysis 10.1. Comparison 10 rofecoxib versus arthrotec, Outcome 1 WITHDRAWALS 6 weeks.

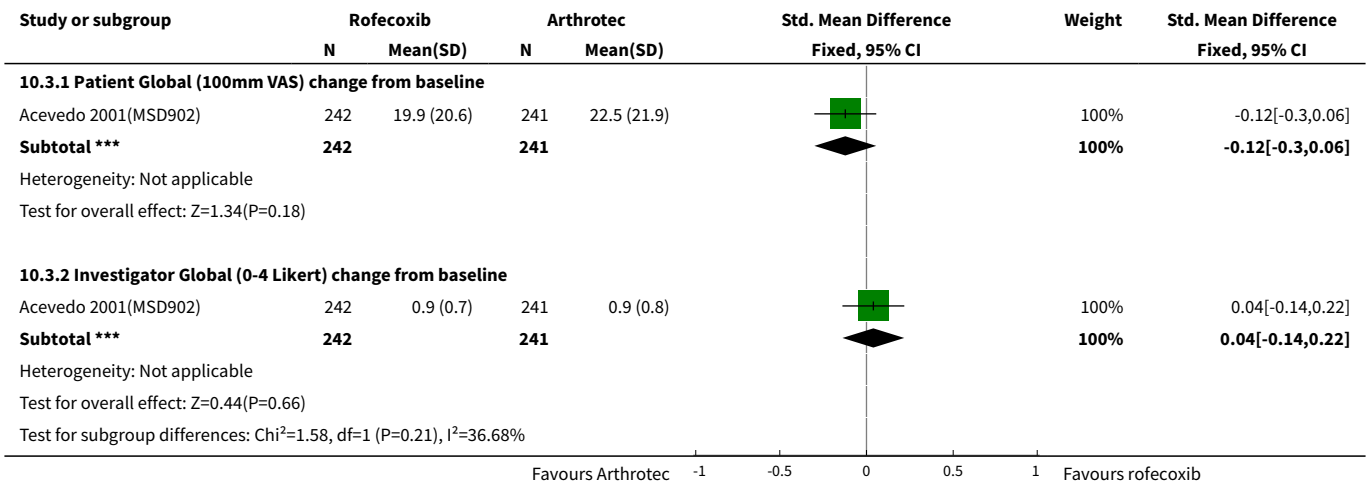


Analysis 10.2. Comparison 10 rofecoxib versus arthrotec, Outcome 2 ADVERSE EVENTS 6 weeks.





Analysis 10.3. Comparison 10 rofecoxib versus arthrotec, Outcome 3 EFFICACY 6 weeks.



ADDITIONAL TABLES

Table 1. Clinical benefit for improvement in patient global assessment

Outcome	Dose	Duration	Event rate rofecoxib	Event rate placebo	Relative Risk(95%CI)	Absolute Risk Differ	NNT
Patient measured Good or excellent response/improved	12.5mg	6 weeks	552/1033	136/473	1.85 (1.59, 2.16)	0.25 (0.19, 0.30)	5 (4, 6)
Patient measured Good or excellent response/improved	25mg	6weeks	220/417	48/165	1.75 (1.35, 2.26)	0.22 (0.13, 0.30)	5 (4, 9)

Table 2. Adverse Events

OUTCOME	DOSE	DURATION	EVENT RATE ROFECOXIB	EVENT RATE PLACEBO	RELATIVE RISK(95%CI)	ABSOLUTE RISK DIFF	NNH (95% CI)
Serious Adverse Events	12.5mg	6 weeks	20/932	2/456	3.95 (1.06, 14.63)	0.02 (0.01, 0.03)	78 (17, 3788)
Serious Adverse Events	25mg	6 weeks	2/378	3/280	0.47 (0.11, 2.08)	-0.01 (-0.03, 0.01)	177 (Not available)
GI events	12.5mg	6 weeks	29/424	14/208	1.02 (0.55, 1.88)	0.00 (-0.04, 0.04)	743 (Not available)
GI events	25mg	6 weeks	20/59	6/60	3.39 (1.47, 7.84)	0.24 (0.10, 0.38)	5 (2, 22)

WHAT'S NEW

Date	Event	Description
19 May 2008	Amended	Converted to new review format. CMSG ID C073-R

HISTORY

Review first published: Issue 1, 2005

Date	Event	Description
17 November 2004	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

*Anti-Inflammatory Agents, Non-Steroidal [adverse effects] [therapeutic use]; *Cyclooxygenase Inhibitors [adverse effects] [therapeutic use]; *Lactones [adverse effects] [therapeutic use]; *Sulfones [adverse effects] [therapeutic use]; Drug Approval; Osteoarthritis [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans