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A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling

TJ Brown, L Hooper, RA Elliott, K Payne,
R Webb, C Roberts, A Rostom and D Symmons

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TJ Brown,[1] L Hooper,[2] RA Elliott,[3] K Payne,[4] R Webb,[5] C Roberts,[6] A Rostom[7] and D Symmons[1*]

[1] arc Epidemiology Unit, University of Manchester, UK
[2] University of Manchester and Central Manchester and Manchester Children's University Hospitals Trust, UK
[3] School of Pharmacy and Pharmaceutical Sciences, University of Manchester, UK
[4] Health Economics Research at Manchester, University of Manchester, UK
[5] School of Psychiatry and Behavioural Sciences, University of Manchester, UK
[6] School of Epidemiology and Health Sciences, University of Manchester, UK
[7] Division of Gastroenterology, Department of Medicine, University of Ottawa, Canada

* Corresponding author

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Abstract

A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling

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[1] arc Epidemiology Unit, University of Manchester, UK
[2] University of Manchester and Central Manchester and Manchester Children's University Hospitals Trust, UK
[3] School of Pharmacy and Pharmaceutical Sciences, University of Manchester, UK
[4] Health Economics Research at Manchester, University of Manchester, UK
[5] School of Psychiatry and Behavioural Sciences, University of Manchester, UK
[6] School of Epidemiology and Health Sciences, University of Manchester, UK
[7] Division of Gastroenterology, Department of Medicine, University of Ottawa, Canada
* Corresponding author

Objectives: To assess the relative effectiveness, patient acceptability, costs and cost-effectiveness of four strategies for the prevention of non-steroidal anti-inflammatory drugs (NSAIDs)-induced gastrointestinal (GI) toxicity: (1) Cox-1 NSAIDs plus histamine-2 receptor antagonist (H_2RA), (2) Cox-1 NSAIDs plus proton pump inhibitors (PPIs), (3) Cox-1 NSAIDs plus misoprostol, and (4) Cox-2 NSAIDs (later expanded to 4a Cox-2 coxib NSAIDs and 4b Cox-2 preferential NSAIDs).

Data sources: Electronic databases up to May 2002.

Review methods: Relevant studies were selected, assessed and analysed. Pooled relative risk ratios (RR) from the systematic review were combined with up-to-date UK resource use and unit costs data in an incremental economic analysis. A probabilistic decision-analytic model was designed and populated with data to carry out incremental economic analysis. Incremental cost-effectiveness ratios (ICERs) were generated for the outcome measure, endoscopic ulcer or serious GI event averted, against total cost, and non-parametric bootstrapping was used to simulate variance of these ICERs.

Results: Of 118 selected trials, including 125 relevant comparisons (which included 76,322 participants) only 138 deaths and 248 serious GI events were reported. Seven comparisons were judged to be at low risk of bias. Comparing the gastroprotective strategies against placebo, there was no evidence of effectiveness of H_2RAs against any primary outcomes (few events reported), PPIs may reduce the risk of symptomatic ulcers [RR 0.09, 95% confidence interval (CI) 0.02 to 0.47], misoprostol reduces the risk of serious GI complications (RR 0.57, 95% CI 0.36 to 0.91) and symptomatic ulcers (RR 0.36, 95% CI 0.20 to 0.67), Cox-2 'preferentials' reduce the risk of symptomatic ulcers (RR 0.41, 95% CI 0.26 to 0.65) and Cox-2 'coxibs' reduce the risk of symptomatic ulcers (RR 0.49, 95% CI 0.38 to 0.62) and possibly serious GI events (RR 0.55, 95% CI 0.38 to 0.80). All strategies except Cox-2 'preferentials' reduce the risk of endoscopic ulcers. There were only 12 direct comparisons between gastroprotective strategies. All they suggest is that Cox-2 preferentials are better than misoprostol for preventing GI complications. Indirect comparisons suggested that PPIs may prevent symptomatic ulcers better than Cox-2 coxibs, but this is very weak evidence. For prevention of endoscopic ulcers PPIs and misoprostol appear more successful than H_2RAs and misoprostol is better than Cox-2 preferentials. There were no UK head-to-head published economic analyses with regard to the main gastroprotective strategies. There were generally insufficient data with regards to cardiac or renal outcomes, serious GI outcomes or life-years gained to populate the mode. Mean (2.5th and 97.5th percentile) costs per endoscopic ulcer averted compared with Cox-1 NSAIDs alone were as follows: Cox-1 plus

H_2RAs, –£186 (–555 to 804); Cox-1 plus PPIs, £454 (251 to 877); Cox-1 plus misoprostol, £54 (–112 to 238); Cox-2 selective NSAIDs, £263 (–570 to 1280), or Cox-2 specific NSAIDs, £301 (189 to 418). With regard to the prevention of endoscopic ulcers, Cox-1 NSAID plus H_2RA is a dominant option. Cost-effectiveness acceptability analysis showed a 95% probability that this combination was less costly and more effective. Cost-effectiveness acceptability frontiers showed that if the decision-maker is willing to pay up to £750 to avoid an endoscopic ulcer, then Cox-1 plus H_2RA is the optimal strategy. If the decision-maker is willing to pay over £750, the optimal strategy is NSAID plus misoprostol. Between £1900 and £3750, Cox-2 selective inhibitors are optimal, and over £3750, Cox-2 specific inhibitors become optimal. NSAID plus PPI is never the optimal strategy. Sensitivity and subgroup analyses suggest that Cox-1 NSAID plus H_2RA and Cox-1 NSAID plus misoprostol become more cost-effective in the older age group. Some conclusions were associated with high levels of uncertainty.

Conclusions: Although there is a very large body of evidence comparing Cox-2 NSAIDs with Cox-1 NSAIDs, this is not matched by studies of the other types of gastroprotectors or by studies directly comparing active gastroprotective strategies. This lack of direct comparisons led to the use of indirect comparisons to help understand the relative efficacy of these strategies. Indirect evidence in itself is weak and was also hampered by lack of evidence in the underlying studies (where the gastroprotectors were compared with placebo). Economic modelling suggests that Cox-1 NSAID plus H_2RA or Cox-1 NSAID plus PPI are the most cost-effective strategies for avoiding endoscopic ulcers in patients requiring long-term NSAID therapy. All strategies other than Cox-2 selective inhibitors reduce the rate of endoscopic ulcer compared with Cox-1 alone. The economic analysis suggests that there may be a case for prescribing H_2RAs in all patients requiring NSAIDs. Misoprostol is more effective, but is associated with a greater cost and GI side-effects which may be unacceptable for patients. However, when assessing serious GI events, the economic analysis is sufficiently weakened by the data available as to render clear practice recommendations impossible. Further large, independent RCTs directly comparing various gastroprotective strategies are needed. These should report items such as major outcomes, primary data, adverse events, assessment of practice and patient preference.

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List of abbreviations

ACCES	arthritis cost consequence evaluation system
ACR	American College of Rheumatology
ARR	absolute risk reduction (or risk difference)
AS	ankylosing spondylitis
BNF	British National Formulary
CCT	controlled clinical trial
CEAC	cost-effectiveness acceptability curve
CEAF	cost-effectiveness acceptability frontier
CI	confidence interval
COX	cyclooxygenase
Cox-1	cyclooxygenase-1
Cox-2	cyclooxygenase-2
CRD	Centre for Reviews and Dissemination
CVD	cardiovascular disease
DDD	defined daily dose
DMARD	disease-modifying anti-rheumatic drug
ECR	extra-contractual referrals
EPU	endoscopically proven ulcer
GAD	Government Actuary's Department
GI	gastrointestinal
GPA	gastroprotective agent
GPRD	General Practice Research Database
H_2RA	histamine-2 receptor antagonist
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
ITT	intention-to-treat
LYG	life-year gained
MA	meta-analysis
MI	myocardial infarction
MIMS	Monthly Index of Medical Specialties
MUCOSA	Misoprostol Ulcer Complications Outcome Safety Assessment
NHP	Nottingham Health Profile
NICE	National Institute for Health and Clinical Excellence
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
PGWB	Psychological General Well-Being Index
PPI	proton pump inhibitor
PUB	perforation, ulcer and bleed
PUD	previous ulcer disease
QALY	quality-adjusted life-year

continued

List of abbreviations *continued*

QoL	quality of life
RA	rheumatoid arthritis
RCT	randomised controlled trial
RR	relative risk
SA	sensitivity analysis
TIA	transient ischaemic attack
UGI	upper gastrointestinal
VIGOR	Vioxx Gastrointestinal Outcome Research
VAS	visual analogue scale
WHO	World Health Organization
WMD	weighted mean difference
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for the treatment of pain (in particular musculoskeletal pain) and stiffness. All NSAID treatment carries some risk of gastrointestinal (GI) toxicity, ranging in severity from mild dyspepsia to GI haemorrhage and perforation. These last complications may lead to hospitalisation, surgery or death. A number of strategies exist to reduce the incidence and impact of NSAID-induced GI toxicity. These include the co-prescription of a histamine-2 receptor antagonist (H_2RA), proton pump inhibitor (PPI) or misoprostol; or the prescription of a Cox-2 preferential or specific NSAID rather than a conventional NSAID. It is unclear which of these strategies is more effective or cost-effective.

Objectives

The aim of this study was to assess the relative effectiveness, patient acceptability, costs and cost-effectiveness of four strategies for the prevention of NSAID induced GI toxicity:

1. Cox-1 NSAIDs plus H_2RAs
2. Cox-1 NSAIDs plus PPIs
3. Cox-1 NSAIDs plus misoprostol
4. Cox-2 NSAIDs (later expanded to 4a Cox-2 coxib NSAIDs and 4b Cox-2 preferential NSAIDs).

The primary outcomes were mortality, health-related quality of life, serious GI complications, symptomatic ulcers, serious cardiovascular or renal illness and side-effects. Serious GI complications were defined as a GI perforation, bleed (including melaena) or obstruction. A symptomatic ulcer was defined as an endoscopic ulcer which is discovered when a patient complains of dyspepsia or has experienced a GI bleed. Secondary outcomes included endoscopic ulcers. An endoscopic ulcer was defined as an ulcer at least 3 mm in diameter and/or that could be distinguished from erosions based on the author's description, for example lesions with unequivocal depth.

Methods

Data sources

The Cochrane Library, MEDLINE, EMBASE, Current Controlled Trials and SIGLE were searched to May 2002. Bibliographies and author contacts were used to identify further studies. Non-English language studies were included.

Study selection

Articles were selected if they were randomised controlled trials (RCTs), assessed a gastroprotective strategy vs placebo, studied adult patients (i.e. not healthy volunteers), had an NSAID exposure of at least 21 days and included at least one of the review outcome measures.

Data extraction

Trial selection, data extraction and quality assessment were performed independently in duplicate. Data on participants, interventions, outcomes and potential effect modifiers were extracted, using a data extraction form designed for this review, and tabulated.

Data synthesis

Where appropriate, the differences in the outcomes were combined across studies using relative risks or weighted mean differences in random effects meta-analysis on RevMan 4.2 software. Heterogeneity was examined visually and using Cochran's test (considered significant at $p < 0.1$). Meta-analysis was also carried out on StatsDirect software for the active gastroprotective agent versus placebo analyses in order to produce weighted relative risk ratios for the economic analysis. Adjusted indirect comparisons were also calculated using the relevant active treatment versus placebo analyses results.

Random effects meta-regression was performed in order to analyse the associations between treatment effect and the following study characteristics: length of follow-up, mean age of participants, and baseline GI status. Funnel plots and related inferential methods were used to assess for evidence of small study effects, including publication bias. As data for direct comparisons between active treatments were often sparse,

adjusted indirect comparisons were also calculated, using the relevant active treatment versus placebo analyses results.

Economic evaluation

Pooled relative risk ratios from the systematic review were combined with up-to-date UK resource use and unit costs data in an incremental economic analysis. As outcome data for the direct comparisons between active treatments were often sparse, adjusted indirect comparisons were calculated using the relevant results from active treatment versus placebo analyses. The five strategies were evaluated from a UK NHS perspective, incorporating drug costs, GP visits and management of adverse events. Published estimates of resource use were used because no detailed resource data were reported in the clinical trials in the meta-analysis. A probabilistic decision-analytic model was designed and populated with data to carry out incremental economic analysis. Incremental cost-effectiveness ratios (ICERs) were generated for the outcome measure, endoscopic ulcer or serious GI event averted, against total cost, and non-parametric bootstrapping was used to simulate variance of these ICERs.

Results

Effectiveness

The electronic and bibliographic searches, plus replies from trial authors, identified 6417 potentially relevant titles and abstracts. From these, 505 full-text papers were collected for further examination. These included relevant systematic reviews, economic papers, cohorts and controlled trials. Once publications had been screened, 118 trials remained, including 125 relevant comparisons. These trials (which included 76,322 participants) reported only 138 deaths and 248 serious GI events. Seven comparisons were judged to be at low risk of bias.

Comparing the gastroprotective strategies against placebo, there was no evidence of effectiveness of H_2RAs against any primary outcomes (few events reported), PPIs may reduce the risk of symptomatic ulcers [relative risk (RR) 0.09, 95% confidence interval (CI) 0.02 to 0.47], misoprostol reduces the risk of serious GI complications (RR 0.57, 95% CI 0.36 to 0.91) and symptomatic ulcers (RR 0.36, 95% CI 0.20 to 0.67), Cox-2 'preferentials' reduce the risk of symptomatic ulcers (RR 0.41, 95% CI 0.26 to 0.65) and Cox-2 'coxibs' reduce the risk of symptomatic ulcers (RR 0.49, 95% CI 0.38 to 0.62) and possibly serious GI events (RR 0.55, 95% CI 0.38 to 0.80). All strategies except Cox-2 'preferentials' reduce the risk of endoscopic ulcers.

There were only 12 direct comparisons between gastroprotective strategies. All they suggest is that Cox-2 preferentials are better than misoprostol for preventing GI complications. Indirect comparisons suggested that PPIs may prevent symptomatic ulcers better than Cox-2 coxibs, but this is very weak evidence. For prevention of endoscopic ulcers PPIs and misoprostol appear more successful than H_2RAs and misoprostol is better than Cox-2 preferentials.

Economic modelling

There were no UK head-to-head published economic analyses with regard to the main gastroprotective strategies. There were generally insufficient data with regards to cardiac or renal outcomes, serious GI outcomes or life-years gained to populate the mode. Mean (2.5th and 97.5th percentile) costs per endoscopic ulcer averted compared with Cox-1 NSAIDs alone were as follows: Cox-1 plus H_2RAs, –£186 (–555 to 804); Cox-1 plus PPIs, £454 (251 to 877); Cox-1 plus misoprostol, £54 (–112 to 238); Cox-2 selective NSAIDs, £263 (–570 to 1280), or Cox-2 specific NSAIDs, £301 (189 to 418). With regard to the prevention of endoscopic ulcers, Cox-1 NSAID plus H_2RA is a dominant option. Cost-effectiveness acceptability analysis showed a 95% probability that this combination was less costly and more effective. Cost-effectiveness acceptability frontiers showed that if the decision-maker is willing to pay up to £750 to avoid an endoscopic ulcer, then Cox-1 plus H_2RA is the optimal strategy. If the decision-maker is willing to pay over £750, the optimal strategy is NSAID plus misoprostol. Between £1900 and £3750, Cox-2 selective inhibitors are optimal, and over £3750, Cox-2 specific inhibitors become optimal. NSAID plus PPI is never the optimal strategy. Sensitivity and subgroup analyses suggest that Cox-1 NSAID plus H_2RA and Cox-1 NSAID plus misoprostol become more cost-effective in the older age group. Some conclusions were associated with high levels of uncertainty.

Conclusions

Although there is a very large body of evidence comparing Cox-2 NSAIDs with Cox-1 NSAIDs, this is not matched by studies of the other types of

gastroprotectors or by studies directly comparing active gastroprotective strategies. This lack of direct comparisons led to the use of indirect comparisons to help understand the relative efficacy of these strategies. Indirect evidence in itself is weak and was also hampered by lack of evidence in the underlying studies (where the gastroprotectors were compared with placebo).

Economic modelling suggests that Cox-1 NSAID plus H_2RA or Cox-1 NSAID plus PPI are the most cost-effective strategies for avoiding endoscopic ulcers in patients requiring long-term NSAID therapy.

Implications for healthcare

All strategies other than Cox-2 selective inhibitors reduce the rate of endoscopic ulcer compared with Cox-1 alone. The economic analysis suggests that there may be a case for prescribing H_2RAs in all patients requiring NSAIDs. Misoprostol is more effective, but is associated with a greater cost and GI side-effects which may be unacceptable for patients. However, when assessing serious GI events, the economic analysis is sufficiently weakened by the data available as to render clear practice recommendations impossible.

Recommendations for research

1. Major outcomes, and also important patient-centred outcomes such as quality of life, should be reported in trials even where individual trials may not be powered to evaluate them, collected centrally and be available for use in research synthesis.
2. There is a need for further large, independent RCTs directly comparing various gastroprotective strategies, in particular PPI plus Cox-1 NSAIDs with Cox-2 NSAIDs alone in patients at high risk of NSAID-induced GI toxicity.
3. Economic analyses should be based on primary data when they are available, rather than adding to the large number of modelling studies,
4. Increased follow-up of patients who experience adverse events with prescription medicines including Cox-2 inhibitors should be implemented to allow a clearer understanding of, and provide better quality data on, incidence rates and practice patterns after mild and major side-effects.
5. There should be an assessment of practice, such as the extent of use of H_2RAs and PPIs with specific Cox-2 inhibitors, willingness to use misoprostol, patient risk factors affecting individual prescribers' use of selective and specific Cox-2 inhibitors and recent events around rofecoxib affecting attitudes to specific Cox-2 inhibitors.
6. There is a need for exploration of patients' preferences around the optimal strategy, understanding of risks and benefits of NSAIDs and Cox-2 inhibitors, wish for involvement in decision-making and reaction to recent events around rofecoxib.

The recommendations from this study can only be tentative owing to the variable quality of research available. Clinical data need to be improved through greater use of head-to-head comparisons and major outcomes and patient-centred outcomes should be more rigorously reported.

Chapter 1
Background

Introduction

In 1999, over 18.5 million courses of non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed in England and Wales.[1] The majority were prescribed for musculoskeletal conditions such as rheumatoid arthritis (RA), osteoarthritis (OA), back pain or soft tissue rheumatism. The estimated cost of these prescriptions was £170 million.[1] This figure excludes the associated costs of prescribing gastroprotective agents (GPAs).

The crucial mode of action of NSAIDs [i.e. the inhibition of the catalysing enzyme cyclooxygenase (COX)] also results in gastrointestinal (GI) side-effects, ranging in severity from mild dyspepsia to GI haemorrhage and perforation. The last two complications can result in hospitalisation, surgery and death. It has been estimated that there are approximately 10,000 hospitalisations and 2000 deaths each year in the UK due to NSAID related side-effects during treatment of musculoskeletal disease.[2]

There are two distinct isoforms of COX: cyclooxgenase-1 (Cox-1) and cyclooxygenase-2 (Cox-2). Cox-1 is the constitutive isoform and performs 'housekeeping' functions including gastroprotection and platelet aggregation. Cox-2 is an inducible form that is involved in the inflammatory response.[3] Although not all the effects of NSAIDs can be attributed to their inhibition of COX, it is now generally accepted that inhibition of Cox-2 contributes to the efficacy of an NSAID whereas inhibition of Cox-1 contributes to its GI toxicity.

Some of the older NSAIDs are thought to have strong Cox-2 characteristics. We have called these Cox-2 preferentials. They include meloxicam, etodolac, nabumetone and nimesulide. Other older NSAIDs we have called Cox-1s. The newer NSAIDs that have been produced and marketed on the basis of their Cox-2 action we have called Cox-2 specifics and 'coxibs'. They include celecoxib and rofecoxib.

All NSAID treatment carries some risk of GI toxicity. Until the introduction of selective and specific Cox-2 inhibitors, the standard means of protecting against NSAID-induced GI toxicity was the co-prescription of a gastroprotective agent (GPA) such as a histamine-2 receptor antagonist (H_2RA), proton pump inhibitor (PPI) or misoprostol (a prostaglandin analogue). H_2RAs reduce gastric acid secretion, prostaglandin analogues have antisecretory properties and PPIs inhibit gastric acid production by blocking the hydrogen–potassium adenosine triphosphate enzyme system (the 'proton pump') of the gastric parietal cell.

Not all patients prescribed NSAIDs are at equal risk of NSAID-induced gastrotoxicity. The major risk factors associated with GI complications are age (risk increases with age), a history of peptic ulceration or GI bleeding, a history of H_2RA use, concomitant use of anticoagulants or corticosteroids, requirement for high dosage of an NSAID and concurrent use of more than one NSAID.[4–6]

Evidence reviewed for the recently published National Institute for Health and Clinical Excellence (NICE) guidelines[1] suggests that Cox-2 and Cox-1 NSAIDs are of equivalent efficacy in their ability to reduce pain and improve physical functioning in patients with arthritis. This evidence also suggests that, although GI adverse events occur more frequently among patients receiving Cox-2 medication than those receiving a placebo, the incidence of these events is markedly lower than among those receiving a conventional NSAID (Cox-1) without gastroprotection.

Cox-2 drugs are more expensive than conventional NSAIDs. The NICE guidelines recommend that Cox-2 medication should not be used routinely for patients with RA or OA, as they are not a 'cost-effective' alternative for patients not considered to be at 'high risk' of developing serious GI side-effects. In addition, selective inhibition of Cox-2 has no effect on platelet function, which may be a disadvantage for patients at risk of cardiovascular atherosclerotic events.[7,8]

There is evidence that all of the four principal protective strategies, (1) Cox-1 NSAID plus H_2RAs, (2) Cox-1 NSAID plus PPIs, (3) Cox-1 NSAID plus misoprostol and (4) Cox-2 NSAID

only, are effective in reducing the incidence of adverse GI effects. However, there are few large randomised controlled trials (RCTs) that directly compare the clinical effectiveness of these four strategies.

Economic evidence

In 2000, Rahme and colleagues estimated that, for every Canadian dollar spent on NSAIDs, $0.66 was spent on their side-effects.[9] In the UK, the annual cost associated with managing toxicity associated with the use of NSAIDs in RA has been estimated to be £58 million[10]. Hence the use of newer, more costly strategies for gastric protection from NSAIDs may be justified if they are associated with savings due to differences in minor or major adverse event rates and their sequelae.

To date, there have been no primary or secondary economic evaluations that examined these protective strategies directly. This means that information on cost-effectiveness is unavailable, either for the effect of these strategies among all patients receiving NSAID treatment or among subgroups of patients stratified by risk status. Furthermore, there is currently no published evidence to suggest which protection strategy has the highest impact on NHS resource use. There are many published costing studies and economic evaluations that compare one protective strategy against the use of an NSAID alone. For example, there are at least 10 published studies assessing the cost-effectiveness of misoprostol. One of these reported that it would cost an additional Can$94,766 to avert one serious adverse event.[11] For patients with previous peptic ulcer disease the cost would be Can$14,943 and for patients aged over 75 years old with previous peptic ulcer disease the cost would be Can$4101. Kristiansen and colleagues reported that the cost per quality-adjusted life-year (QALY) of misoprostol was US$72,700 in the absence of risk factors, less than US$16,000 with one risk factor and became cost saving with two or three risk factors.[12] These, and many similar studies, suggest that gastric protection strategies, when appropriately targeted, can have an impact on healthcare provider spending.

Most studies in this area use secondary rather than primary methods, synthesising clinical RCT data with cost data obtained from other sources. In order to assess differences in resource use between different gastric protection strategies, it is necessary to obtain both acquisition costs and accurate resource use information for the treatment of minor and major adverse events. Supporting this, McCabe and colleagues, comparing the cost-effectiveness of newer versus older NSAIDs, concluded that the variation in management of minor and major adverse events affected overall costs as much as the choice of NSAID.[13] A multinational study in 2001 on the resource use associated with NSAID-induced gastric toxicity suggests that there are wide variations in practice patterns between countries, with the UK having one of the lowest levels of resource use.[14] The total cost of care was driven by the rates of endoscopy and other diagnostic tests, and hospitalisation expenses, rather than drug costs. The NSAID-related cost of ulcers and treatment of other NSAID-related iatrogenic events in the UK has been estimated in a number of observational studies [2,15–17]

This report examines the quality of cost data currently available for use in economic evaluations, the quality of the economic evaluations themselves and their generalisability to normal practice in the UK.

Chapter 2

Hypotheses tested in the review

The aim of this study was to assess the relative effectiveness, patient acceptability, costs and cost-effectiveness of four strategies for the prevention of NSAID-induced toxicity. The four strategies under investigation in the initial protocol were:

1. Cox-1 NSAIDs plus H_2RAs
2. Cox-1 NSAIDs plus PPIs
3. Cox-1 NSAIDs plus misoprostol
4. Cox-2 NSAIDs.

However, when the results of the initial review were analysed, it became clear that it would be more appropriate to split the Cox-2 NSAIDs into two categories, Cox-2 coxibs and Cox-2 preferentials. Hence the five strategies under investigation became:

1. Cox-1 NSAIDs plus H_2RAs
2. Cox-1 NSAIDs plus PPIs
3. Cox-1 NSAIDs plus misoprostol

4a. Cox-2 coxib NSAIDs

4b. Cox-2 preferential NSAIDs.

This systematic review has built on an earlier published review of effectiveness[18] while expanding the perspective to include use of Cox-2 inhibitors, broader aspects of patient benefits [in the form of health-related quality of life (QoL) and patients' preferences], cost and cost-effectiveness. The review also expanded on areas covered by earlier published reviews by assessing the clinical and economic impact of recent therapeutic developments in this area.

This study had six principal objectives:

1. To assess the effectiveness of the five preventive strategies on mortality, health-related QoL, serious GI complications, symptomatic ulcers, serious cardiovascular or renal illness and side-effects.
2. To indicate the rate of change in the evidence base since the original review was carried out.[18]
3. To review the evidence on patients' preferences, relative cost and cost-effectiveness of the five preventive strategies in the prevention of NSAID-induced GI morbidity.
4. To synthesise the evidence using decision-analytic models to determine relative cost-effectiveness and to quantify levels of uncertainty around that cost effectiveness.
5. To focus the results on subgroups of patients that are known to be at increased risk of NSAID-induced GI side-effects.
6. To assess whether further primary research is necessary to fulfil these objectives adequately.

The following definitions were used: serious GI complication, a GI perforation, bleed (including melaena) or obstruction; and symptomatic ulcer, an endoscopic ulcer which is discovered when a patient complains of dyspepsia or has experienced a GI bleed.

Principal research questions of the systematic review

The principal research question addressed by the review of effectiveness was: are there differences in the effectiveness of the five preventive strategies on mortality, health-related QoL, serious GI complications, symptomatic ulcers, serious cardiovascular or renal illness and side-effects?

Secondary questions addressed included the following. Does the effectiveness of the five strategies vary according to:

1. whether participants have a history of peptic ulceration or GI bleeding?
2. whether participants have a history of H_2RA use?
3. whether participants concurrently use anticoagulants or corticosteroids?
4. whether participants are using more than one NSAID?
5. initial age of the participants?
6. the number of initial risk factors (elderly, history of peptic ulceration or GI bleeding, history of H_2RA use, concurrent use of anticoagulants or corticosteroids, use of more than one NSAID)?
7. length of exposure?
8. initial dose of NSAID used?
9. whether usual or slow-release NSAIDs are used?

We made the following assumptions:

1. All NSAIDs (excluding aspirin) have greater efficacy than simple analgesics (such as paracetamol and codeine) in reducing pain and improving physical function.
2. All NSAIDs (excluding aspirin and simple analgesics) are of equal efficacy based on equivalent dose. Lister and colleagues compared several NSAIDs and found that all had equivalent efficacy at population level, although one drug may work better than another in a particular individual.[20]

Principal research questions of the economic modelling

The principal research questions addressed by the economic modelling were:

1. Do any differences in the clinical effectiveness of the five strategies translate into economically important differences in patient preferences and valuations of that impact on their health, QoL and acceptability?
2. Do any differences in the clinical effectiveness of the five strategies translate into economically important differences in resource utilisation and costs associated with their use?
3. Do any differences in patient valuations or costs result in one or more of the five strategies dominating the other alternatives in terms of
   (a) net savings and equivalent or improved patient outcome
   (b) improved patient outcome and equivalent cost or net savings
   (c) improved patient outcome and higher cost, with a lower incremental cost-effectiveness ratio (ICER) than other alternatives?

The perspective of the study included:

- the NHS in terms of the direct costs of providing GI protection for NSAID use and related follow-up care
- the patient in terms of the outcomes and direct costs of managing GI protection for NSAID use and related follow-up care.

The economic modelling made use of the results of the systematic review of effectiveness and also other systematically collected studies including UK health economic data.

Chapter 3

Methodology, systematic review of effectiveness

Data sources and search strategy

The Cochrane Library [including the Cochrane Controlled Trials Register (CENTRAL), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, NHS Economic Evaluation Database and Health Technology Assessment Database] was searched (on CD-ROM, Issue 2, 2002), as were MEDLINE (on Ovid, searched 1966 to May 2002) and EMBASE (on Ovid, searched 1980 to May 2002). Current Controlled Trials and SIGLE were also searched using versions of a structured electronic search strategy developed for this review (see Appendix 1 for the full electronic search strategies). LILACS was not available to be searched (the website was not working over several months). Extensive handsearching of journals and conference proceedings was carried out to compile CENTRAL, so no additional handsearching was carried out for this review. The searching and inclusion/exclusion processes were carried out independently of Rostom and colleagues' review,[21] but each was used to check the results of the other.

The results of electronic searches were downloaded, de-duplicated against previously downloaded references and stored on Reference Manager software. Assessment of the final list of titles and abstracts was through Reference Manager software, and each study was coded with reasons for rejection, or copied to a file for collection of the full paper.

Bibliographies of included studies and of identified systematic reviews were checked for potentially relevant studies. These were checked against the list of studies already assessed for inclusion and new potentially relevant studies were collected. This process identified that several potentially important studies on etodolac had been missed in the original search strategy. The search was, therefore, edited and re-run, ensuring that it collected these studies. The main electronic searches were run in May 2002, so only studies published before June 2002 were included. We excluded studies published after this as, without a comprehensive search later than May 2002, the studies that we might come across fortuitously were likely to be those most publicised, and therefore would potentially introduce selection bias. The exception was a paper by Chan and colleagues,[22] where an earlier abstract had been included, but the data from the full publication were more comprehensive, so were used instead.

Contact authors of all included studies were sent a list of studies included so far and asked to provide information about any published, unpublished or ongoing studies not identified (see Appendix 1e for a copy of the letter).

Attempts were made to obtain full-text translations and/or evaluations of all potentially relevant non-English language articles.

To locate the controlled clinical trials (CCTs) and cohort studies that were sought to inform about mortality, separate searches were run on MEDLINE and EMBASE (see Appendix 1d for the EMBASE electronic search strategy; the MEDLINE strategy employed a very similar methodological filter). Authors of two large cohort studies which appeared to be powered to assess mortality were contacted and asked if they, or any other researchers of whom they were aware, had assessed mortality in a way that was relevant to this review.

Study selection

Assessment of clinical effectiveness: all outcomes

Types of study

For studies of clinical effectiveness only individually randomised CCTs were included. Quasi-randomised, cluster-randomised and crossover studies, and any study without a concurrent control, were excluded.

Healing studies (where participants started out with endoscopic and/or symptomatic ulcers) were not included for assessment of GI-type outcomes, but were considered for inclusion for deaths, cardiovascular disease and renal outcomes.

Types of participant

Studies of adults (18 years or older) were included.

Types of intervention

Included interventions were as follows:

- Cox-1 NSAIDs plus H_2RAs compared with Cox-1 NSAIDs (alone or with placebo gastroprotection)
- Cox-1 NSAIDs plus PPIs compared with Cox-1 NSAIDs (alone or with placebo gastroprotection)
- Cox-1 NSAIDs plus misoprostol compared with Cox-1 NSAIDs (alone or with placebo gastroprotection)
- Cox-2 coxib inhibitors compared with Cox-1 NSAIDs alone
- Cox-2 preferential NSAIDs compared with Cox-1 NSAIDs alone
- Any of the active interventions above compared with any other active intervention.

The intervention period was at least 3 weeks (21 days).

Generic and trade names of the various NSAIDs and GPAs included in the review are given in Appendices 2a and 2b. The acceptable dose ranges of NSAIDs and the GPAs are given in Appendix 2c (these are based on recommendations in the BNF (2003).[23] Studies or study arms with lower doses in at least 20% of participants were excluded. Higher doses were allowed.

Aspirin was not included as an NSAID. However, the use of aspirin as an NSAID in up to 20% of participants in an otherwise included study or arm was accepted.

Outcomes

Primary clinical outcomes

- Serious GI complications [including haemorrhage, recurrent upper gastrointestinal (UGI) bleeds, perforation, pyloric obstruction or melaena, including death from any of these].
- Symptomatic ulcers (an endoscopic ulcer which is discovered when a patient complains of dyspepsia or has experienced a GI bleed).
- Serious cardiovascular or renal illness leading to contact with primary or secondary healthcare [including angina, myocardial infarction (MI), stroke, transient ischaemic attack (TIA) or renal failure, including death from any of these].
- Health-related QoL measures (generic measures, excluding disease-specific measures of arthritis pain or disability).
- Mortality.

Secondary clinical outcomes:

- GI symptoms (nausea, vomiting, dyspepsia, abdominal pain or diarrhoea).
- Endoscopically proven ulcers (EPUs, at least 3 mm in diameter and/or could be distinguished from erosions based on the author's description, for example lesions with unequivocal depth).
- Anaemia.
- Occult bleeding.
- Drop-outs (both overall and due to GI symptoms).

This was not a survival analysis. Secondary outcome measures were assessed to the latest point available in each included study. Outcomes were assessed as numbers of people having events, and within each outcome attempts were made to prevent participants being counted twice (for example, a person with gastric and duodenal endoscopic ulcers was counted only once for the outcome of endoscopic ulcers), but each participant might appear with several different outcomes (for example, a person who died from a perforated ulcer would be counted as one person with a serious GI complication, one person with a symptomatic ulcer and one death).

Assessment of clinical effectiveness: mortality

RCTs were unlikely to be powered to assess differences in mortality. For this reason, the systematic review aimed to include other (lower) levels of evidence relating to mortality.

Types of study

Quasi-randomised trials, non-randomised parallel clinical trials (with concurrent controls) (CCTs), and cohort studies (with at least 500 participants) were sought and included where mortality data were collected.

Types of participant

Studies of adults (18 years or older) who had taken NSAIDs for at least 3 weeks were included.

Types of interventions

Included comparisons were as follows (as in RCTs, above):

- Cox-1 NSAIDs plus H_2RAs compared with Cox-1 NSAIDs (alone or with placebo gastroprotection)
- Cox-1 NSAIDs plus PPIs compared with Cox-1 NSAIDs (alone or with placebo gastroprotection)
- Cox-1 NSAIDs plus misoprostol compared with Cox-1 NSAIDs (alone or with placebo gastroprotection)
- Cox-2 coxib NSAIDs compared with Cox-1 NSAIDs alone

TABLE 1 *Summary of study types eligible for inclusion in this review by outcome measure*

Outcome	Study type allowed
Serious GI complications	RCTs (no ulcers at baseline)
Symptomatic ulcers	RCTs (no ulcers at baseline)
Serious cardiovascular or renal illness	RCTs (no ulcers at baseline)
	RCTs (with ulcers at baseline)
Health-related QoL	RCTs (no ulcers at baseline)
	RCTs (with ulcers at baseline)
Mortality	RCTs (no ulcers at baseline)
	RCTs (with ulcers at baseline)
	CCTs or cohort studies
GI symptoms	RCTs (no ulcers at baseline)
Endoscopic ulcers	RCTs (no ulcers at baseline)
Anaemia	RCTs (no ulcers at baseline)
Occult bleeding	RCTs (no ulcers at baseline)
Drop-outs, total	RCTs (no ulcers at baseline)
Drop-outs, due to GI symptoms	RCTs (no ulcers at baseline)

- Cox-2 preferential NSAIDs compared with Cox-1 NSAIDs alone
- Any of the active interventions above compared with any other active intervention.

Outcomes

Mortality, assessed at a maximum of three points during each study:

- early (the latest point available from 3 to 8 weeks, 21 to 60 days, of follow-up)
- medium term (the latest point from 9 to 51 weeks of follow-up)
- late (the latest available point over 52 weeks of follow-up).

Study types eligible for inclusion by outcome measure are summarised in *Table 1*.

Methods for assessment of inclusion

An 'inclusion/exclusion' form (developed specifically for the review) was used to assess inclusion (see Appendix 3). Only studies that satisfied the criteria of Appendix 3a or 3b were included in the systematic review of effectiveness. Studies that satisfied criteria according to Appendix 3c were collected for potential use in the economic modelling only.

Titles and abstracts identified by the search strategy were assessed independently by two reviewers (against the inclusion/exclusion form criteria). Articles were rejected on initial screen only if the reviewer could determine from the title, abstract and controlled text that the article was not a report of an RCT or suitable alternative study design, or the trial did not address the use of any of the five treatment strategies, or the aforesaid interventions were not compared with other active treatments, older NSAIDs alone or placebo, or the trial was exclusively in children less than 18 years old or in healthy volunteers, or the period of NSAID intake was of less than 3 weeks (21 days) duration, or none of our stated outcomes was measured (this last was not assumed from the title and abstract, but only on assessment of the full text of the paper). When a title/abstract could not be rejected with certainty, by either of the reviewers, the full text of the article was obtained for further evaluation.

Full text articles were formally assessed for inclusion, again using the inclusion/exclusion form. Inclusion of studies was assessed independently by two reviewers and differences between reviewers' results were resolved by discussion and, when necessary, in consultation with a third reviewer. Reviewers were not masked to the source and authors of the studies.[24] A flow chart of the selection process was produced.[25]

Quality assessment

Included studies were first graded into those that were RCTs and those that were not. Quality assessment of RCTs included information on randomisation procedure, allocation concealment, blinding of participants, providers of care and outcome assessors and losses to follow-up.[26,27] Agreement was formally assessed for allocation concealment using Cohen's kappa.[28] The quality assessment sheet is shown in Appendix 4a.

Quality assessment of studies other than RCTs included assessment of internal validity based on criteria suggested by the Centre for Reviews and Dissemination (CRD)[24] and an appropriate assessment tool was developed for a range of study types[29] (see Appendix 4b).

Two reviewers independently assessed the quality of included studies (not masked to the study authors). Differences between reviewers' results were resolved by discussion and, when necessary, through consultation with a third reviewer.

A summary risk of bias was obtained after agreed duplicate assessment of allocation concealment and baseline comparability. These were felt to be the two most important indicators of potential bias. If either or both criteria were classed as 'inadequate', the summary risk of bias was marked as 'high'. If either or both criteria were classified as 'unclear', the summary risk of bias was assessed as 'moderate'. If both criteria were 'adequate', the summary risk of bias was recorded as 'low'.

Data extraction

A data extraction form was designed for this review, piloted on several papers and then formalised following discussion by the whole team (Appendix 4). The following types of data were extracted and tabulated:

- participants, interventions and outcomes (as described in the inclusion criteria section, p. 5)
- potential effect modifiers (such as previous GI problems, previous history of H_2RA use, concomitant use of anticoagulants and/or corticosteroids, use of more than one NSAID, follow-up time, mean age of participants, number of initial risk factors for GI toxicity, usual or slow release NSAID formulation and initial NSAID dose)
- information or advice given to participants regarding potential side-effects and how to deal with them, and how this information was provided.

Mortality data were extracted from cohort studies as unadjusted data and maximally adjusted data, and noted factors adjusted for.

Two reviewers independently extracted original reports of trial results. Differences between reviewers' extraction results were resolved by detailed discussion, re-reading of original publications and, when necessary, in consultation with a third reviewer, the review team or external advisors to the review (see Acknowledgements).

Agreement between the two independent reviewers was assessed for the following criteria:

- number of participants assessed at the end of the study for total GI symptoms for each study arm
- total number of drop-outs at study end for each arm
- total numbers of participants with GI symptoms in each arm
- allocation concealment.

Allocation concealment was measured categorically (possible choices for each reviewer were 'A, adequate', 'B, unclear', or 'C, inadequate'). Agreement was formally assessed for allocation concealment using Cohen's kappa.[28] The other criteria were measured as continuous variables, so kappa scores were not appropriate. These criteria were simply assessed as proportion of papers for which agreement occurred before any discussion took place.

Data synthesis

Meta-analysis

Data on the included studies were tabulated. Where appropriate, differences in outcomes for each comparison were combined across studies using relative risks (RRs) or weighted mean differences (WMDs) in random effects meta-analysis (MA)[30] on RevMan 4.2 software. Heterogeneity was examined visually and using Cochran's test (considered significant at $p < 0.1$).

MA was also carried out on StatsDirect software for the active GPA versus placebo analyses in order to produce weighted absolute risk reductions (ARRs) for the economic analysis. The original plan was to calculate the ARRs from the weighted RRs produced in the MA in RevMan software. However, there were problems in dealing with analyses where no event occurred in one arm. In this situation, RevMan software adds 0.5 events to each arm. This was realistic for computing RRs, but created distorted ARRs and it was difficult to compute the 95% confidence intervals (CIs).

Indirect comparisons

As data for direct comparisons between active treatments were often sparse, adjusted indirect comparisons were also calculated using the relevant active treatment versus placebo analyses

results, by the method described in another HTA report (project 96/51/99, as yet unpublished by the HTA; some data have been published by Song and colleagues[31] based on a method by Bucher and colleagues[32]). Where direct comparisons relied on the results of studies that randomised participants to intervention A or intervention B, for the indirect comparisons studies that randomised to intervention A or placebo were relied on, and other studies that randomised to intervention B or placebo. In this case the results of the MA of intervention A versus placebo and the MA of intervention B versus placebo were used. Where T_{HP} was the result of the MA of the direct comparison of H_2RA versus placebo and T_{MP} was the result of the MA of the direct comparison of misoprostol versus placebo, the estimate of the adjusted indirect comparison of H_2RA versus misoprostol (T'_{HM}) was calculated by

$$T'_{HM} = T_{HP} - T_{MP}$$

and its standard error was

$$SE(T'_{HM}) = \sqrt{(SE(T_{HP})^2 + SE(T_{MP})^2}$$

where $SE(T_{HP})$ and $SE(T_{MP})$ are the standard errors of T_{HP} and T_{MP}, respectively.

The results of these indirect comparisons are not strong evidence on their own. They are ideally used as evidence supplementary to direct comparisons. However, indirect comparisons do usually agree with the results of direct comparisons within single RCTs.[31]

Meta-regression and subgrouping

Random effects meta-regression was performed in order to analyse the associations between treatment effect and the following study characteristics: length of follow-up (length of the study in weeks); mean age of participants (in years); and baseline GI status (by percentage of participants with a history of GI ulcers). The outcome studied was symptomatic ulcers. Where insufficient studies provided data on symptomatic ulcers to make meta-regression meaningful, endoscopic ulcers were used as an outcome instead. Meta-regression used the 'metareg' command in STATA software,[33] treatment effect was the natural logarithm of the relative risk [ln(RR)] of symptomatic or endoscopic ulcers and weighting was based on the standard error of ln(RR).

The intention was to perform random effects meta-regression to assess the effect of the number of initial risk factors for GI toxicity on the development of symptomatic ulcers. However, this was not reported frequently enough to make this possible. It was also the intention to use meta-regression to explore the effect of initial NSAID dose on the development of symptomatic ulcers, but very few included studies started with low-dose NSAIDs and titrated the dose, making this analysis impossible.

Subgroup analysis was performed, where possible, to assess the effects of duration of treatment on the RR of all primary outcomes. The studies were categorised as 'short-term' (intervention period of 3–8 weeks), 'medium-term' (9–51 weeks) and 'long-term' (12 months or longer).

Further subgrouping was performed to explore the effects of initial risk of NSAID-induced GI toxicity and baseline age on symptomatic ulcers (or endoscopic ulcers where there were insufficient studies reporting symptomatic ulcers). Studies were categorised as follows, where possible, for baseline GI status:

1. Normal gut on endoscopy for all participants.
2. Some participants normal, others have some erosions and/or haemorrhages on endoscopy but no frank ulcers.
3. All participants have abnormal gut on baseline endoscopy (no ulcers or up to 50% recently healed ulcers).
4. All participants had recently healed ulcers on baseline endoscopy (at least 50% recently healed ulcers).

Age-based subgroups were mean age <65 years and mean age ≥65 years at baseline. Where data on subgroups within individual studies were provided for symptomatic or endoscopic ulcers, these were used. However, this was rare, so average baseline GI status and age for the whole study group were used to categorise studies into subgroups. This weakens the likelihood of any relationship being seen.

As meta-regression suggested no relationship between baseline GI status or age and RR of symptomatic (or endoscopic) ulcers, these subgroupings were not performed for RR of outcomes. However, subgroupings were performed using ARR outcomes (for the economic analyses) to assess the relationship between baseline GI status or age and ARR of serious GI complications, symptomatic ulcers and endoscopic ulcers.

There were insufficient data to perform subgrouping to explore the effect of H_2RA use,

concomitant medication or use of more than one NSAID. Very few studies reported any kind of participant education regarding dealing with potential side-effects and so subgrouping on different levels of education was impossible.

Treatment of Cox-2 preferentials in the review

Cox-2 preferentials are NSAIDs that are neither Cox-1 nor Cox-2 specific as they have intermediate characteristics. They include etodolac, meloxicam, nabumetone and nimesulide. In our original analysis plan, studies including these drugs were classified both as a Cox-1 and a Cox-2. For example, a study which compared diclofenac plus misoprostol versus nabumetone would be analysed in the comparison 'misoprostol plus Cox-1 versus placebo plus Cox-1' and also the comparison 'misoprostol plus Cox-1 versus Cox-2'. Where these drugs were compared with a Cox-1 alone they were classified as a Cox-2. For example, a study that compared nimesulide with diclofenac would be analysed in the comparison 'Cox-2 versus Cox-1'. Studies in which two Cox-2 preferential drugs were directly compared were excluded, as they did not fit into any of the predefined comparisons. Cox-2 preferentials were subject to removal in sensitivity analyses for all outcomes wherever they occurred (e.g. when 20% or more of the participants in any arm were prescribed a Cox-2 preferential).

However, during the final assessment of the original analysis, the relationship between the preferentials, Cox-1 NSAIDs and Cox-2 coxibs were checked. When the Cox 2 trials were stratified by their status as coxib or preferential Cox-2 versus Cox-1 NSAIDs (see Appendix 5), it was clear that the preferential Cox-2 effects were distinct from those of the Cox-1s. At the same time, the authors felt that there were clinical and economic reasons not to pool the preferentials with the coxibs. For this reason, the review analyses were re-run with the Cox-2 preferentials comprising a distinct arm.

Sensitivity analyses

Sensitivity analyses were used to assess the robustness of the results to the summary risk of bias (where studies with a 'high' risk of bias were removed), higher than recommended daily dose (where studies, or study arms, with a higher than recommended dose of any NSAID or GPA were removed) and naproxen. Naproxen has been reported as having cardioprotective effects (unlike the other Cox-1 drugs), so studies prescribing naproxen to 20% or more of the participants in any arm were excluded in sensitivity analyses of the outcomes 'serious cardiovascular or renal events' and 'deaths'.

Funnel plots and related inferential methods were used to assess for evidence of small study effects, including publication bias.[34] These were carried out on StatsDirect software, using Egger and colleagues[35] and Begg and Mazumdar's[36] tests. All of these methods have low power to detect small study effects (which may include bias) where there are few studies reporting relevant outcomes.

Chapter 4

General systematic review results

Study flow

The electronic and bibliographic searches, plus replies from trial authors, identified 6417 potentially relevant titles and abstracts (see *Figure 1* for the flow diagram). Almost 6000 of these were excluded on the basis of title, abstract and keywords. A total of 505 full-text papers were collected for further examination (these included relevant systematic reviews, economic papers, cohorts and controlled trials).

No healing studies, non-RCT studies or cohort studies were eventually included in the review

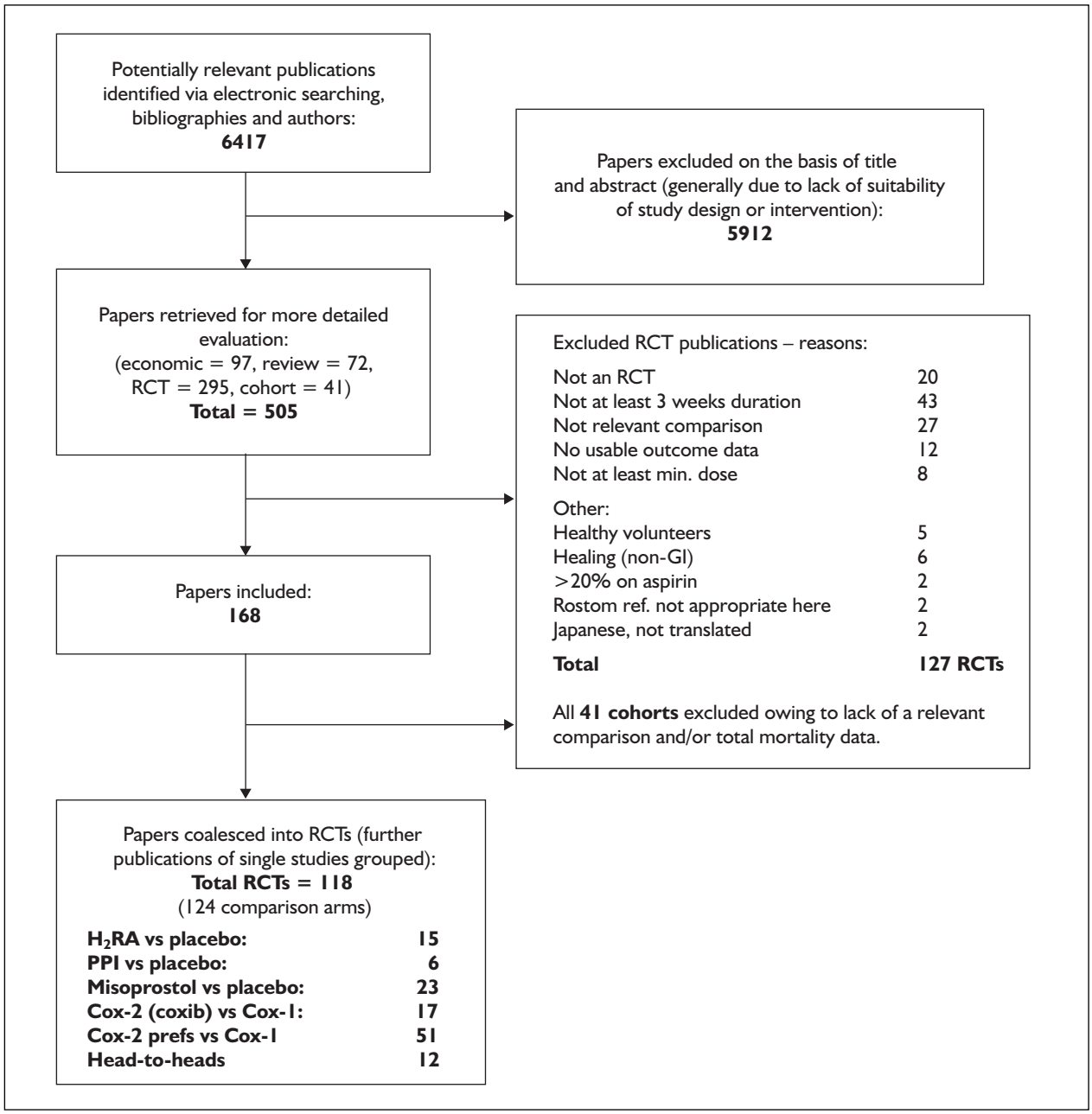

FIGURE 1 *Flow diagram of systematic review (QUOROM statement[25] flow diagram)*

(although several healing studies had follow-on 'maintenance' or 'prevention' phases, which were included). None of the cohort studies identified provided relevant comparisons or mortality data, and writing to authors of related studies confirmed that there appear to be no relevant published cohort data on mortality.

Excluded studies

Of the full publications collected, 295 were potential RCTs; 125 of these were excluded because they were of insufficient duration (less than 3 weeks, 43 studies), lacked a relevant comparison (27 studies), not randomised (20 studies), lacked useable outcome data (12 studies), used less than the minimum dose of NSAIDs and/or GPAs (eight studies), were healing studies without relevant non-GI outcomes (six studies), involved healthy volunteers (five studies), included more than 20% of participants on aspirin rather than NSAIDs (two studies) or were included in Rostom and colleagues' systematic review[21] but not considered relevant for our review (two studies). A further two papers in Japanese could not be translated for assessment (all other foreign language papers were translated to the point where it was clear that they did not fulfil the inclusion criteria or we could use their data).

Once publications had been collated into individual trials, we were left with 118 trials, including 125 relevant study arms.

Contact with trialists

Attempts were made to elicit further information from the contact authors of all included studies (including the etodolac studies that were collected later than the main studies). Where a viable email address was found, this was used to send a short message with an attached personalised letter/reply form. Where an email address could not be obtained, or where an email address 'bounced back' as unviable, a letter was sent by post (similarly, a covering letter with a personalised letter/reply form for each included study).

Replies were received for 23 of the 118 studies. Extra outcome data were provided for only eight of these studies.[37–44] Five offered data on outcomes not previously recorded for that study, five offered information that no events had occurred in some outcomes and four offered data differing from those already collected from the study publication(s). Replies about the same eight studies and one further study[45] provided extra information on study quality (method of randomisation, allocation concealment, etc.).

Two of the trialists who replied but did not provide extra study information suggested other useful studies for inclusion or provided information about whether data for one group of patients had been published in more than one context. Five said that they could not access the data, but that they would be available from the relevant pharmaceutical company. Other replies included notification of death of the main author, notes that pharmaceutical companies were considering providing data (no further contact occurred), authors saying they had no access to data as the studies were published many years ago, or a reprint of the study with no further details.

The extra information obtained for the nine studies (8% of the total) increased the number of outcomes with available information for that trial, clarified published numbers and improved study quality assessments.

Data extraction inter-rater agreement

Data were extracted first for the H_2RA versus placebo studies. The remaining comparisons were extracted in the order they appear in this report and in *Table 2*). Agreement scores were generally lowest in the first group of studies. Agreement levels were 76% on numbers of participants assessed at the end of the study for GI symptoms and numbers of participants with GI symptoms. Agreement levels were lower for the numbers of drop-outs (overall 58%), partly because details of numbers randomised, numbers assessed and numbers of drop-outs were often reported in a confusing way, and so were difficult to assess.

Kappa scores for inter-rater agreement on allocation concealment were also low but varied enormously from negative numbers (worse than those expected by chance) to 0.55 ('moderate agreement') for the direct comparisons. The kappa score for all the studies included in the review was 0.36 or 'fair agreement'. The scores appear low partly because the levels of expected agreement are high, so that observed agreement has to be very high to reach a good kappa score.

TABLE 2 *Levels of agreement on data extraction*

	Agreement on no. of participants assessed at end (%)	**Agreement on total no. of drop-outs (%)**	**Agreement on no. of participants with GI symptoms (%)**	**Kappa score for allocation concealment**
H_2RA vs placebo studies	54	46	62	–0.05 Observed agreement 0.769 Expected agreement 0.787
PPI vs placebo studies	60	20	80	Not assessable, total agreement
Misoprostol vs placebo studies	86	64	82	–0.05 Observed agreement 0.909 Expected agreement 0.913
Cox-2 vs Cox-1 studies	76	62	78	0.54 Observed agreement 0.948 Expected agreement 0.886
Direct comparisons	100	60	80	0.55 Observed agreement 0.800 Expected agreement 0.560
Total data from all comparisons	76	58	77	0.36 Observed agreement 0.956 Expected agreement 0.931

Chapter 5

H_2RA plus NSAID versus placebo plus NSAID: systematic review – included studies, results, analysis and robustness

Included studies

Table 3 summarises the included studies. For a complete table of characteristics of included studies, see Appendix 6a.

Characteristics of studies

Fifteen RCTs were included in this comparison, from 13 published papers (one as a book chapter) and one abstract. A total of 2621 participants were randomised to relevant study arms. Studies varied in size from eight participants per arm[50] to 285 per arm.[53] Nine studies were multicentre, two were single centre and three unclear. Studies were conducted in Europe (10 studies, of which four included sites in the UK), the USA (four studies) and Japan (one study). Publication dates were from 1987 to 1997. Additional data on outcomes were not added for any of these studies following contact with authors.

Participants

Eleven studies included adults with osteoarthritis (OA): 1365 participants with OA in eight studies (three groups[47,51,54] did not state how many had OA). Two studies included no participants with OA[52,56] and two included only participants with OA.[45,53]

Ten studies included adults with RA: 399 participants with RA in eight studies (two groups[47,51] did not state how many had RA). Three studies included no participants with RA[45,53,54] and one included only participants with RA.[56]

Five studies included adults with other types of arthritis, including 57 people in three studies (two studies did not give numbers). Eight studies did not include people with other types of arthritis. Two studies did not state what type of arthritis its participants had.[46,49]

The mean duration of arthritis in these studies varied from 0 years (where all participants were newly diagnosed[53]) to 22 years.[56] Duration of arthritis was not stated in nine trials.

Recruitment was from rheumatology clinics in four studies, both rheumatology and orthopaedic clinics in two studies, 'outpatients and inpatients' in one study, general practice in one study and was not stated in seven studies.

The mean age of participants ranged from 43[49] to 67[56] years old. Mean age was not stated in three studies.[46,47,53]

Participants' GI tract status varied at baseline. Three studies recruited participants with Lanza scores of zero (undamaged GI surfaces).[48,49,57] One study only recruited patients with normal gastric mucosa.[46] One study recruited people with no more than one or two erosions or haemorrhages.[52] Three studies only excluded participants with frank ulcers at baseline endoscopy.[45,54,55] In two studies all participants had erosions or haemorrhages, but no ulcers, at baseline.[51,57] One study included some people with normal GI tracts, some with erosions and some with ulcers.[50] In three studies all had had ulcers recently, but these had healed before randomisation.[47,56,58] In one study no baseline endoscopy was carried out, but some participants had GI symptoms.[53]

The baseline risk status of participants varied between studies. A positive history of ulcers was reported in a proportion of participants in three studies[45,48,55] and in all participants in three other studies[47,56,58] an absence of history of ulcers was reported in one study[57] and an absence of history of ulcers and bleeds in all participants was reported in two other studies.[51,53] A history of H_2RA use was reported in the study by Ehsanullah and colleagues.[48] Yanagawa[52] reported the proportion of participants with cardiovascular disease and/or renal/hepatic disease and Rugstad and colleagues[53] reported the number of participants taking cardiovascular drugs concurrently. Many studies did not report previous

TABLE 3 *Brief characteristics of included H_2RA versus placebo studies*

Study	*N*	Participants	Interventions
Bianchi Porro, 1987[46] (book chapter) **Summary risk of bias:** moderate	**Allocated:** a 127, b 119	**Baseline GI status:** baseline endoscopy performed and excluded participants without normal gastric mucosa **Type of arthritis:** rheumatic disease	Ranitidine plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 4 weeks
Roth, 1987[47] **Summary risk of bias:** moderate	**Allocated:** a 14, b 12	**Baseline GI status:** baseline endoscopy performed and excluded participants with ulcer (had to have improvement from grade II or III following 8 weeks of cimetidine or placebo) **Type of arthritis:** RA, related rheumatic disorders, OA	Cimetidine plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 10 months
Ehsanullah, 1988[48] **Summary risk of bias:** high	**Allocated:** a 146, b 151	**Baseline GI status:** baseline endoscopy performed and excluded participants without zero Lanza score **Type of arthritis:** OA: a 96, b 101. RA: a 28, b 34. Other: a 2, b 2	Ranitidine plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 8 weeks
Robinson, 1989[49] **Summary risk of bias:** moderate	**Allocated:** a 72, b 72	**Baseline GI status:** baseline endoscopy performed and excluded participants without zero endoscopy score **Type of arthritis:** primarily arthritis	Ranitidine plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 8 weeks
Swift 1989[50] **Summary risk of** bias: moderate	**Allocated:** a 8, b 8, c 8	**Baseline GI status:** baseline endoscopy performed: 4 participants had ulcers, 19 had erosions of other types and 1 had normal endoscopy **Type of arthritis:** rheumatoid disease 20, OA 3, cervical spondylosis 1	Ranitidine plus mixed NSAIDs (b, c) vs placebo plus mixed NSAIDs (a) **Duration:** 14 weeks (2 × 7-week treatment periods)
Simon, 1990[51] **Summary risk of bias:** moderate	**Allocated:** 48 in total	**Baseline GI status:** baseline endoscopy performed and participants with frank ulcers were excluded (but not haemorrhages and/or erosions) **Type of arthritis:** AS, RA, OA	Ranitidine plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 4–8 weeks (treatment continued after 4 weeks if erosions not healed)
Yanagawa, 1991[52] **Summary risk of bias:** moderate	**Allocated:** a 37, b 43	**Baseline GI status:** baseline endoscopy performed, excluded participants with more than erosion or haemorrhage at more than two sites and more than one area of the stomach or duodenum **Type of arthritis:** RA, spondylosis deformans, lumbago, degenerative gonarthrosis, scapulohumeral periarthritis, cervico-omo-brachial syndrome, others	Ranitidine plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 8 weeks
Levine, 1993[45] **Summary risk of bias:** moderate	**Allocated:** a 248, b 248	**Baseline GI status:** baseline endoscopy performed and excluded participants with acute ulcer **Type of arthritis:** OA	Nizatidine plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 3 months
Rugstad, 1994[53] **Summary risk of bias:** moderate	**Allocated:** a 285, b 285	**Baseline GI status:** no endoscopy performed, some participants had GI symptoms **Type of arthritis:** newly diagnosed OA: a 73, b 71	Cimetidine plus mixed NSAIDs vs placebo plus mixed NSAIDs (a) **Duration:** 4 weeks

continued

TABLE 3 *Brief characteristics of included H_2RA versus placebo studies (cont'd)*

Study	*N*	Participants	Interventions
Simon, 1994[54] (abstract) **Summary risk of bias:** moderate	**Allocated:** a 102, b 100, c 103	**Baseline GI status:** baseline endoscopy performed and excluded participants with ulcers **Type of arthritis:** OA	Famotidine plus mixed NSAIDs (b, c) vs placebo plus mixed NSAIDs (a) **Duration:** 12 weeks
Taha, 1996[55] **Summary risk of bias:** moderate	**Allocated:** a 93, b 95, c 97	**Baseline GI status:** baseline endoscopy performed and excluded participants with ulcers **Type of arthritis:** RA: a 76, b 80. OA: a 17, b 15	Famotidine plus mixed NSAIDs (b, c) vs placebo plus mixed NSAIDs (a) **Duration:** 24 weeks
Ten Wolde, 1996[56] **Summary risk of bias:** high	**Allocated:** a 15, b 15	**Baseline GI status:** baseline endoscopy performed and excluded participants with active ulcer (or included after ulcer healing with ranitidine 300 mg × 2 daily for 4 weeks) **Type of arthritis:** RA: a 13, b 22	Ranitidine plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 12 months
Van Groenendael, 1996[57] **Summary risk of bias:** moderate	**Allocated:** Study 1: a 29, b 29 Study 2: a 18, b18	**Baseline GI status:** baseline endoscopy performed and participants excluded if more than zero Lanza score (non-erosive) in Study 1 and if not 1–3 Lanza score (erosive but without peptic ulcer disease) in Study 2; all participants had to present with dyspeptic complaints **Type of arthritis:** Study 1: OA: a 18, b 19, RA: a 11, b 10 Study 2: OA: a 12, b 7, RA: a 5, b 10	Ranitidine plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** Study 1: 4 weeks Study 2: 4 weeks
Hudson, 1997[58] **Summary risk of bias:** moderate	**Allocated:** a 39, b 39	**Baseline GI status:** baseline endoscopy performed and participants only included with healed ulcers following healing study or in the 4 weeks following (patients without ulceration prior to the healing study entered a prophylaxis study[55]) **Type of arthritis:** RA: a 33, b 34, OA: a 6, b 5	Famotidine plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 24 weeks

AS, ankylosing spondylitis.

GI history, concomitant illness or concurrent treatment.

Interventions

Included studies compared placebo with daily doses of:

- 300 mg ranitidine[46,48,49,51,52,57]
- 600 mg ranitidine[56]
- 300 or 600 mg ranitidine[50]
- 40 mg famotidine[54,55]
- 80 mg famotidine[54,55,58]
- 400 mg cimetidine[47]
- 800 mg cimetidine[53]
- 300 mg nizatidine.[45]

The recommended daily doses in the BNF[23] are ranitidine 150–300, famotidine 20, cimetidine 400 and nizatidine 150 mg/day, so seven of the 15 studies prescribed GPAs above the recommended dose. All of these drugs were divided into two daily doses, and alongside a mixture of NSAIDs (these were generally the NSAIDs that patients were already prescribed before the start of the study).

Patient education was not mentioned in any study. The maximum duration of intervention was short term (3–8 weeks) in eight studies, medium term (9–51 weeks) in six studies and long-term (12 months) in one study.[56]

Antacids were permitted or prescribed alongside the H_2RA in five studies, not allowed in four studies and not mentioned in six studies. Washout was reported in three studies, unclear in nine studies and not carried out in one study. Aspirin

use was permitted in five studies, unclear in seven studies and not permitted in one study.

Study quality

The summary risk of bias was 'moderate' for 13 studies and 'high' for two studies.[48,56]

The method of randomisation was incompletely described in all studies, although the studies by the groups of Ehsanullah[48] ('predetermined randomisation code generated by Glaxo'), Taha[55] ('computer generated schedule, stratified by type of arthritis'), Ten Wolde,[56] Van Groenendael[57] ('predetermined randomisation list'), Yanagawa[52] ('envelope method') and Swift[50] ('randomly allocated by pharmacist') provided more than the word 'randomised' or 'randomly'.

No study was felt to have adequate allocation concealment (all were 'unclear').

Baseline characteristics appeared comparable in seven studies,[45,51,52,55,57,58] not in two[48,56] and unclear in the other six. Where baseline comparability was described as unclear, this was usually due to insufficient information being reported for assessment, mainly regarding duration of arthritis.

Participant blinding was stated in all 15 trials. Only one study explicitly reported blinding of the outcome assessor.[52] All studies were termed 'double blind' but it was not clear whether this referred to some or all of the outcome assessors or healthcare providers in addition to the participants themselves.

A priori sample size calculations were performed in three studies.[45,48,53] It was unclear whether they had been performed in the other studies.

Funding was by a pharmaceutical company in eight studies.[45,47,49,55–58] There was a suggestion of such funding in a further three studies (in Swift and colleagues[50] Glaxo provided the placebo, in Ehsanullah and colleagues[48] Glaxo generated the randomisation sequence and the contact author worked for Glaxo, in Simon and colleagues[54] the affiliation of the contact author was Merck). Funding was not mentioned in four studies.[46,51–53] Merck funded two studies, Eli Lilly one, Glaxo four and Smith Kline and French one.

Seven studies performed analysis on their primary outcome according to the intention-to-treat (ITT) principle. In one study it was unclear and in six studies some participants were excluded from analyses.

Compliance was assessed in nine studies,[45,48,49,51,53,55,57,58] but only two studies reported the results of this assessment in both arms (Taha and colleagues[55] stated that 12 of 93 in the placebo arm and 11 of 95 and 14 of 97 in the active arms, had 'poor compliance', and Rugstad and colleagues[53] reported that 92% in the placebo group and 94% in the active cimetidine arm took at least 70% of the study medication.

Publication bias

The number of included studies with data on symptomatic ulcers was too small to use these trials for the assessment of publication bias. Instead, the 12 studies with data on endoscopic ulcers were used. The funnel plot did not strongly suggest publication bias, nor did analyses using tests by Egger and colleagues[35] ($p = 0.68$) or by Begg and Mazumdar[36] ($p = 0.48$) (see Appendix 7a).

Results

Results are summarised in *Table 4* and forest plots are shown in *Figures 2–10*.

Primary outcomes

Information on serious GI complications was provided by only four studies (three of which reported a total absence of these problems). One serious GI event occurred in the placebo group of the Levine and colleagues' study:[45] gastritis causing a UGI tract haemorrhage. Symptomatic ulcers were mentioned in only two studies, only one of which reported a symptomatic ulcer in the H_2RA group (Taha and colleagues[55] reported withdrawal owing to a symptomatic oesophageal ulcer in their 40-mg famotidine arm).

Serious cardiovascular or renal illness was reported as absent in two studies and present in two studies. Levine and colleagues[45] reported two events in the placebo group (both non-fatal MIs) and Taha and colleagues[55] reported two events in the H_2RA group (one cerebrovascular accident in the 40-mg famotidine arm and one new-onset angina in the 80-mg famotidine arm) and one in the placebo group (one non-fatal MI).

No study provided data on health-related QoL measures.

TABLE 4 *H_2RA versus placebo meta-analysis (MA) and sensitivity analysis (SA) results*

Outcome	Analysis	No. of included RCTs	No. of participants	No. of events	RR (random effects)	95% CI	Heterogeneity *p*-value
Serious GI events	MA	4	894	1	0.33	0.01 to 8.14	NR
	SA quality	4	894		0.33	0.01 to 8.14	NR
	SA dosage	2	93		NE	NE	
Symptomatic ulcers	MA	2	343	1	1.46	0.06 to 35.53	NR
	SA quality	2	343		1.46	0.06 to 35.53	NR
	SA dosage	1	58		NE	NE	
Serious CV or renal events	MA	2	781	5	0.53	0.08 to 3.46	0.42
	SA quality	2	781		0.53	0.08 to 3.46	0.42
	SA dosage	0					
	SA naproxen	0					
QoL	MA	0					
Deaths	MA	6	721	1	3.00	0.13 to 68.26	NR
	SA quality	5	691		NE	NE	
	SA dosage	2	93		NE	NE	
	SA naproxen	4	147		3.00	0.13 to 68.26	NR
GI symptoms	MA	4	1385	201	0.72	0.56 to 0.92	0.88
	SA quality	3	1088		0.71	0.55 to 0.93	0.72
	SA dosage	2	377		0.66	0.37 to 1.15	0.57
Endoscopic ulcers	MA	12	1747	250	0.55	0.44 to 0.70	0.83
	SA quality	10	1464		0.57	0.44 to 0.73	0.74
	SA dosage	6	540		0.49	0.30 to 0.80	0.81
Anaemia	MA	1	496	1	3.00	0.12 to 73.29	NR
	SA quality	1	496		3.00	0.12 to 73.29	NR
	SA dosage	0					
Occult bleed	MA	0					
Total drop-out	MA	10	2118	362	0.97	0.84 to 1.12	0.57
	SA quality	6	1821		0.99	0.85 to 1.14	0.63
	SA dosage	6	743		0.99	0.82 to 1.20	0.41
Drop-outs due to GI symptoms	MA	7	1225	57	0.71	0.43 to 1.20	0.54
	SA quality	2	898		0.79	0.26 to 2.41	0.27
	SA dosage	3	390		0.74	0.34 to 1.64	NR

MA, meta-analysis; NE, no events and so no results; NR, not relevant (e.g. tests of heterogeneity when only one study is included in the analysis); SA, sensitivity analysis, removing studies on the basis of the quality stated.

The presence or absence of deaths could be ascertained in only six studies, of which five reported 'no deaths'. One study[56] reported one death in its ranitidine arm (due to pneumonia).

Secondary outcomes

Data on total numbers of people with GI symptoms were provided by four studies. GI symptoms were noted in 201 of the 1385 participants in these studies. Although no individual study showed a significant improvement in total GI symptoms in the H_2RA group, MA suggests significant benefits of H_2RAs compared with placebo (RR 0.72, 95% CI 0.56 to 0.92) with no suggestion of heterogeneity ($p = 0.88$). SA, excluding studies on the basis of study quality or Cox-2 preferentials, did not alter the size or significance of the results. However, removing high-dose studies (studies with doses above recommended levels) resulted in a non-significant relative risk.

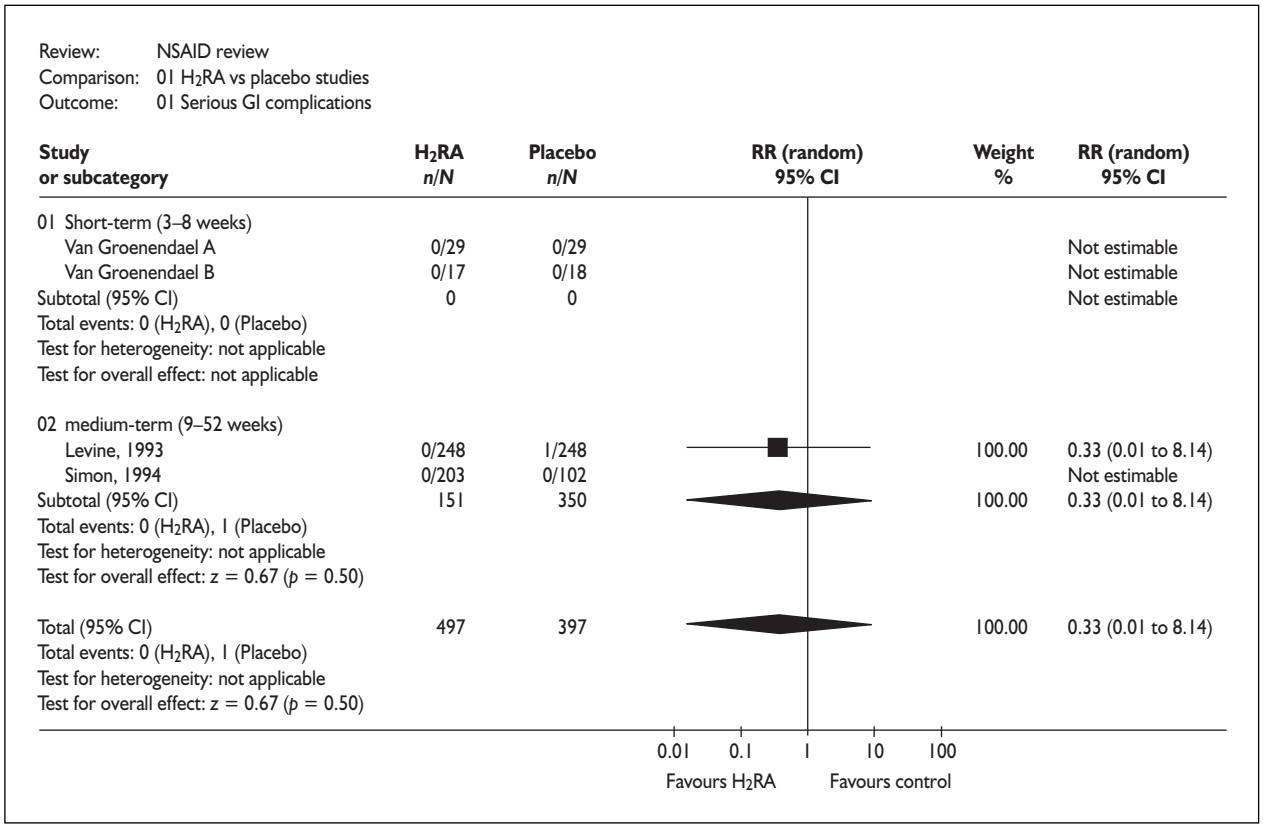

FIGURE 2 *Forest plot of H_2RA versus placebo, outcome serious GI complications*

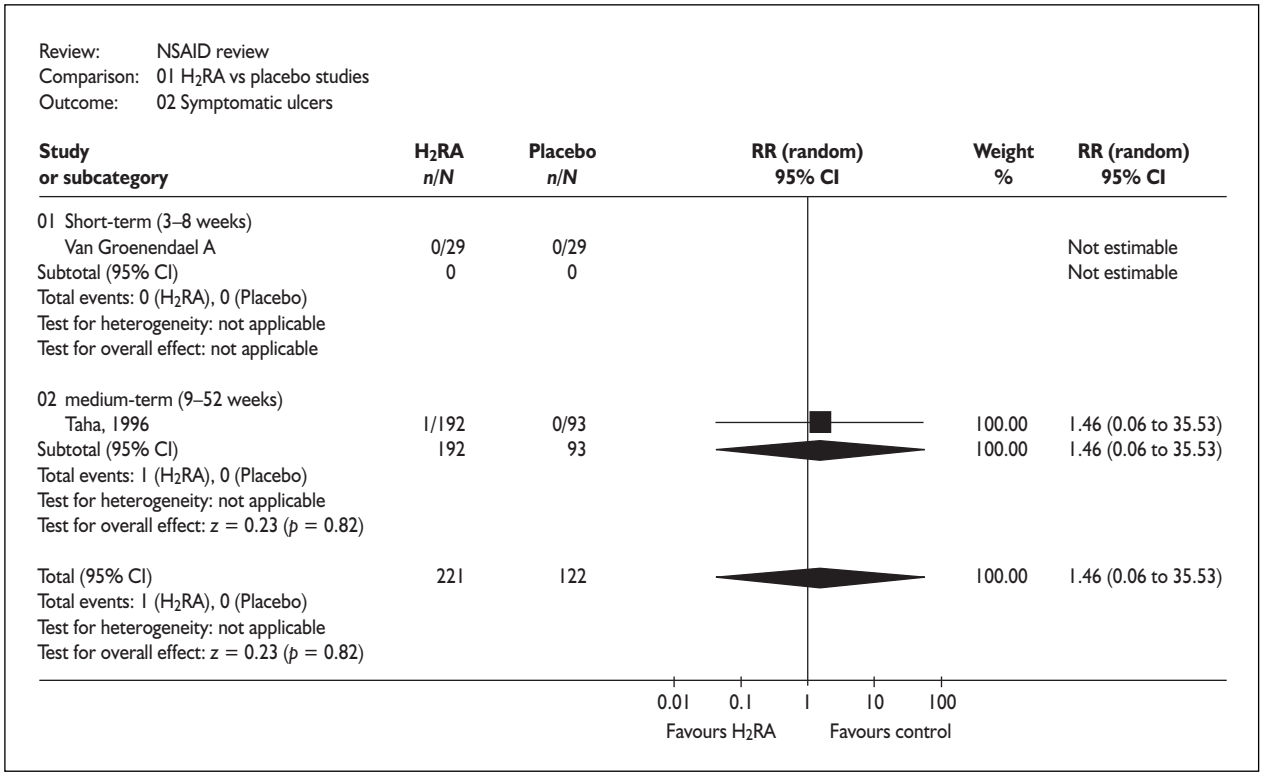

FIGURE 3 *Forest plot of H_2RA versus placebo, outcome symptomatic ulcers*

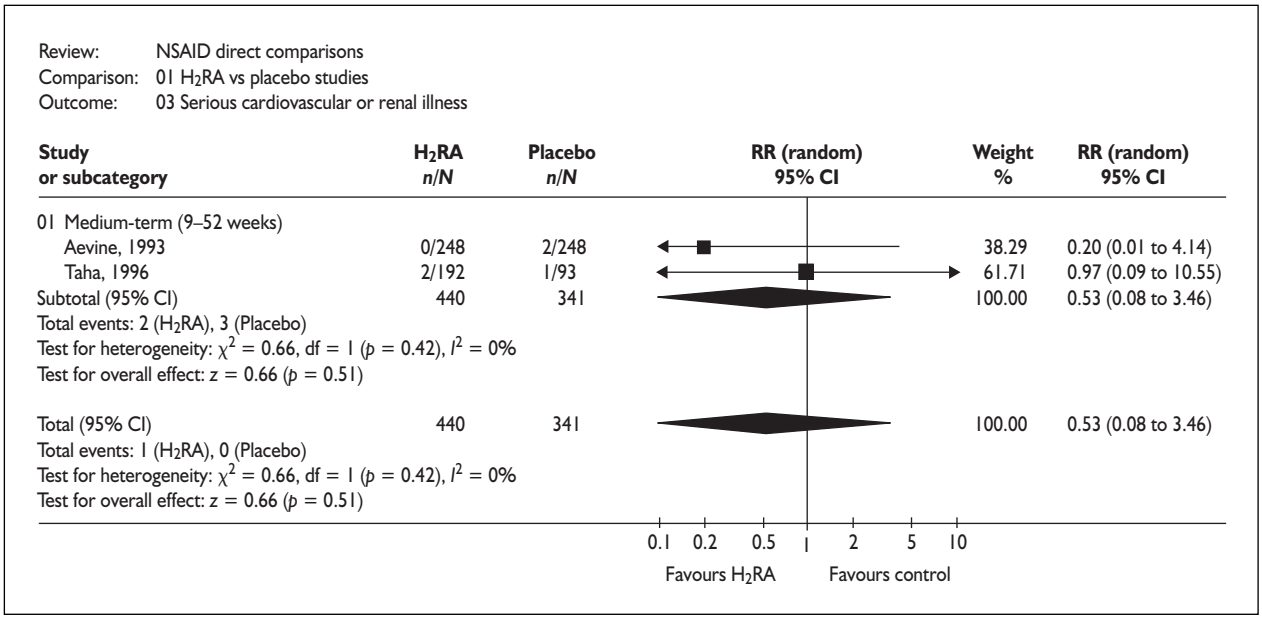

FIGURE 4 *Forest plot of H_2RA vs placebo, outcome serious cardiovascular or renal illness*

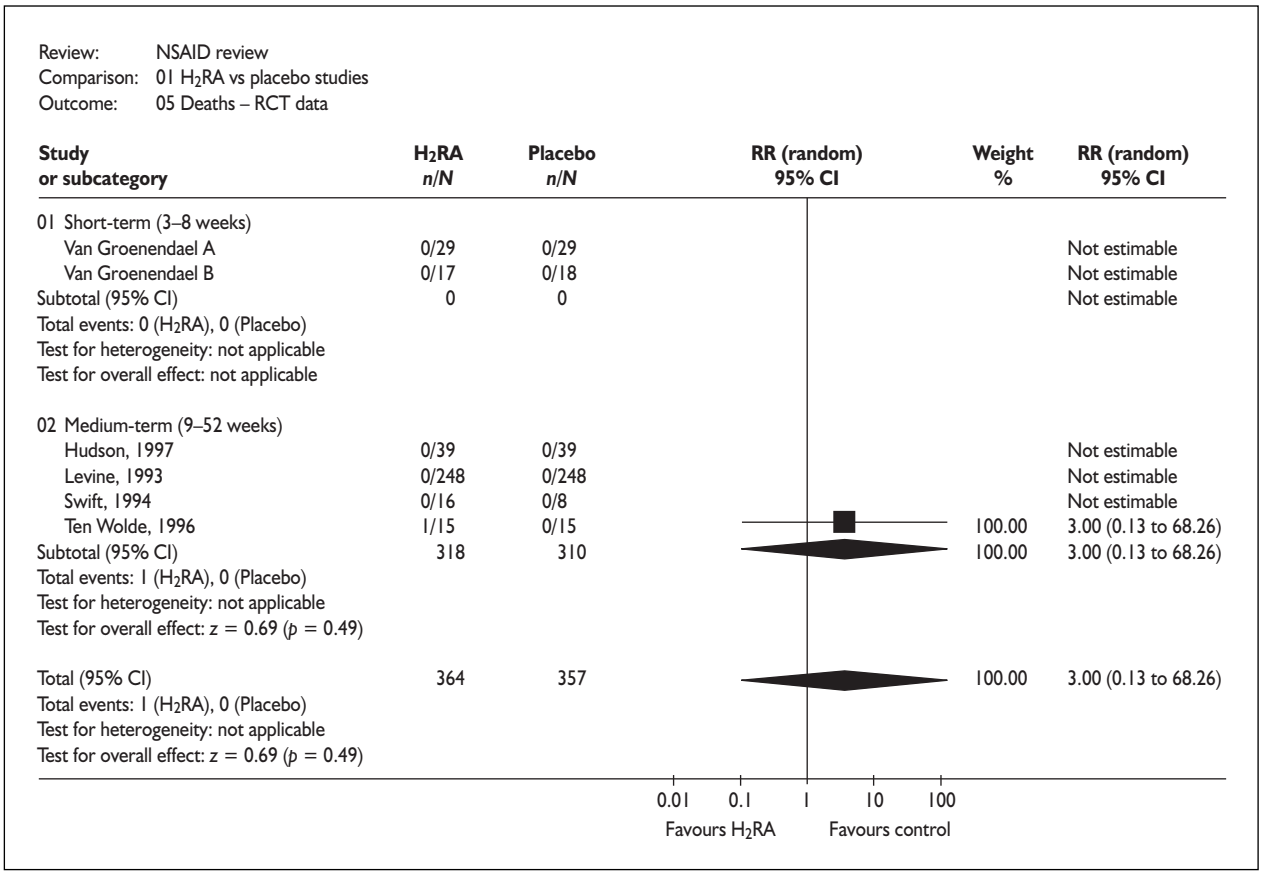

FIGURE 5 *Forest plot of H_2RA vs placebo, outcome deaths*

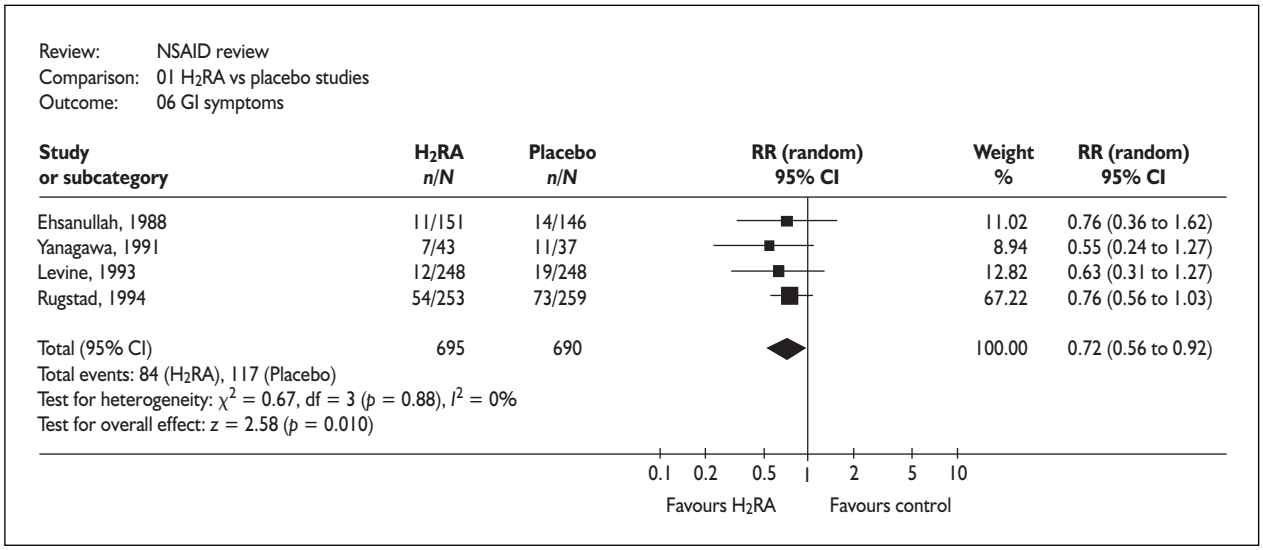

FIGURE 6 *Forest plot of H_2RA versus placebo, outcome GI symptoms*

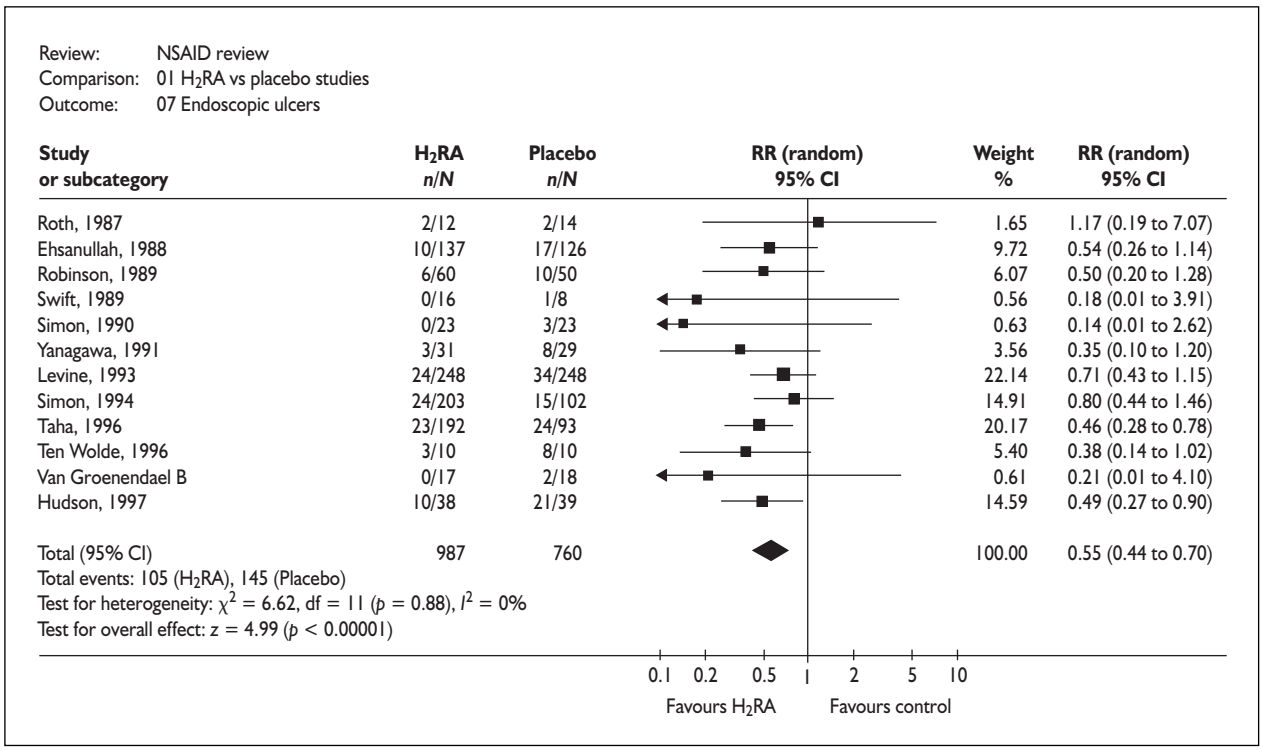

FIGURE 7 *Forest plot of H_2RA versus placebo, outcome endoscopic ulcers*

Twelve studies provided data on total numbers of people with endoscopic ulcers. Endoscopic ulcers were seen in 250 of 1747 participants. The RR of developing at least one gastroduodenal ulcer was 0.55 (95% CI 0.44 to 0.70) in the H_2RA groups compared with placebo, with no suggestion of heterogeneity ($p = 0.83$). SA, excluding studies on the basis of quality, dose or Cox-2 preferentials, made no difference to the size or significance of the outcome.

Anaemia was mentioned in only one study (Levine 1993),[45] which noted anaemia in only one participant in the H_2RA group. Occult bleeding was not recorded as an outcome in any of the included studies.

Total drop-outs were calculable or reported in 10 studies. A total of 362 of 2118 participants dropped out early (17%). Drop-outs did not occur more or less often in the H_2RA group (RR 0.97,

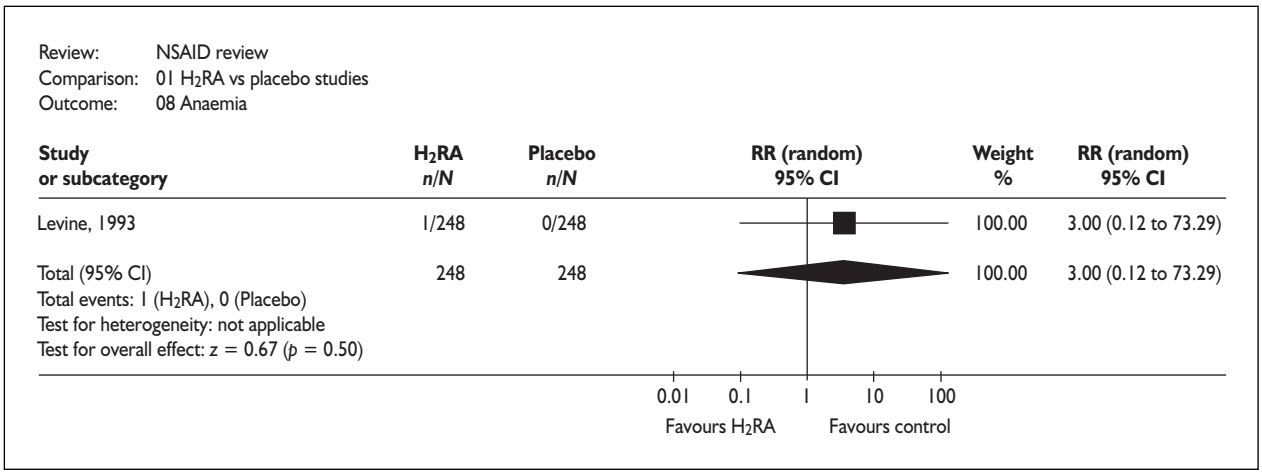

FIGURE 8 *Forest plot of H_2RA versus placebo, outcome anaemia*

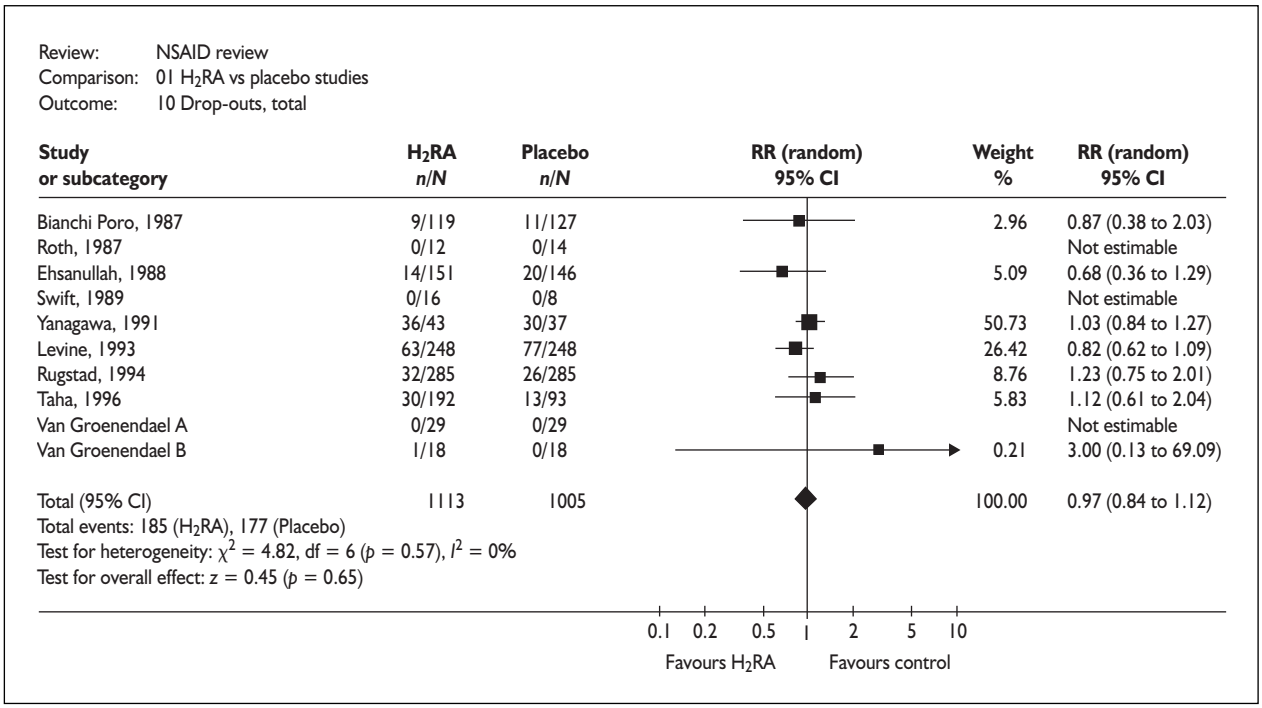

FIGURE 9 *Forest plot of H_2RA versus placebo, outcome total drop-outs*

95% CI 0.84 to 1.12) with no suggestion of heterogeneity ($p = 0.57$). The results were not materially altered when the studies were omitted on the basis of quality, Cox-2 preferentials or high dose.

The numbers of drop-outs due to GI symptoms were reported in seven studies (although four of these reported no drop-outs due to such symptoms). Overall, 57 of 1226 dropped out owing to GI symptoms (5%), giving an RR in the H_2RA group of 0.71 (95% CI 0.43 to 1.20) with no suggestion of heterogeneity ($p = 0.54$). The results were not materially altered when the studies were omitted on the basis of quality, Cox-2 preferentials or high dose.

Meta-regressions and subgrouping

Subgrouping by study duration was carried out for all primary analyses. However, in this comparison all studies reporting primary outcome data had medium follow-up periods (9–51 weeks).

Meta-regressions were carried out to explore the relationship between ln (RR) of endoscopic ulcers and study duration, baseline GI status (quantified

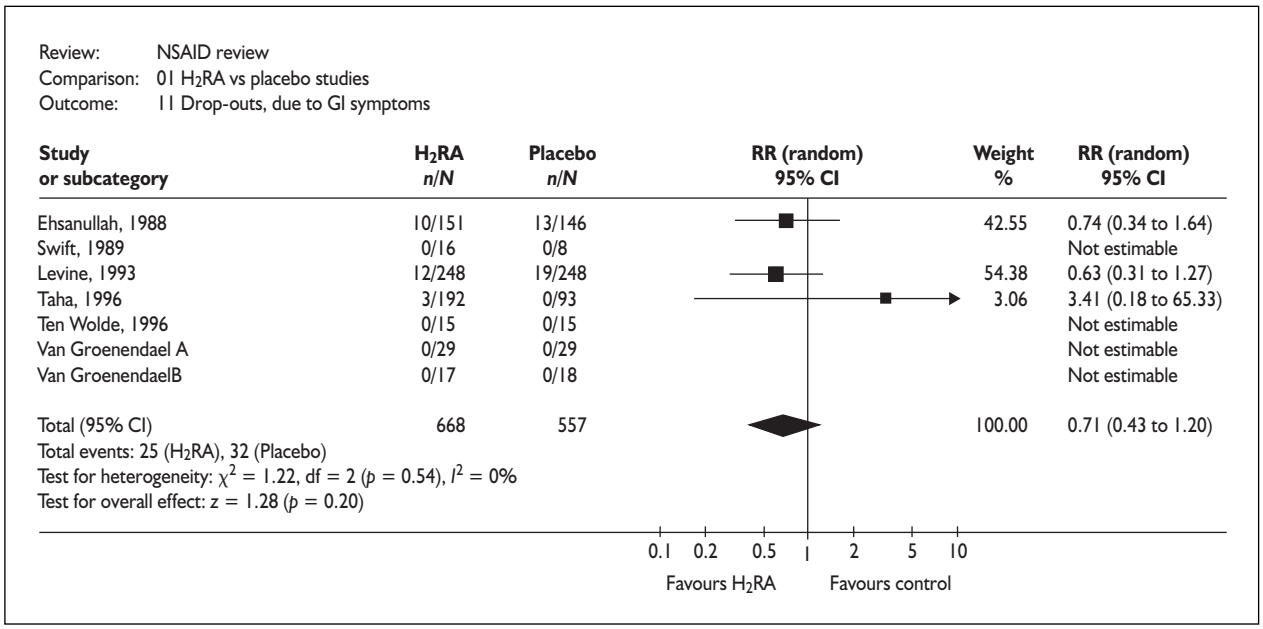

FIGURE 10 *Forest plot of H_2RA vs placebo, outcome drop-outs due to GI symptoms*

by the percentage of participants with a history of ulcers or bleeds) and mean age at baseline. No significant relationships were seen. See Appendix 8 for further details.

ARRs were calculated for the economic analysis (Appendix 9a). We attempted to subgroup ARRs for serious GI events, symptomatic ulcers and endoscopic ulcers by baseline GI status and by age. There were only useful data to subgroup on endoscopic ulcers. There was a suggestion of increased protection offered by H_2RAs as baseline GI status got worse and in older participants (not formally tested). See Appendix 9b for further details.

Summary

Studies comparing H_2RAs plus NSAIDs versus placebo plus NSAIDs generally included a mixture of participants with OA and RA, of middle age and with a varied baseline risk. Half of the studies gave H_2RA doses well over those now recommended. Study quality was far from ideal, with no study reporting adequate allocation concealment and half of the studies having unclear baseline comparability. Eleven of the 15 included RCTs reported funding by pharmaceutical companies. There was no suggestion of publication bias.

Very few studies reported on the primary outcomes. There were insufficient data to allow conclusions to be drawn regarding the effect of H_2RA compounds compared with placebo on serious GI complications, symptomatic ulcers, serious cardiovascular disease (CVD) or renal illness, QoL or death.

More data were provided on GI symptoms and endoscopic ulcers, both of which appear to be significantly reduced in participants randomised to take H_2RAs compared with placebo (although the significance of the effects on GI symptoms was lost with SA removing high-dose studies). However, the quality of the studies was not high and it is possible that these results may be biased. Total drop-outs and drop-outs due to GI symptoms were not significantly different between the placebo and H_2RA groups.

Chapter 6

PPI plus NSAID versus placebo plus NSAID: systematic review – included studies, results, analysis and robustness

Included studies

Table 5 summarises the included studies. For a complete table of characteristics of included studies, see Appendix 6b.

Characteristics of studies

Six RCTs were included in this comparison, randomising 1358 participants. Studies varied in size from 34[63] to 296 participants[62] per arm. Three studies were multicentre and included participants from several countries[59,61,62] and another study was conducted in various centres in North America.[64] Two studies were single centre and both were conducted at the same centre in Italy.[60,63] Five studies were conducted in Europe, two of which also included sites in the UK.[61,62] Publication dates were from 1996 to 2002. Additional data on outcomes were not added for any of these studies following contact with authors.

Participants

Five studies included adults with OA. One study only recruited participants with OA[60] and four studies included adults with RA.[59,61–63] Two studies included adults with other types of arthritis,[59,62] including 138 people (no other details were provided). (Two participants in the trial by Ekstrom and colleagues[59] and 26 participants in the trial by Cullen and colleagues[61] are not described.) The study by Graham and colleagues[64] does not report details of participants' disease status. Only one study[63] reported the duration of arthritis (mean of 5.1 years in the placebo group and 4.4 years in the pantoprazole group).

Recruitment was from a rheumatology unit in one study,[60] 'outpatients' in another study[63] and was not mentioned in three studies.[59,61,62] The mean age of participants ranged from 52[60] to 62[64] years old.

Participants' GI tract status varied at baseline. One study recruited participants with normal UGI on endoscopy.[60] One study recruited people free of ulcers and with no more than 10 gastric and 10 duodenal erosions.[61] One study recruited participants with a Lanza score of 0, 1 or 2 (from normal or hyperaemic gastroduodenal mucosa to presence of up to 10 erosions, submucosal haemorrhages or petechiae.[63] One study recruited patients with a history of dyspepsia or uncomplicated peptic ulcer disease.[59] The study by Hawkey and colleagues[62] recruited participants who had had successful healing of ulcers or more than 10 erosions. Successful healing was defined as the absence of ulcers and fewer than five erosions and not more than mild dyspeptic symptoms. In the study by Graham and colleagues,[64] all participants were required to have a history of gastric ulcer; two-thirds of the participants had recently completed a healing trial for NSAID-associated gastric ulcer; participants were excluded with ulcers of ≥5 mm diameter or >25 erosions.

Two studies[59,61] also reported the proportion of participants with a history of ulcers.

Interventions

Included studies compared placebo with daily doses of:

- 20 mg omeprazole[59–62]
- 40 mg pantoprazole[63]
- 15 mg lansoprazole[64]
- 30 mg lansoprazole.[64]

The recommended daily dose of omeprazole in the BNF[23] is 20 mg/day. The recommended daily dose of pantoprazole is 20 mg/day and therefore the dose of pantoprazole in Bianchi Porro and colleagues' study[63] was higher than recommended. The recommended daily dose of lansoprazole is 15–30 mg/day. All of these drugs were given in a single daily dose, and alongside a mixture of NSAIDs (these were generally the NSAIDs that patients were already prescribed before the start of the study).

Patient education was not mentioned in any study. The maximum duration of two studies was from 3 to 8 weeks, three studies were of 12 weeks duration and one study was 24 weeks long.

TABLE 5 *Brief characteristics of included PPI versus placebo studies*

Study	*N*	Participants	Interventions
Ekstrom, 1996[59] **Summary risk of bias:** high	**Allocated:** a 91, b 86	**Baseline GI status:** no baseline endoscopy performed but excluded participants without history of previous dyspepsia or uncomplicated peptic ulcer disease **Type of arthritis:** OA: a 54, b 49. RA: a 8, b 14. Other: a 28, b 22	Omeprazole plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 3 months
Bianchi Porro, 1998[60] **Summary risk of bias:** moderate	**Allocated:** a 57, b 57	**Baseline GI status:** baseline endoscopy performed and excluded participants without normal UGI endoscopy **Type of arthritis:** OA: a 53, b 50	Omeprazole plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 3 weeks
Cullen, 1998[61] **Summary risk of bias:** moderate	**Allocated:** a 86, b 83	**Baseline GI status:** baseline endoscopy performed and excluded participants who were not free of ulcers and with ≤ 10 gastric erosions and 10 or fewer duodenal erosions **Type of arthritis:** OA: a 41, b 38. RA: a 31, b 33	Omeprazole plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 6 weeks
Hawkey, 1998b[62] OMNIUM **Summary risk of bias:** moderate	**Allocated:** a 155, b 274, c 296 (7 participants unaccounted for)	**Baseline GI status:** endoscopy performed and excluded participants without treatment success following 4–8 weeks healing phase (omeprazole 20 mg/day vs omeprazole 40 mg/day vs misoprostol 200 μg /day); treatment success defined as absence of ulcers in the stomach or duodenum and the presence of fewer than five gastric erosions, fewer than five duodenal erosions and not more than mild symptoms of dyspepsia (corresponded to a 2-point reduction in Lanza scale from grade 4 to grade 2) **Type of arthritis:** OA: a 70, b 129, c 142. RA: a 56, b 107, c 118. Other: a 25, b 33, c 30. Combination: a 5, b 5, c 6	Misoprostol plus mixed NSAIDs (c) vs omeprazole plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 6 months
Bianchi Porro, 2000[63] **Summary risk of bias:** high	**Allocated:** a 34, b 70	**Baseline GI status:** baseline endoscopy performed and excluded participants without lesions grade 0, 1 or 2 **Type of arthritis:** OA: a 15, b 24. RA: a 19, b 46	Pantoprazole plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 12 weeks
Graham, 2002[64] **Summary risk of bias:** low	**Allocated:** a 134, b 134, c 136, d 133	**Baseline GI status:** baseline endoscopy performed, patients had to be without *H. pylori*, have history of endoscopically documented gastric ulcer with or without coexisting duodenal ulcer or GI bleeding (2/3 participants had previously completed participation in a healing trial for NSAID-associated gastric ulcer); excluded patients with gastric or duodenal ulcer crater at least 5 mm in diameter or more than 25 erosions or erosive reflux oesophagitis **Type of arthritis:** no details	lansoprazole (c, d) plus mixed NSAIDs vs misoprostol (b) plus mixed NSAIDs vs mixed NSAIDs (a) **Duration:** 12 weeks

Antacids were permitted or prescribed alongside the PPI in one study[63] and not mentioned in the other studies. None of the studies mentioned whether other analgesics were permitted and only one study reported that low-dose aspirin was allowed.

Study quality

Summary risk of bias was 'high' in two studies,[59,63] 'moderate' in three and 'low' in one.[64]

The method of randomisation was incompletely described in five studies, although the study by Bianchi Porro and colleagues[63] stated that a 'computer-generated randomisation list' was used.

Allocation concealment was adequate in one study (by Graham and colleagues,[64] following a response to a reviewer request for extra data); the other studies were assessed as 'unclear'. Baseline characteristics appeared comparable in four studies and not comparable in two.[59,63]

Five trials stated that participants were blinded but in four it was not clear whether the outcome assessors were also blinded. All studies were termed 'double blind' but it was not clear whether this referred to some or all of the outcome assessors or healthcare providers in addition to the participant themselves. In the study by Graham and colleagues,[64] participants and outcome assessor were blinded.

A priori sample size calculations were detailed in five studies and it was unclear whether they had been performed in the other study.[60]

All of the studies excluded some participants from analyses and therefore did not use the ITT principle.

Funding was by a pharmaceutical company (Astra) in three studies[59,61,62] and TAP Pharmaceutical Products in another study.[64] There was a suggestion of pharmaceutical funding in a further study (in Bianchi Porro and colleagues' study,[63] one of the authors worked for Byk Gulden Italia) and funding was not reported in one study.[60]

Compliance was assessed in four studies,[61–64] with three reporting the results of this assessment (Cullen and colleagues[61] stated that 97.4–99.4% of participants took at least 75% of their medication, Bianchi Porro and colleagues[63] that tablets were counted and that data from four participants in each arm were censored by week 4 for not taking at least 70% of NSAIDs and PPIs and Graham and colleagues[64] reported that compliance was 90% in both lansoprazole and placebo groups).

Two studies[59,62] excluded participants from analyses if they developed more than 10 erosions or more than mild dyspeptic symptoms[59] or moderate dyspepsia.[62] This may have biased the results as participants were withdrawn who may later have developed an ulcer or serious GI complications.

Publication bias

The number of included studies with data on symptomatic ulcers was too small to use these trials for assessment of publication bias. Instead, the studies with data on endoscopic ulcers were used (six studies). The funnel plot did not strongly suggest publication bias, nor did analyses using tests by Egger[35] ($p = 0.50$). There was some suggestion of small study effects in the test by Begg and Mazumdar[36] ($p = 0.02$), but the test was not robust owing to the small number of studies (see Appendix 7b).

Results

Results are summarised in *Table 6* and forest plots are shown in *Figures 11–18*.

Primary outcomes

Information on serious GI complications was provided by four studies. Ekstrom and colleagues,[59] reported a total absence of these problems, Bianchi Porro and colleagues[60] reported serious GI bleeding in one of 53 participants on placebo and 0 of 50 participants on omeprazole, Graham and colleagues[64] reported one case of GI haemorrhage in the PPI group and Hawkey and colleagues[62] reported one case of perforated duodenal ulcer in the placebo group. The RR of serious GI complications was not significantly different in the PPI and placebo groups (RR 0.46, 95% CI 0.07 to 2.92). SA did not alter the significance of the results.

Symptomatic ulcers were mentioned in only two studies (Ekstrom and colleagues[59] reported 11 symptomatic ulcers in 90 placebo participants compared with one in 85 participants taking omeprazole, and Cullen and colleagues[61] reported symptomatic ulcers in six of 85 participants on placebo compared with 0 of 83 participants on omeprazole). Overall the RR of symptomatic

TABLE 6 *PPI versus placebo meta-analysis (MA) and sensitivity analysis (SA) results*

Outcome	Analysis	No. of included RCTs	No. of participants	No. of events	RR (random effects)	95% CI	Heterogeneity *p*-value
Serious GI events	MA	4	1108	3	0.46	0.07 to 2.92	0.65
	SA quality	3	933		0.46	0.07 to 2.92	0.65
	SA dosage	4	1108		0.46	0.07 to 2.92	0.65
Symptomatic ulcers	MA	2	343	18	0.09	0.02 to 0.47	0.91
	SA quality	1	168		0.08	0.00 to 1.38	NR
	SA dosage	2	343		0.09	0.02 to 0.47	0.91
Serious CV or renal events	MA	2	496	3	0.78	0.10 to 6.26	0.63
	SA quality	1	401		0.50	0.03 to 7.87	NR
	SA dosage	1	401		0.50	0.03 to 7.87	NR
	SA naproxen	1	95		1.41	0.06 to 33.62	NR
QoL	MA	0					
Deaths	MA	1	401	1	0.17	0.01 to 4.05	NR
	SA quality	1	401		0.17	0.01 to 4.05	NR
	SA dosage	1	401		0.17	0.01 to 4.05	NR
	SA naproxen	0					
GI symptoms	MA	1	175	45	0.43	0.24 to 0.76	NR
	SA quality	0					
	SA dosage	1	175		0.43	0.24 to 0.76	NR
Endoscopic ulcers	MA	6	1358	281	0.37	0.30 to 0.46	0.43
	SA quality	4	1101		0.35	0.28 to 0.44	0.62
	SA dosage	5	1276		0.35	0.28 to 0.44	0.75
Anaemia	MA	0		0			
Occult bleed	MA	0		0			
Total drop-outs	MA	3	946	116	0.98	0.62 to 1.53	0.24
	SA quality	3	946		0.98	0.62 to 1.53	0.24
	SA dosage	3	946		0.98	0.62 to 1.53	0.24
Drop-outs due to GI symptoms	MA	2	279	48	0.45	0.26 to 0.78	0.51
	SA quality	0					
	SA dosage	1	175		0.43	0.24 to 0.76	NA

NR, not relevant (e.g. tests of heterogeneity when only one study is included in the analysis).

ulcers was lower in those randomised to PPIs (RR 0.09, 95% CI 0.02 to 0.47) with no significant heterogeneity. There were no studies with high doses, but SA removing poor resulted in loss of significance.

Serious cardiovascular or renal illness was reported in two studies (Bianchi Porro and colleagues[63] reported an MI in one of the 65 participants on pantoprazole but none in the 30 participants on placebo, Graham and colleagues[64] reported one case of severe coronary artery disorder secondary to coronary artery disease in the PPI group and one case of severe chest pain secondary to coronary artery disease in the placebo group). Significant effects were not seen in the main MA or any of the SAs.

Only one study (by Hawkey and colleagues,[62] reported by Yeomans and colleagues[65]) provided data on health-related QoL measures. This study followed the Nottingham Health Profile (NHP) and the Psychological General Well-Being Index (PGWB) during a healing phase and then a follow-on prevention phase (the phase included here). During the prevention phase, 'the health-related

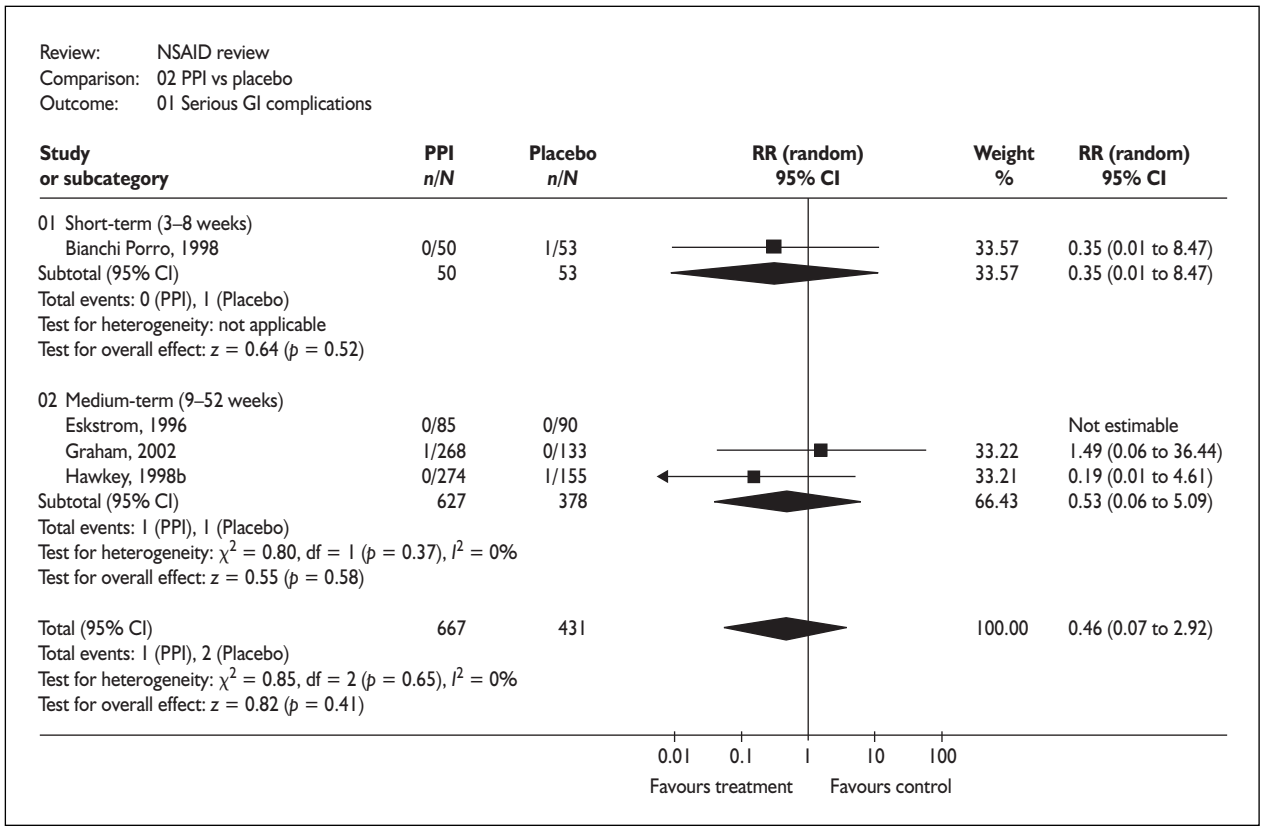

FIGURE 11 *Forest plot of PPI versus placebo, outcome serious GI complications*

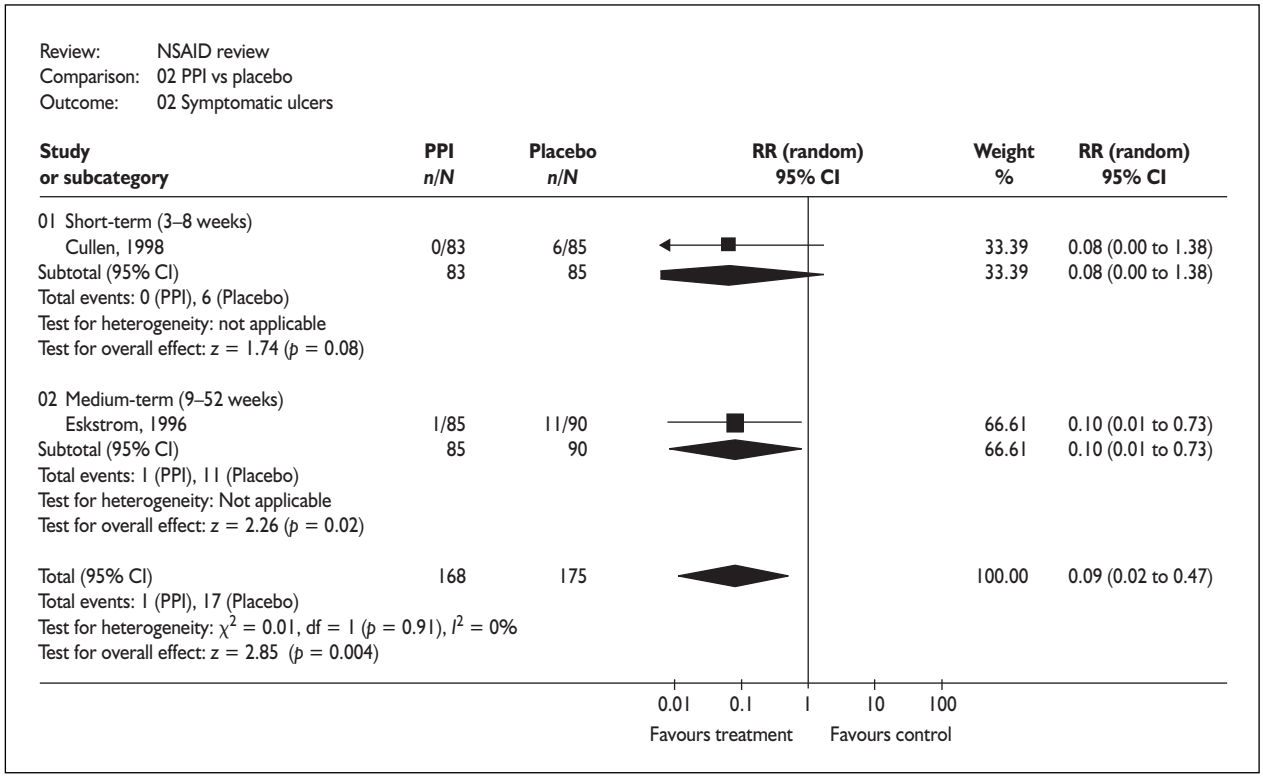

FIGURE 12 *Forest plot of PPI versus placebo, outcome symptomatic ulcers*

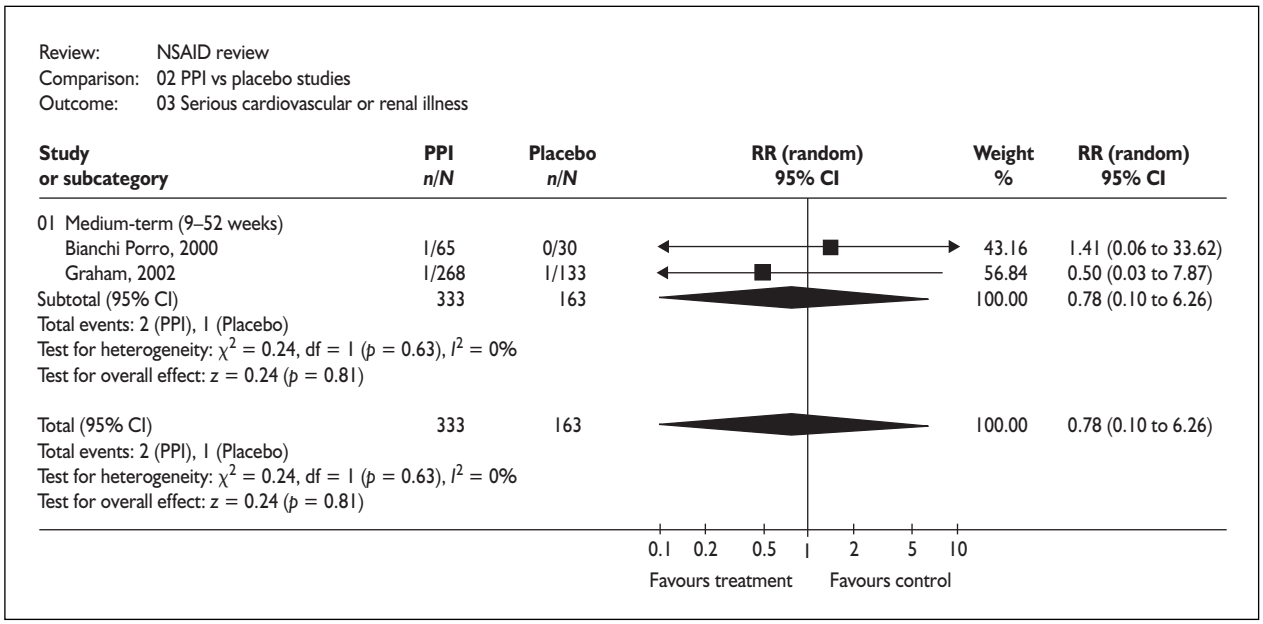

FIGURE 13 *Forest plot of PPI versus placebo, outcome serious cardiovascular or renal illness*

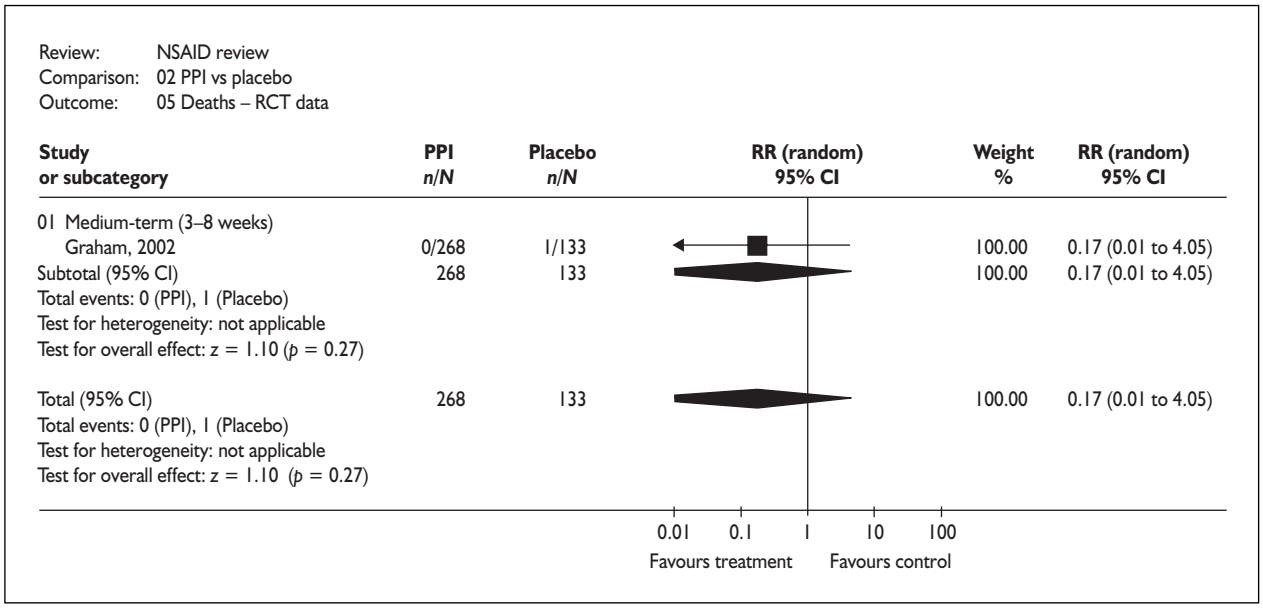

FIGURE 14 *Forest plot of PPI versus placebo, outcome deaths*

QoL assessed by the NHP was preserved'. No further data, or data by intervention group, were presented. Similarly, the PGWB index was maintained at 'the same level' as after healing. (See Appendix 10a for further details on QoL outcomes.)

The presence or absence of deaths could not be ascertained in five studies. One study reported one death in the placebo arm due to possible pulmonary embolism.[64]

Secondary outcomes

Data on total numbers of people with GI symptoms were provided by only one study. GI symptoms were noted in 45 of the 175 participants by Ekstrom and colleagues.[59] This study suggested significantly fewer GI symptoms in participants on PPIs compared with placebo (RR 0.42, 95% CI 0.24 to 0.76). This study was assessed as at high risk of bias, so significance was lost when this SA was run, but not in SAs run on the basis of dose or Cox-2 preferentials.

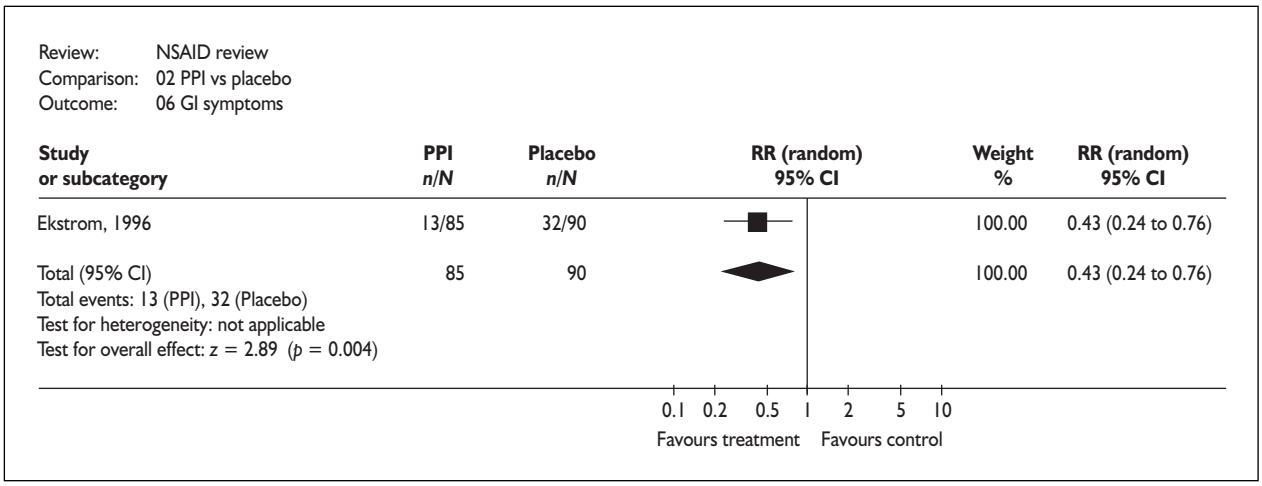

FIGURE 15 *Forest plot of PPI versus placebo, outcome GI symptoms*

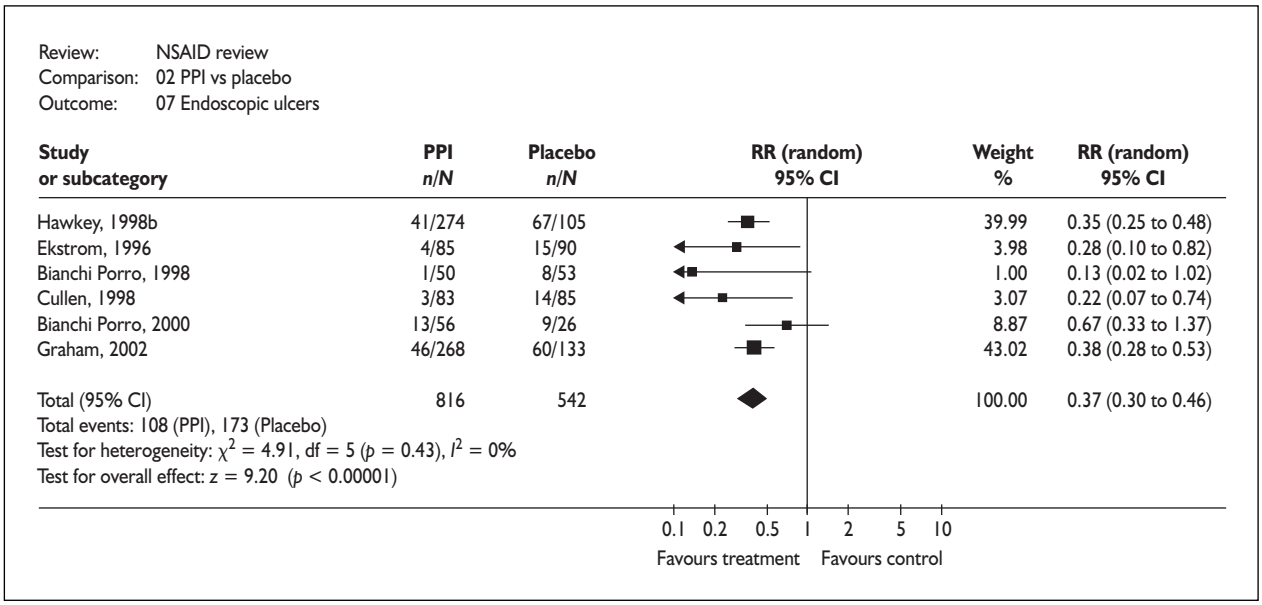

FIGURE 16 *Forest plot of PPI versus placebo, outcome endoscopic ulcers*

All six studies provided data on total numbers of people with endoscopic ulcers. Endoscopic ulcers were seen in 281 of 1358 participants. The RR of developing at least one gastroduodenal ulcer was 0.37 (95% CI 0.30 to 0.46) in the PPI groups compared with placebo, with no suggestion of heterogeneity ($p = 0.43$). The effect size and significance were not materially altered when studies were omitted on the basis of quality, Cox-2 preferentials or high dose.

Neither anaemia nor occult bleeding was reported as an outcome in any of the included studies. Total drop-outs were calculable or reported in three of the six studies. A total of 116 of 946 participants dropped out early (12%). Drop-outs did not occur more or less often in the PPI group (RR 0.99, 95% CI 0.62 to 1.53) with no suggestion of heterogeneity ($p = 0.24$). No studies were omitted in any SAs.

Numbers of drop-outs due to GI symptoms were reported in two studies. Overall 48 of 279 dropped out due to GI symptoms (17%), giving an RR in the PPI group of 0.45 (95% CI 0.26 to 0.78) with no suggestion of heterogeneity ($p = 0.51$). SA, removing studies with a high risk of bias, removed both studies that provided data. Other SAs did not affect the size or significance of the effect.

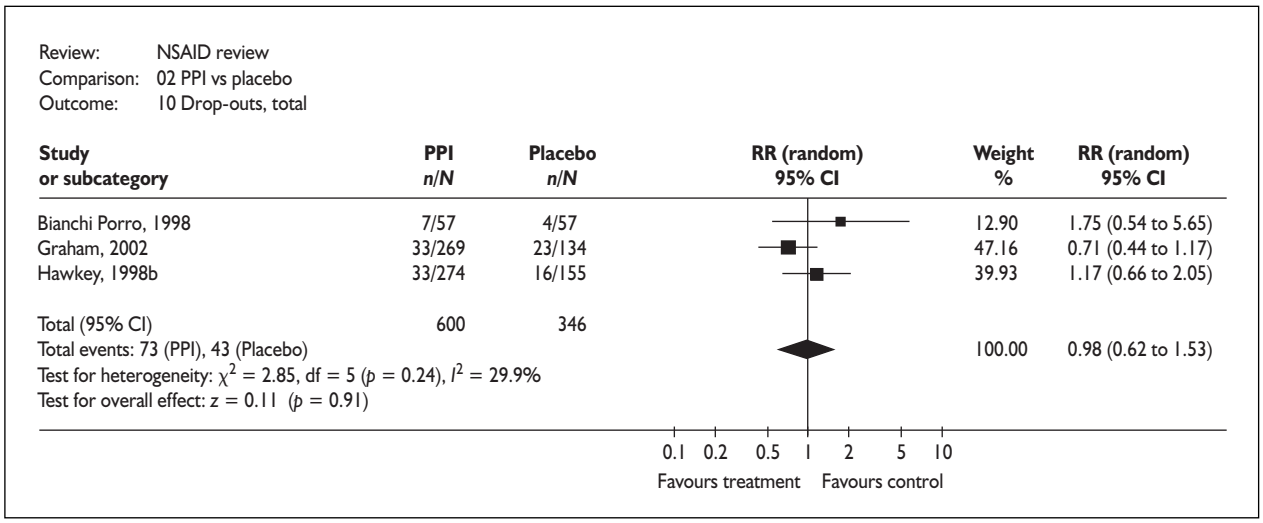

FIGURE 17 *Forest plot of PPI versus placebo, outcome total drop-outs*

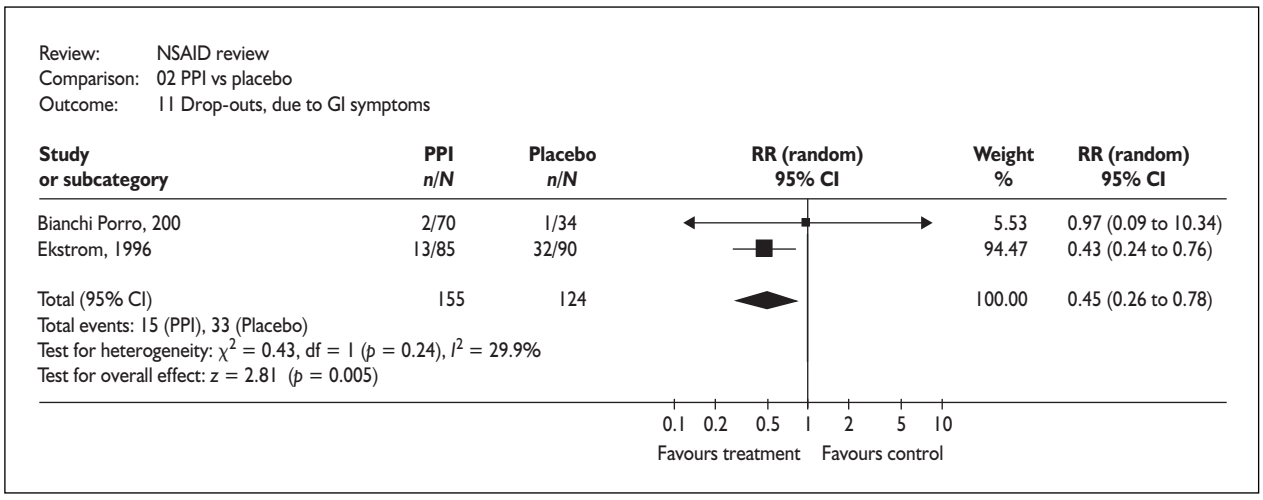

FIGURE 18 *Forest plot of PPI versus placebo, outcome drop-outs due to GI symptoms*

Meta-regressions and subgrouping

Subgrouping by study duration was carried out for all primary analyses (see figures). In this comparison, only two primary outcomes included data from more than one follow-up period, serious GI events and symptomatic ulcers. There was no suggestion of different effects with different study durations for these outcomes, but there were very few events.

Meta-regressions were carried out to explore the relationship between ln RR of endoscopic ulcers and study duration, baseline GI status (quantified by the percentage of participants with a history of ulcers or bleeds) and mean age at baseline. No statistically significant relationships were seen. See Appendix 8 for further details.

ARRs were calculated for the economic analysis (Appendix 9a). We attempted to subgroup ARRs for serious GI events, symptomatic ulcers and endoscopic ulcers by baseline GI status and by age. There were only useful data to subgroup on endoscopic ulcers. There appeared to be increased protection offered by PPIs for those with poorer baseline GI status compared with those who entered the studies with a normal gut (not formally tested). There were no studies with participants with a mean age of 65 years or more. See Appendix 9b for further details.

Summary

Six RCTs were included in this comparison. They included middle-aged participants with both OA

and RA and with varied baseline GI status. Only one study gave doses of PPI over those currently recommended. The summary risk of bias was 'low' in one study, 'moderate' in three and 'high' in two. Pharmaceutical companies funded five of the studies. There was no suggestion of publication bias.

Overall, very few studies reported on this review's primary outcomes, and it was not possible to draw conclusions on the effect of PPIs compared with placebo on serious GI complications, serious CVD or renal illness, QoL or death. The suggestion that symptomatic ulcers were significantly reduced in participants taking PPIs as compared with placebo was lost on SA.

Endoscopic ulcers appear to be significantly reduced in participants randomised to take PPIs compared with placebo and the results do not alter on SA. However, the quality of the studies was not high and it is possible that this result may be biased. Suggestions that GI symptoms and drop-outs due to GI symptoms were reduced in those on PPIs were lost on SA (when studies at higher risk of bias were removed). Total drop-outs were not significantly different between placebo and PPI groups.

Chapter 7

Misoprostol plus NSAID versus placebo plus NSAID: systematic review – included studies, results, analysis and robustness

Included studies

Table 7 summarises the included studies. For a complete table of characteristics of included studies, see Appendix 6c.

Characteristics of studies

Twenty-three RCTs were included in this comparison, from 22 published papers. They included 52 relevant treatment arms, randomising 16,945 participants (68% women). Studies varied in size from 20 to 4439 participants per arm. Ten studies were carried out in at least two countries, ten were multicentre studies within a single country, one was single centre and two unclear. Studies were conducted in Europe (10 studies, of which three included sites in the UK), North America (12 studies), South America (one study), Asia (one study), Australia (two studies) and three studies did not name countries, but included several. Publication dates were from 1988 to 2002. Additional data on outcomes were added for one trial following contact with authors (Raskin and colleagues[43]).

Participants

Seven studies included only adults with OA (2835 participants) and six studies included only adults with RA (9934 participants). Nine studies included participants with both OA and RA (3908 participants) and seven of these studies included at least one participant with other types of arthritis (always a minority of participants, and including seronegative spondarthropathy, psoriatic arthritis, ankylosing spondylitis, Reiter's syndrome, individuals with both OA and RA or 'other'). One study (268 participants) did not state whether, or what type of, arthritis was included.[64]

The mean duration of arthritis in these studies varied from 3 to 13 years, although ranges from less than 6 months to over 15 years were described in four studies and duration of arthritis was not stated in 11. The mean age of participants ranged from 38 to 70 years (not stated in two studies).

Participants' GI tract status varied at baseline. Six studies included (all or some) participants who had recently completed ulcer-healing therapies. Four studies excluded people with current ulcers and three studies excluded those with active GI disease. Six studies allowed up to 10 erosions or petechiae, three up to three erosions or petechiae on endoscopy, but no frank ulcers. One study only recruited participants with 'normal' baseline endoscopies.

Interventions

Of the 27 active treatment arms with misoprostol, all provided daily doses within the recommended range (400–800 µg/day):

- 400 µg misoprostol (six arms)
- 600 µg misoprostol (three arms)
- 800 µg misoprostol (eight arms)
- 400–600 µg misoprostol (eight arms)
- 600–800 µg misoprostol (one arm)
- 400–800 µg misoprostol (one arm).

Misoprostol was always given in the appropriate number of 200-µg doses (except for one study that gave single 400-µg doses), and eight arms gave misoprostol combined with diclofenac in a fixed combination (Arthrotec). Most other studies gave misoprostol with a mixture of NSAIDs (usually the NSAID used before the study), but one arm gave misoprostol with ibuprofen and two with diclofenac.

Patient education was not mentioned in any study. Ten studies were short term (3–8 weeks), 10 were medium term (9–51 weeks) and three were long term (all 52 weeks).

Study quality

Overall, the summary risk of bias was assessed as high in four studies,[73,77,78,80] moderate in 18 studies and low in one study.[64]

The method of randomisation was reasonably well described in only two studies[43,64] and incompletely

TABLE 7 *Brief characteristics of misoprostol versus placebo included studies*

Study	*N*	Participants	Interventions
Graham, 1988[66] **Summary risk of bias:** moderate	**Allocated:** a 138, b 143, c 140	**Baseline GI status:** baseline endoscopy performed and excluded patients with endoscopic ulcers (or joined after 4–8 weeks of treatment with misoprostol or placebo with a healed ulcer); participants had abdominal pain thought related to NSAIDS **Type of arthritis:** OA	**Comparison:** misoprostol plus mixed NSAIDs (b, c) vs placebo plus mixed NSAIDs (a) **Duration:** 12 weeks
Bolten, 1989[67] **Summary risk of bias:** moderate	**Allocated:** a 36, b 31	**Baseline GI status:** baseline endoscopy performed and patients excluded with peptic ulcer but included patients with lesion and upper abdominal complaints **Type of arthritis:** RA	**Comparison:** misoprostol plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 4 weeks
Chandrasekaran, 1991[68] **Summary risk of bias:** moderate	**Allocated:** a 45, b 45	**Baseline GI status:** normal endoscopy **Type of arthritis:** OA: a 15, b 15. RA: a 15, b 15	Comparison: misoprostol plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 4 weeks
Geis, 1991[69] **Summary risk of bias:** moderate	**Allocated:** a 99, b 96	**Baseline GI status:** no more than 3 erosions and/or 10 petechial haemorrhages at baseline endoscopy (some had >10 erosions, oozing or intraluminal blood or ulceration originally but had undergone treatment with misoprostol to improve GI status) **Type of arthritis:** RA, OA	Comparison: misoprostol plus diclofenac (b) vs placebo plus diclofenac (a) **Duration:** 52 weeks
Saggioro, 1991[70] **Summary risk of bias:** moderate	**Allocated:** a 84, b 82	**Baseline GI status:** no more than 3 erosions or petechiae at baseline endoscopy, no GI symptoms **Type and duration of arthritis (years):** RA: a 14, b 10. OA: a 70, b 72. a 4.73 years; b 4.94 years	**Comparison:** misoprostol plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 28 days (±4 days)
Bolten, 1992[71] **Summary risk of bias:** moderate	**Allocated:** a 183, b 178	**Baseline GI status:** no more than 10 erosions on baseline endoscopy **Type of arthritis:** OA	**Comparison:** diclofenac and misoprostol (b) vs diclofenac (a) **Duration:** 4 weeks
Doherty, 1992[72] **Summary risk of bias:** moderate	**Allocated:** a 227, b 228	**Baseline GI status:** those with active GI disease were excluded (no baseline endoscopy) **Type of arthritis:** OA	**Comparison:** diclofenac and misoprostol (b) vs diclofenac (a) **Duration:** 4 weeks
Melo Gomes, 1992[73] **Summary risk of bias:** Study 1: moderate Study 2: high	**Allocated:** Study 1: a 175, b 164 Study 2: a 183, b 178	**Baseline GI status:** no more than 10 erosions or any ulcers at baseline endoscopy, ~60% of participants had normal mucosa on baseline **Type of arthritis:** RA (study 1), OA (study 2)	**Comparison:** diclofenac and misoprostol (b) vs diclofenac (a) **Duration:** Study 1 = 12 weeks Study 2 = 4 weeks
Verdickt, 1992[74] **Summary risk of bias:** moderate	**Allocated:** a 175, b 164	**Baseline GI status:** no more than 10 erosions in stomach, and/or 10 erosions in duodenum, oesophageal, gastric, pyloric channel or duodenal ulcer at baseline endoscopy Normal mucosa: a 107, b 101 No more than 10 erosions: a 68, b 63 **Type of arthritis:** RA	**Comparison:** diclofenac and cisoprostol (b) vs diclofenac (a) **Duration:** 12 weeks

continued

TABLE 7 *Brief characteristics of misoprostol versus placebo included studies (cont'd)*

Study	*N*	Participants	Interventions
Graham, 1993[75] **Summary risk of bias:** moderate	**Allocated:** a 323, b 320	**Baseline GI status:** no ulcer or erosions of 3 mm or more at baseline endoscopy **Type of arthritis:** 75% OA	**Comparison:** misoprostol plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 12 weeks
Henriksson, 1993[76] **Summary risk of bias:** moderate	**Allocated:** a 20, b 20	**Baseline GI status:** baseline endoscopy performed and excluded patients with symptomatic ulcer or treatment for peptic ulcer in last 30 days (1 of 20 in placebo group had an asymptomatic ulcer, 5 of 20 in placebo group had erosions, 5 of 19 in misoprostol group had erosions, 15 of 39 had haemorrhagic lesions and 13 of 39 had normal mucosa) **Type of arthritis:** RA: a 20, b 19	**Comparison:** misoprostol plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 4 weeks
Melo Gomes, 1993[77] **Summary risk of bias:** high	**Allocated:** a 210, b 217, c 216	**Baseline GI status:** no more than 10 erosions in the stomach or 10 erosions in the duodenum, or oesophageal, gastric, pyloric channel, or duodenal ulcer at baseline endoscopy **Type of arthritis:** OA	**Comparison:** diclofenac sodium/misoprostol (c) vs piroxicam (b) vs naproxen (a) **Duration:** 4 weeks
Roth, 1993[78] **Summary risk of bias:** high	**Allocated:** b 53, c 60	**Baseline GI status:** no more than 3 erosions at baseline endoscopy Normal endoscopy: b 18, c 27 Hyperaemia: b 20, c 17 3 or less erosions: b 15, c 13 **Type of arthritis:** OA	**Comparison:** misoprostol plus ibuprofen (c) vs ibuprofen (b) **Duration:** 12 weeks
Delmas, 1994[79] **Summary risk of bias:** moderate	**Allocated:** a 103, b 73, c 80	**Baseline GI status:** 0–3 erosions at baseline endoscopy **Type of arthritis:** OA 77, inflammatory joint disease 123, other 56	**Comparison:** misoprostol plus mixed NSAIDs (b, c) vs placebo plus mixed NSAIDs (a) **Duration:** 28 days
Elliott, 1994[80] **Summary risk of bias:** high	**Allocated:** a 43, b 40	**Baseline GI status:** baseline ulcer did not show frank ulcer or if they had an ulcer and were treated with 3 months of open treatment with ranitidine and then no ulcer present on endoscopy (in total 12 had healed ulcers) **Type of arthritis:** OA: a 14, b 22, RA: a 22, b 15. Other: a 7, b 3	**Comparison:** misoprostol plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 12 months
Viana de Queiroz, 1994[81] **Summary risk of bias:** moderate	**Allocated:** a 169, b 177	**Baseline GI status:** excluded participants with active GI disease (which included peptic ulcer) but no baseline endoscopy **Type of arthritis:** RA	**Comparison:** misoprostol and diclofenac (b) vs placebo and diclofenac (a) **Duration:** 12 weeks
Agrawal, 1995[82] **Summary risk of bias:** moderate	**Allocated:** a 191, b 193	**Baseline GI status:** <3 erosions following open label treatment with Misoprostol (for >10 erosions or ulcer or visible vessel or oozing or intraluminal blood) **Type of arthritis:** OA: a 92, b 99. RA: a 99, b 93. One participant had neither OA nor RA	Comparison: misoprostol and diclofenac (b) vs placebo and diclofenac (a) **Duration:** 52 weeks

continued

TABLE 7 *Brief characteristics of misoprostol versus placebo included studies (cont'd)*

Study	*N*	Participants	Interventions
Raskin, 1995[43] **Summary risk of bias:** moderate	**Allocated:** unclear	**Baseline GI status:** baseline endoscopy performed and excluded patients without upper GI symptoms (but excluded endoscopic evidence of gastric or duodenal ulcers, any oesophageal erosions, a mucosal defect of any size with perceptible depth, a gastric or duodenal mucosal defect 0.3 cm or more) **Type of arthritis:** OA: a 341, b 347, c 356, d: 180. RA: a 73, b 69, c 71, d 25. Other: a 32, b 42, c 43, d 21	**Comparison:** misoprostol plus mixed NSAIDs (b, c, d) vs placebo plus mixed NSAIDs (a) **Duration:** 12 weeks
Silverstein, 1995[6] **Summary risk of bias:** moderate	**Allocated:** a 4439, b 4404	**Baseline GI status:** without active peptic ulcer disease in last 30 days but no baseline endoscopy **Type of arthritis:** RA	**Comparison:** misoprostol plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 6 months
Bocanegra, 1998[83] **Summary risk of bias:** moderate	**Allocated:** a 154, b 175, c 152	**Baseline GI status:** free of ulcers and with 10 or fewer erosions in stomach or duodenum on baseline endoscopy **Type of arthritis:** OA	**Comparison:** misoprostol and diclofenac (b, c) vs diclofenac (a) **Duration:** 6 weeks
Hawkey, 1998b[62] OMNIUM **Summary risk of bias:** moderate	**Allocated:** a 155, c 296 (7 participants unaccounted for)	**Baseline GI status:** endoscopy performed and excluded participants without treatment success following 4–8 weeks healing phase (omeprazole 20 mg/day vs omeprazole 40 mg/day vs misoprostol 200 μg /day); treatment success defined as absence of ulcers in the stomach or duodenum and the presence of fewer than five gastric erosions, fewer than five duodenal erosions and not more than mild symptoms of dyspepsia (corresponded to a 2-point reduction in Lanza scale from grade 4 to grade 2) **Type of arthritis:** OA: a 70, c 142. RA: a 56, c 118. Other: a 25, c 30. Combination: a 5, c 6	**Comparison:** misoprostol plus mixed NSAIDs (c) vs placebo plus mixed NSAIDs (a) **Duration:** 6 months
Graham, 2002[64] **Summary risk of bias:** low	**Allocated:** a 134, b 134	**Baseline GI status:** baseline endoscopy performed, patients had to be without *H. pylori*, have history of endoscopically documented gastric ulcer with or without coexisting duodenal ulcer or GI bleeding (2/3 participants had previously completed participation in a healing trial for NSAID-associated gastric ulcer); excluded patients with gastric or duodenal ulcer crater at least 5 mm in diameter or more than 25 erosions or erosive reflux oesophagitis **Type of arthritis:** no details	**Comparison:** misoprostol (b) plus mixed NSAIDs vs mixed NSAIDs (a) **Duration:** 12 weeks

described in the rest. Allocation concealment was judged as adequate in only one study;[64] the rest were all 'unclear'.

Participant blinding was stated in 20 trials, but was unclear in two and not done in one study. Most studies stated that they were 'double blinded', but it was usually not clear whether the treatment providers or outcome assessors were blinded. Outcome assessors were clearly blinded in four studies, not in one and unclear in the remainder.

A priori sample size calculations were detailed in eight studies, but it was unclear whether they had been performed in the other studies.

Baseline characteristics appeared comparable in 13 studies, not comparable in four and unclear in six.

Funding was by a pharmaceutical company in 11 studies. There was a suggestion of such funding in a further seven studies (where one or more authors appear to be employed by a pharmaceutical company). One study reported a large number of sponsoring bodies, one of which was a pharmaceutical company. Funding was not mentioned at all in four studies.

Compliance was assessed in 12 studies, and seven studies reported the results of this assessment in both arms (see Appendix 6c for further details).

Publication bias

The number of included studies with data on symptomatic ulcers was too small to use these trials for assessment of publication bias. Instead, the studies with data on endoscopic ulcers were used (18 studies). The funnel plot did not suggest publication bias, nor did analyses using tests by Egger and colleagues[35] ($p = 0.26$) or by Begg and Mazumdar[36] ($p = 0.58$) (see Appendix 7c).

Results

Results are summarised in *Table 8* and forest plots are shown in *Figures 19–28*.

Primary outcomes

Information on serious GI complaints was provided by 10 studies (five of which reported a total absence of these problems), 75 events in over 11,000 participants. The meta-analysis showed a significant decrease in serious events in those on misoprostol (RR 0.57, 95% CI 0.36 to 0.91). There is no suggestion of heterogeneity ($p = 0.81$), and both SAs suggested a significantly beneficial effect of misoprostol.

Symptomatic ulcers were mentioned in two studies (with symptomatic ulcers in both arms), 44 symptomatic ulcers in almost 9000 participants. Misoprostol significantly reduced symptomatic ulcers (RR 0.36, 95% CI 0.20 to 0.67), with no suggestion of heterogeneity ($p = 0.52$). SA did not alter the RR, or lose statistical significance.

Serious cardiovascular or renal illness was reported as absent in one study and present in at least one arm in two further medium-term studies. In total, four events were reported in 2300 participants, with no significant difference between the misoprostol or control arms (RR 1.78, 95% CI 0.26 to 12.07) and no suggestion of heterogeneity ($p = 0.88$). SA on the basis of study quality or high dosage removed no studies. Removing studies with naproxen removed all studies.

Only one study (by Hawkey and colleagues,[62] reported by Yeomans and colleagues[65]) provided data on health-related QoL measures. This study followed the NHP and the PGWB during a healing phase and then a follow-on prevention phase (the phase included here). During the prevention phase, 'the health-related QoL assessed by the NHP was preserved'. No further data, or data by intervention group, were presented. Similarly, the PGWB index was maintained at 'the same level' as after healing. (See Appendix 10a for further details on QoL outcomes.)

The presence or absence of deaths could be ascertained in only seven studies, of which four reported 'no deaths'. Thirty-five deaths were reported in over 12,000 participants. There was no significant difference between mortality in the misoprostol and control groups (RR 0.89, 95% CI 0.46 to 1.74), with no suggestion of heterogeneity ($p = 0.99$). SA on the basis of study quality or high dosage removed no studies, and removing studies with naproxen removed all but one study, which reported no deaths.

Secondary outcomes

Data on total numbers of people with GI symptoms were provided by five studies, 1218 (62%) of the 1973 participants. MA suggested no significant difference between GI symptoms in misoprostol and placebo groups (RR 0.97, 95% CI 0.70 to 1.35) with evidence of heterogeneity ($p = 0.01$). SAs do not alter these results.

Eighteen studies provided data on people with endoscopic ulcers in either the stomach or duodenum or both, 658 (11%) of 6082 participants. The RR of developing at least one endoscopically visible gastroduodenal ulcer was 0.33 (95% CI 0.27 to 0.41) in the misoprostol groups compared with placebo, with no suggestion of heterogeneity ($p = 0.17$). SAs do not remove the significance of this result or show any further heterogeneity.

TABLE 8 *Misoprostol versus placebo meta-analysis (MA) and sensitivity analysis (SA) results*

Outcome	Analysis	No. of included RCTs	No. of participants	No. of events	RR (random effects)	95% CI	Heterogeneity *p*-value
Serious GI events	MA	10	11507	75	0.57	0.36 to 0.91	0.81
	SA quality	8	10781	70	0.59	0.37 to 0.95	0.81
	SA dosage	10	11507	75	0.57	0.36 to 0.91	0.81
Symptomatic ulcers	MA	2	8913	44	0.36	0.20 to 0.67	0.52
	SA quality	1	8841	48	0.34	0.18 to 0.64	NR
	SA dosage	2	8913	44	0.36	0.20 to 0.67	0.52
Serious CV or renal events	MA	3	2306	4	1.78	0.26 to 12.07	0.88
	SA quality	3	2306	4	1.78	0.26 to 12.07	0.88
	SA dosage	3	2306	4	1.78	0.26, 12.07	0.88
	SA naproxen	0					
QoL	MA	0					
Deaths	MA	7	12068	35	0.89	0.46 to 1.74	0.99
	SA quality	7	12068	35	0.89	0.46 to 1.74	0.99
	SA dosage	7	12068	35	0.89	0.46 to 1.74	0.99
	SA naproxen	0					
GI symptoms	MA	5	1973	1218	0.97	0.70 to 1.35	0.01
	SA quality	5	1973	1218	0.97	0.70 to 1.35	0.01
	SA dosage	5	1973	1218	0.97	0.70 to 1.35	0.01
Endoscopic ulcers	MA	18	6082	658	0.33	0.27 to 0.41	0.17
	SA quality	14	4971	587	0.35	0.28 to 0.42	0.23
	SA dosage	18	6082	658	0.33	0.27 to 0.41	0.17
Anaemia	MA	1	113	1	2.66	0.11 to 63.84	NR
	SA quality	0					
	SA dosage	1	113		2.66	0.11 to 63.84	NR
Occult bleed	MA	1	8843	16	0.46	0.16 to 1.32	NR
	SA quality	1	8843	16	0.46	0.16 to 1.32	NR
	SA dosage	1	8843	16	0.46	0.16 to1.32	NR
Total drop-out	MA	17	15275	4772	1.11	1.00 to 1.23	0.09
	SA quality	15	14519	4664	1.15	1.10 to 1.21	0.61
	SA dosage	17	15275	4772	1.11	1.00 to 1.23	0.09
Drop-outs due to GI symptoms	MA	10	12295	2332	1.36	1.26 to 1.46	0.80
	SA quality	8	11569	2303	1.36	1.26 to 1.46	0.82
	SA dosage	10	12295	2332	1.36	1.26 to 1.46	0.80

NR, not relevant (e.g. tests of heterogeneity when only one study is included in the analysis).

Anaemia was mentioned in only one study, which noted anaemia in only one participant in the misoprostol group (of 113 participants in total). Occult bleeding was recorded as an outcome in only one of the included studies, in 16 (0.2%) of 8843 participants. There was no significant difference in occult bleeding between the misoprostol and placebo groups (RR 0.46, 95% 0.16 to 1.32). SAs do not alter these results.

Total drop-outs were calculable or reported in 17 studies; 4772 (31%) of 15,275 participants dropped out early. Drop-outs were more frequent in the misoprostol group (RR 1.11, 95% CI 1.00 to 1.23) with some suggestion of heterogeneity ($p = 0.09$). SA, removing studies with a high risk of bias, increased the significance of the results and removed heterogeneity.

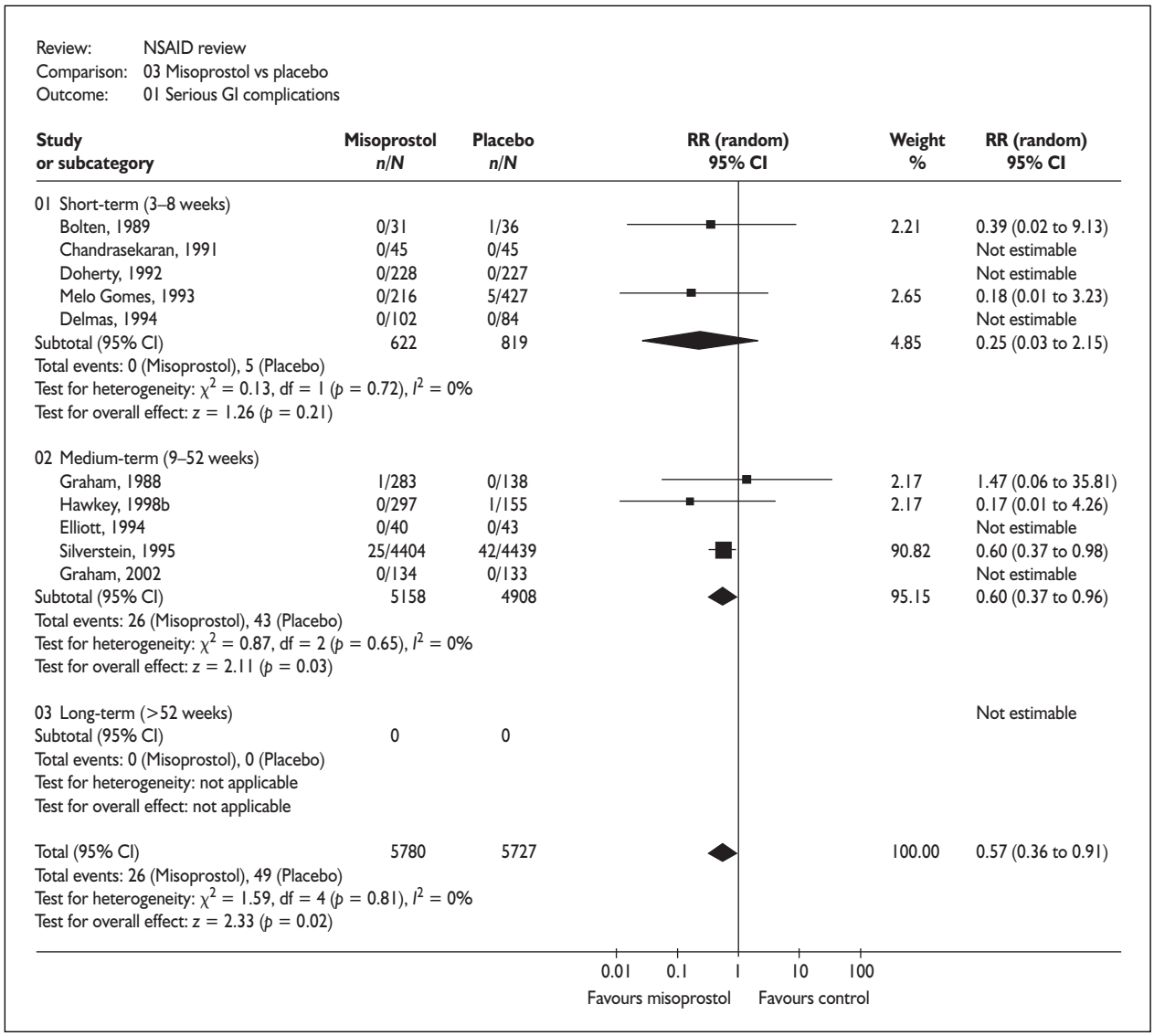

FIGURE 19 *Forest plot of misoprostol versus placebo, outcome serious GI complications*

The numbers of drop-outs due to GI symptoms (suggesting reasonably severe symptoms warranting early discontinuation) were reported in 10 studies; 2332 (19%) of 12,295 participants dropped out, significantly more in the misoprostol group (RR 1.36, 95% CI 1.26 to 1.46) with no suggestion of heterogeneity ($p = 0.80$). SAs did not alter these results.

Meta-regressions and subgrouping

Subgrouping by study duration was carried out for all primary analyses (see figures). In this comparison, only one primary outcome included events from more than one follow-up period: serious GI events (*Figure 19*). Subgrouping by study duration made no obvious difference to the overall results and heterogeneity appeared in the medium-term studies.

Meta-regressions were carried out to explore the relationship between ln (RR) of endoscopic ulcers and study duration, baseline GI status (quantified by the percentage of participants with a history of ulcers or bleeds) and mean age at baseline. See Appendix 8 for further details. The only comparison that showed any suggestion of a significant relationship was that of study duration on endoscopic ulcers in the misoprostol vs placebo trials. However, removing the trial with the largest weight in the MA (by Hawkey and colleagues[62]), resulted in loss of the significance of the relationship on meta-regression. Ordering the forest plot by study duration (*Figure 24*) did suggest a reduced effect of

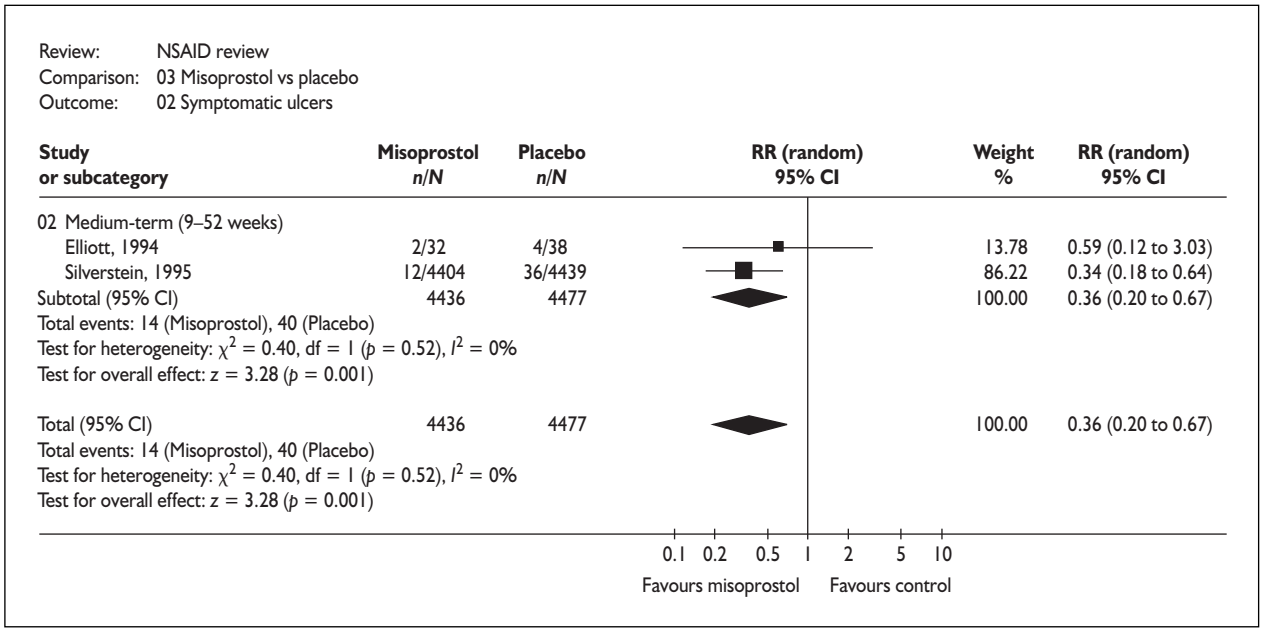

FIGURE 20 *Forest plot of misoprostol versus placebo, outcome symptomatic ulcers*

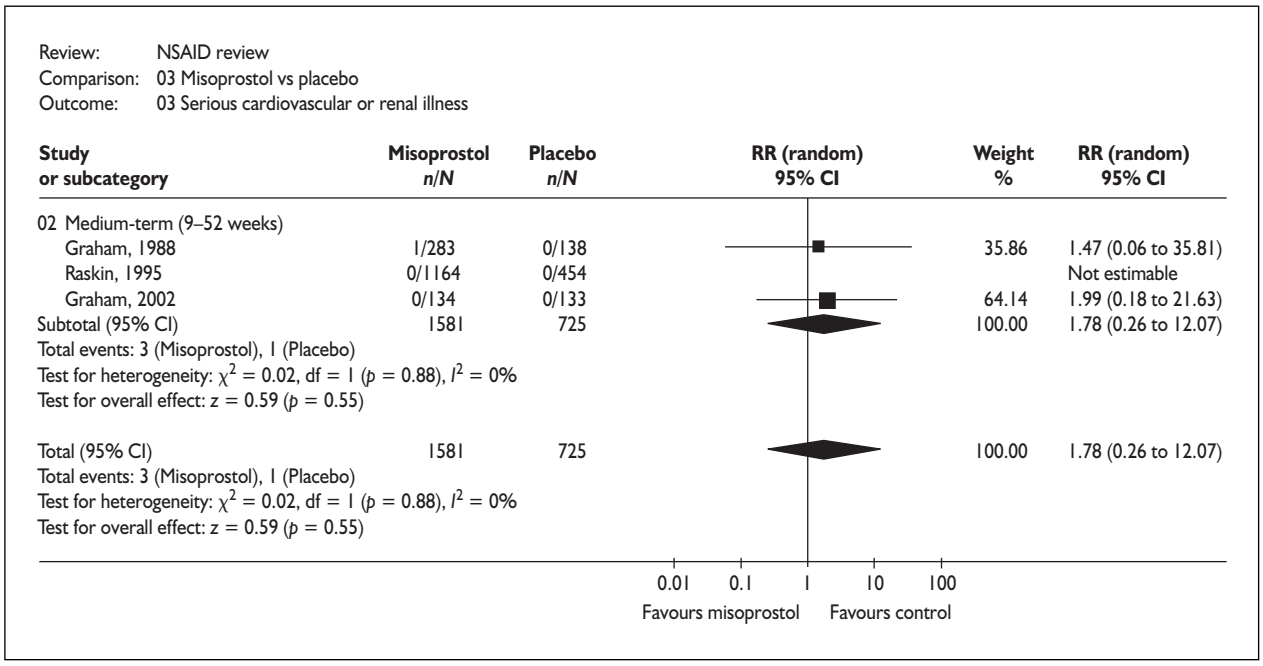

FIGURE 21 *Forest plot of misoprostol versus placebo, outcome serious cardiovascular or renal illness*

misoprostol in preventing endoscopic ulcers over time.

ARRs were calculated for the economic analysis (Appendix 9a). We attempted to subgroup ARRs for serious GI events, symptomatic ulcers and endoscopic ulcers by baseline GI status and by age. Statistical heterogeneity was clearer for ARRs than for RR and, although subgrouping tended to reduce heterogeneity, there were no further clear trends in the data.

Summary

This comparison included 23 studies (16,945 participants) comparing the long-term effects of misoprostol versus placebo in combination with

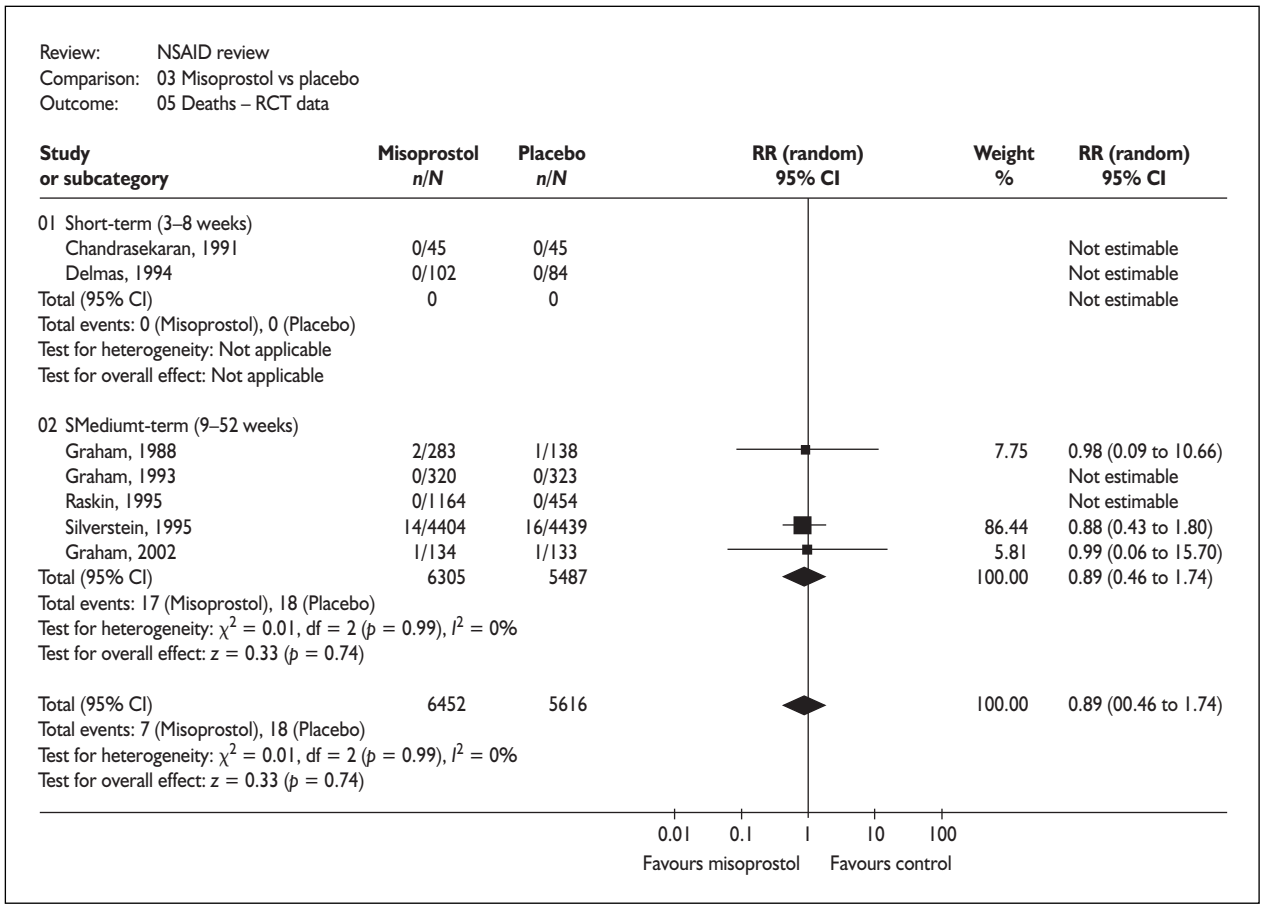

FIGURE 22 *Forest plot of misoprostol versus placebo, outcome deaths*

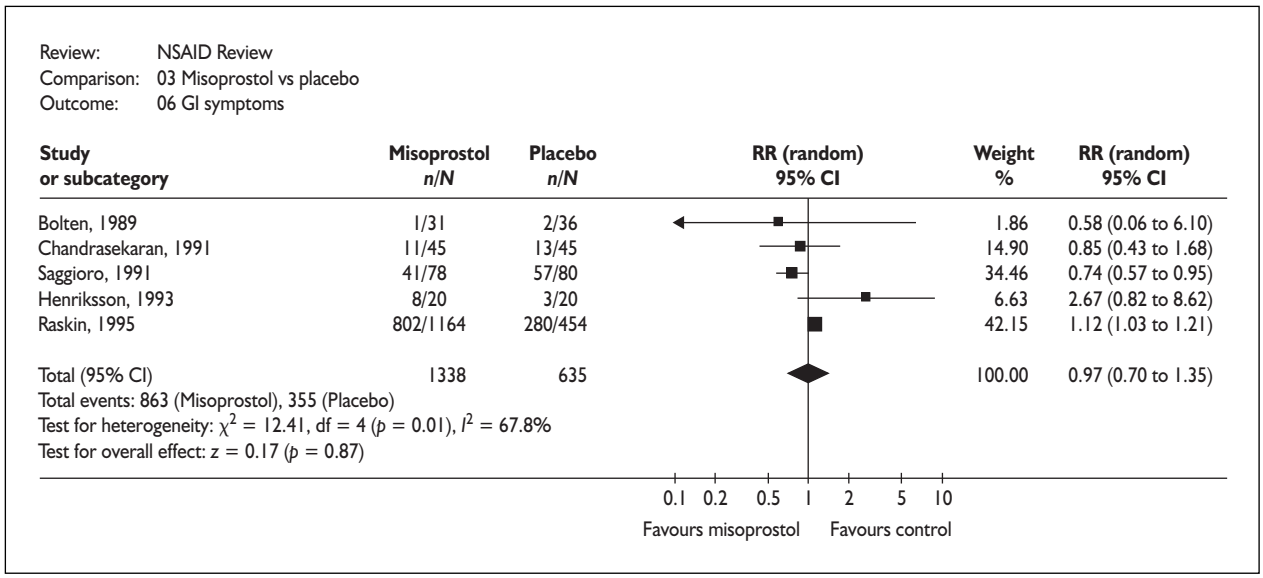

FIGURE 23 *Forest plot of misoprostol vs placebo, outcome gastrointestinal symptoms*

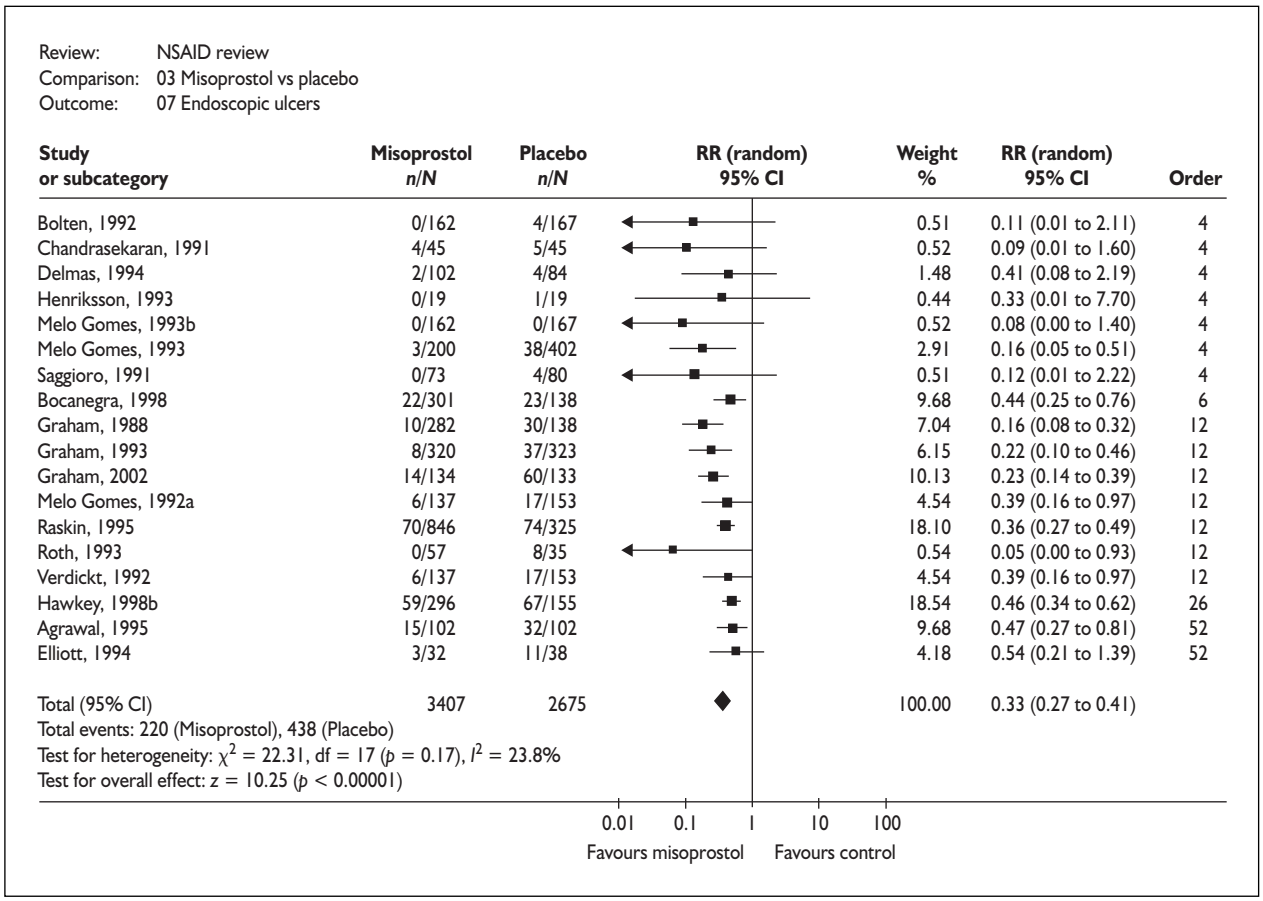

FIGURE 24 *Forest plot of misoprostol versus placebo, outcome endoscopic ulcers (ordered by study duration)*

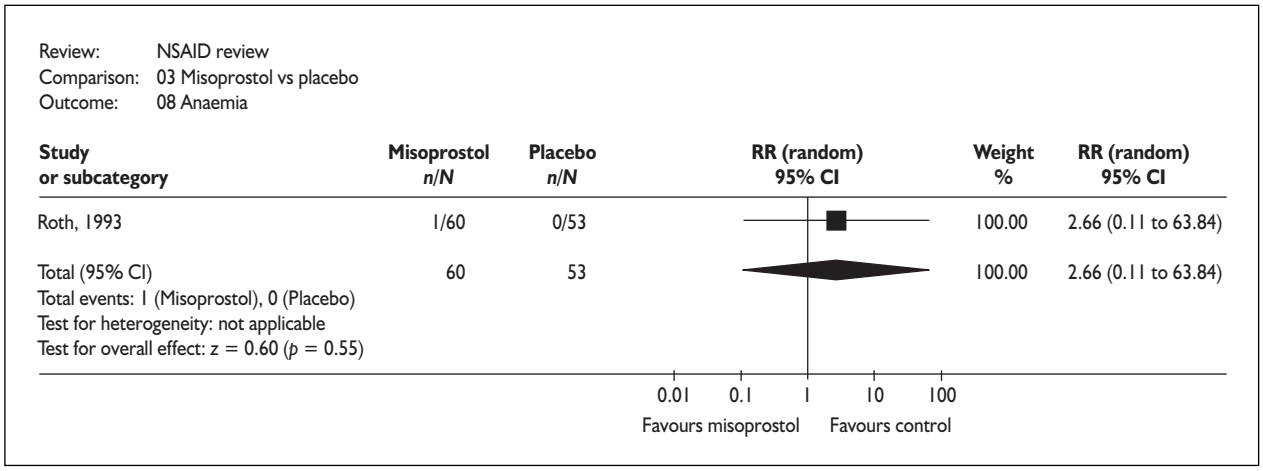

FIGURE 25 *Forest plot of misoprostol versus placebo, outcome anaemia*

NSAIDs. Participants were people with RA and OA, mean ages from 38 to 70 years, with normal GI status through to recently healed ulcers. Misoprostol doses were all within the current recommended range. Studies were from 4 to 52 weeks' duration.

One study was assessed as at 'low' risk of bias, 18 at 'moderate' risk and four at 'high' risk. Allocation concealment was adequate in one study and baseline characteristics were judged 'comparable' in 13. Eighteen studies reported funding by pharmaceutical companies. There was no suggestion of publication bias.

Misoprostol significantly reduced serious GI complaints, symptomatic ulcers and endoscopic ulcers (stable to sensitivity analysis and

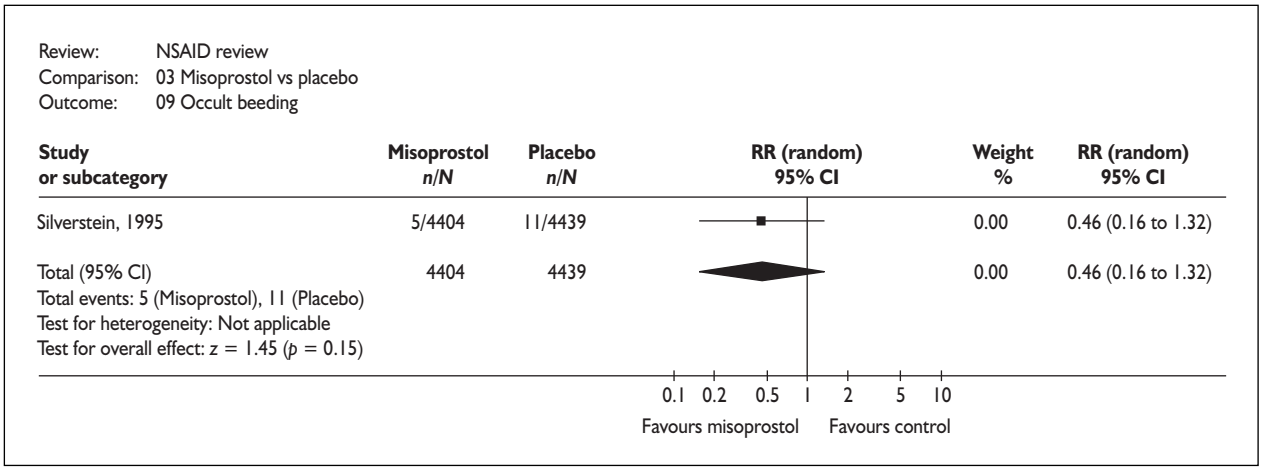

FIGURE 26 *Forest plot of misoprostol versus placebo, outcome occult bleeding*

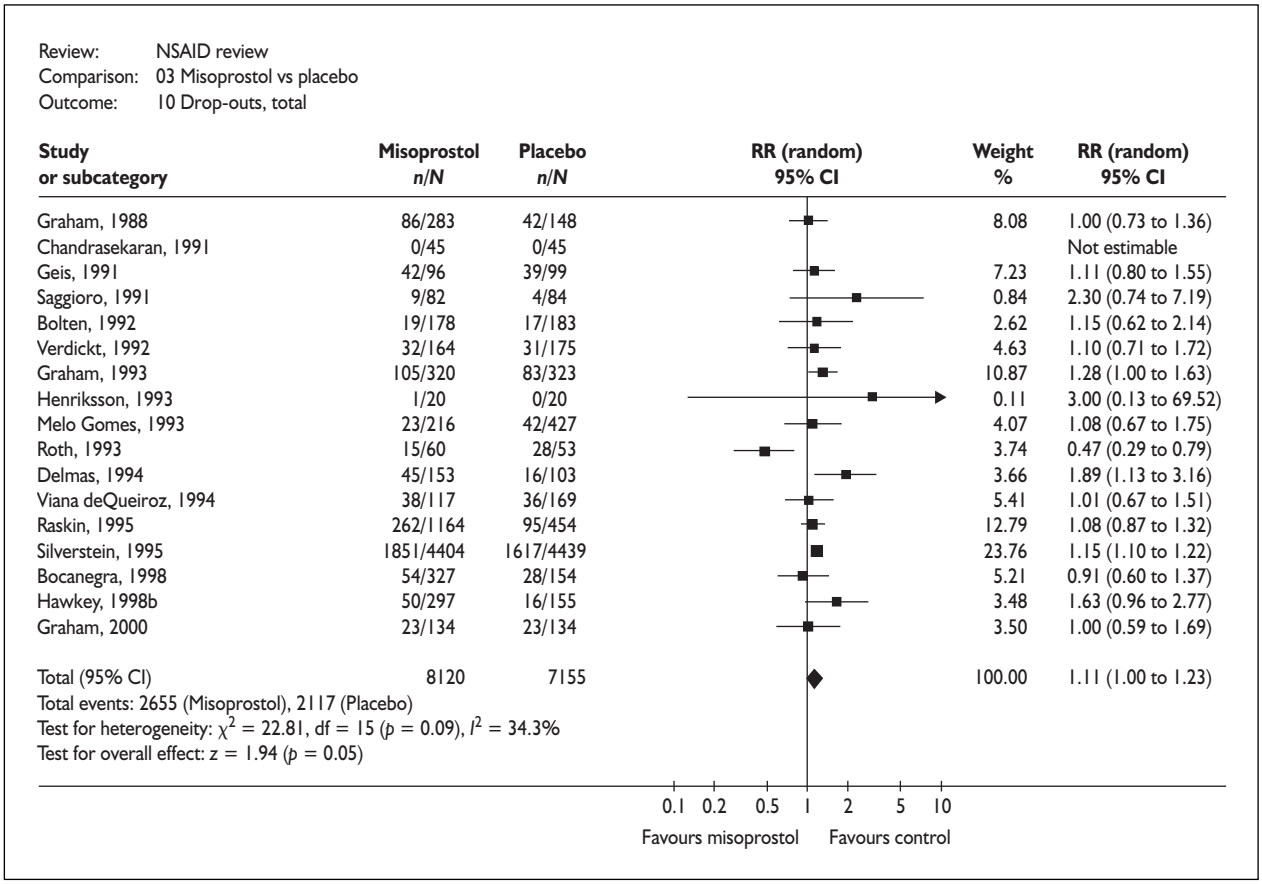

FIGURE 27 *Forest plot of Misoprostol versus placebo, outcome total drop-outs*

with no suggestion of heterogeneity). No significant effects of misoprostol on serious cardiovascular or renal illness, deaths, anaemia or occult bleeding were seen, but few events were recorded. GI symptoms were recorded in greater numbers, but with no significant difference between misoprostol or placebo arms. However, total drop-outs and drop-outs due to GI symptoms were significantly more frequent in misoprostol arms, suggesting that symptoms with misoprostol may have been of greater severity.

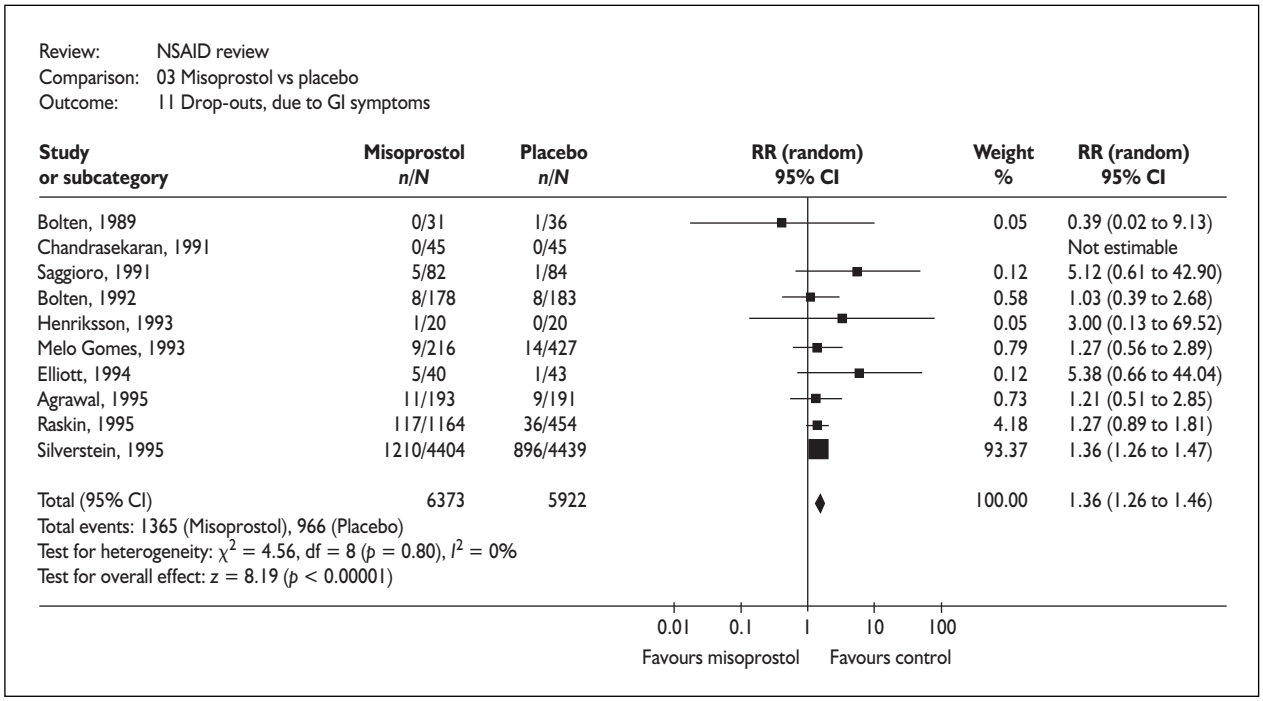

FIGURE 28 *Forest plot of misoprostol versus placebo, outcome drop-outs due to GI symptoms*

Chapter 8

Cox-2 coxib NSAID versus Cox-1 NSAID: systematic review – included studies, results, analysis and robustness

Included studies

Table 9 summarises the included studies. For a complete table of characteristics of included studies, see Appendix 6d.

Characteristics of studies

Seventeen RCTs were included in this comparison, involving 25,564 participants (73% women) randomised to arms relevant to this comparison. Studies varied in size from 170[93] to 8076 participants.[87]

Ten studies were conducted in more than one country, seven in multiple centres based in one country only. Studies were conducted in Europe, South America, North America, New Zealand, Australia and Africa. Publication dates were from 1999 to 2002. Outcome data were added for two studies, by Laine and colleagues[41] and Goldstein and colleagues,[39] following contact with the authors.

Participants

Eleven studies only included adults with OA, three studies only included adults with rheumatoid RA two studies included participants with both OA and RA[39,89] and one study only recruited participants with ankylosing spondylitis (AS).[93] Fifteen studies reported the duration of arthritis: range of study means from 7 to 11 years. The mean age of participants ranged from 38[93] to 64 years.[90]

Only six of the 17 studies reported performing an endoscopy at baseline and in all of these participants with an ulcer at baseline were excluded from the study. Of the 11 studies that did not report performing an endoscopy at baseline, six excluded participants with active peptic ulcer disease, three excluded those with active GI bleeding or faecal occult blood, one did not exclude anyone on the basis of GI status and one provided no details.

Interventions

Nine studies prescribed celecoxib, seven prescribed rofecoxib and one valdecoxib, often with several different dose arms:

- 200 mg celecoxib (six arms)
- 400 mg celecoxib (five arms)
- 800 mg celecoxib (two arms)[86,89]
- 12.5 mg rofecoxib (four arms)
- 25 mg rofecoxib (six arms)
- 50 mg rofecoxib (three arms)[41,87,91]
- 5 mg valdecoxib (one arm)
- 10 mg valdecoxib (one arm)
- 20 mg valdecoxib (one arm).

Two studies prescribed celecoxib and three studies prescribed rofecoxib at doses above the maximum recommended dose in at least one arm. Valdecoxib has no maximum recommended dose in the UK. The control arms were prescribed diclofenac (four studies), naproxen (six studies), ibuprofen (six studies) or ketoprofen (one study).

The duration of the trials ranged from 6 to 52 weeks. Six studies were short term (3–8 weeks' duration), nine studies were medium term (9–51 weeks) and two studies were long term (52 weeks or longer). Patient education was not mentioned in any study.

Study quality

The summary risk of bias was 'low' for three studies,[88–90] 'moderate' for 13 studies and 'high' for one study.[85]

Randomisation sequence was often described as computer generated, and details of stratification were often provided. Only three trials reported using a method of randomisation where allocation concealment could be assessed by the reviewers as 'adequate'.[88–91]

Baseline characteristics appeared comparable in 14 studies, unclear in two studies and did not appear comparable in one study.

In all included trials, participants were assessed as being blind to the intervention they received. In eight studies, outcome assessors' blinding was

TABLE 9 *Brief characteristics of Cox-2 coxib versus Cox-1 included studies*

Study	*N*	Participants	Interventions
Bensen, 1999[84] **Summary risk of bias:** moderate	**Allocated:** a 198, b 197, c 202	**Baseline GI status:** oesophageal or gastroduodenal ulceration within 30 days prior to start of study were excluded, endoscopy not performed **Type of arthritis:** OA	**Comparison:** celecoxib (b, c) vs naproxen (a) **Duration:** 12 weeks
Emery, 1999[85] **Summary risk of bias:** high	**Allocated:** a 329, b 326	**Baseline GI status:** active or suspected peptic ulceration or GI bleeding excluded but no baseline endoscopy **Type of arthritis:** RA	**Comparison:** celecoxib (b) vs diclofenac SR (a) **Duration:** 24 weeks
Laine, 1999[41] **Summary risk of bias:** moderate	**Allocated:** a 183, b 195, c 186	**Baseline GI status:** without active duodenal, gastric or oesophageal ulcers, pyloric obstruction or erosive oesophagitis on baseline endoscopy **Type of arthritis:** OA	**Comparison:** rofecoxib (b, c) vs ibuprofen (a) **Duration:** 24 weeks
Simon, 1999[86] **Summary risk of bias:** moderate	**Allocated:** a 225, b 240, c 235, d 218	**Baseline GI status:** baseline endoscopy performed and excluded patients with oesophageal, gastric or duodenal ulcer or more than 10 erosions **Type of arthritis:** RA	**Comparison:** celecoxib (b, c, d) vs naproxen **Duration:** 12 weeks
Bombardier, 2000[87] **Summary risk of bias:** moderate	**Allocated:** a 4029, b 4047	**Baseline GI status:** excluded if had positive test for faecal occult blood at baseline, endoscopy not performed **Type of arthritis:** RA	**Comparison:** rofecoxib (b) vs naproxen (a) **Duration:** median 9 months
Cannon, 2000[88] **Summary risk of bias:** low	**Allocated:** a 268, b 259, c 257	**Baseline GI status:** no baseline endoscopy, GI status not assessed, people with history of gastroduodenal ulcer or GI bleeding were allowed to participate **Type of arthritis:** OA	**Comparison:** rofecoxib (b, c) vs diclofenac (a) **Duration:** 52 weeks
CLASS, 2000[89] **Summary risk of bias:** low	**Allocated:** a 2009 b 2019, c 4031	**Baseline GI status:** baseline endoscopy performed and patients excluded if had oesophageal, gastric, pyloric channel or duodenal ulcer **Type of arthritis:** OA/RA	**Comparison:** celecoxib (c) vs diclofenac (b) vs ibuprofen (a) **Duration:** 26–65 weeks
Day, 2000[90] **Summary risk of bias:** low	**Allocated:** a 249, b 244, c 242	**Baseline GI status:** no baseline endoscopy **Type of arthritis:** OA	**Comparison:** rofecoxib (b, c) vs ibuprofen (a) **Duration:** 6 weeks
Hawkey, 2000[91] **Summary risk of bias:** moderate	**Allocated:** a 193, b 195, c 193	**Baseline GI status:** baseline endoscopy performed and participants excluded if pyloric obstruction, erosive oesophagitis or oesophageal, gastric or duodenal ulcers; participants with gastroduodenal erosions were permitted to enter trial **Type of arthritis:** OA	**Comparison:** rofecoxib (b, c) vs ibuprofen (a) **Duration:** 16–24 weeks
Saag, 2000A[92] **Summary risk of bias:** moderate	**Allocated:** a 230, b 231, c 232	**Baseline GI status:** no baseline endoscopy performed, patients excluded if had evidence of active GI bleeding **Type of arthritis:** OA	**Comparison:** rofecoxib (b, c) vs ibuprofen (a) **Duration:** 6 weeks

continued

TABLE 9 *Brief characteristics of Cox-2 coxib versus Cox-1 included studies (cont'd)*

Study	*N*	Participants	Interventions
Saag 2000B[92] **Summary risk of bias:** moderate	**Allocated:** a 221, b 219, c 227	**Baseline GI status:** no baseline endoscopy performed, patients excluded if had evidence of active GI bleeding **Type of arthritis:** OA	**Comparison:** rofecoxib (b, c) vs ibuprofen (a) **Duration:** 6 weeks
Dougados, 2001[93] **Summary risk of bias:** moderate	**Allocated:** A 90, b 80	**Baseline GI status:** no baseline endoscopy was performed but participants were excluded if had ulcer in previous year **Type of arthritis:** AS	**Comparison:** celecoxib (b) vs ketoprofen (a) **Duration:** 6 weeks
Goldstein, 2001[39] **Summary risk of bias:** moderate	**Allocated:** a 267, b 270	**Baseline GI status**: baseline endoscopy performed and excluded participants with ulcers **Type of arthritis:** OA and RA	**Comparison:** celecoxib (b) vs naproxen (a) **Duration:** 12 weeks
Kivitz, 2001[94] **Summary risk of bias:** moderate	**Allocated:** a 207, b 207, c 213	**Baseline GI status:** no baseline endoscopy performed, patients excluded if they had been diagnosed with or treated for oesophageal/gastroduodenal ulceration within 30 days of receiving the study drug **Type of arthritis:** OA	**Comparison:** celecoxib (b, c) vs naproxen (a) **Duration:** 12 weeks
McKenna, 2001[95] **Summary risk of bias:** moderate	**Allocated:** a 199, b 201	**Baseline GI status:** no baseline endoscopy performed, excluded if had active GI disease **Type of arthritis:** OA	**Comparison:** celecoxib (b) vs diclofenac (a) **Duration:** 6 weeks
Kivitz, 2002[96] **Summary risk of bias:** moderate	**Allocated:** a 205, b 201, c 206, d 202	**Baseline GI status:** baseline endoscopy performed and excluded participants with 10 or more oesophageal, gastric or duodenal erosions or oesophageal, gastric, pyloric channel or duodenal ulcer **Type of arthritis:** OA	**Comparison:** valdecoxib (b, c, d) vs naproxen (a) **Duration:** 12 weeks
McKenna, 2002[97] **Summary risk of bias:** moderate	**Allocated:** unclear (completed: a ?309, b ?320)	**Baseline GI status:** no baseline endoscopy performed, but peptic ulceration and GI bleeding excluded **Type of arthritis:** OA	**Comparison:** celecoxib (b) vs diclofenac (a) **Duration:** 6 weeks

'unclear'. In nine, the authors reported explicitly that the outcome assessors were blinded. *A priori* sample size calculations were performed in 15 studies and not mentioned in the remaining two.

Five studies analysed their primary outcome data using the ITT principle. Eight studies did not, as they excluded participants from analysis, and in four studies it was unclear. A method for assessment of compliance was reported in seven studies. Results of compliance assessment were reported in four studies.

Pharmaceutical companies were named as funders of 14 trials, and in the remaining three studies there was a suggestion of funding by a pharmaceutical company (at least one author was employed by a pharmaceutical company).

Publication bias

There were enough included studies (12) with data on symptomatic ulcers to use these trials for assessment of publication bias. The funnel plot was not assessable for publication bias, nor were analyses using tests by Egger and colleagues[35] ($p = 0.90$) or Begg and Mazumdar[36] ($p > 0.99$) (see Appendix 7d).

Results

Results are summarised in *Table 10* and forest plots are shown in *Figures 29–39*.

Primary outcomes

Information on serious GI events was provided by 11 studies (of which one reported a total absence

TABLE 10 *Cox-2 coxib versus Cox-1 meta-analysis (MA) and sensitivity analysis (SA) results*

Outcome	Analysis	No. of included RCTs	No. of participants	No. of events	RR (random effects)	95% CI	Heterogeneity *p*-value
Serious GI events	MA	11	21454	114	0.55	0.38 to 0.80	0.75
	SA quality	10	20799	113	0.56	0.38 to 0.81	0.67
	SA dosage	9	4824	13	0.39	0.14 to 1.04	0.97
Symptomatic ulcers	MA	11	21722	281	0.49	0.38 to 0.62	0.78
	SA quality	10	21067	280	0.49	0.38 to 0.62	0.70
	SA dosage	9	5274	39	0.44	0.24 to 0.81	0.82
Serious CV or renal events	MA	8	19295	241	1.19	0.80 to 1.75	0.27
	SA quality	8	19295	241	1.19	0.80 to 1.75	0.27
	SA dosage	6	3251	43	1.03	0.50 to 2.12	0.34
	SA naproxen	6	10680	197	1.00	0.76 to 1.32	0.56
QoL	MA	1	No usable data				
Deaths	MA	6	18113	78	1.02	0.55 to 1.92	0.26
	SA quality	6	18113	78	1.02	0.55 to 1.92	0.26
	SA dosage	4	2069	6	0.37	0.03 to 3.96	0.17
	SA naproxen	4	9498	41	0.68	0.10 to 4.64	0.10
GI symptoms	MA	9	12738	5184	0.81	0.74 to 0.89	0.10
	SA quality	8	12083	4907	0.82	0.75 to 0.90	0.17
	SA dosage	8	4552	1294	0.78	0.71 to 0.85	0.67
Endoscopic ulcers	MA	6	3343	522	0.25	0.21 to 0.30	0.66
	SA quality	5	2913	481	0.25	0.21 to 0.30	0.52
	SA dosage	6	2853	465	0.23	0.19 to 0.28	0.62
Anaemia	MA	4	9191	464	0.62	0.51 to 0.74	0.54
	SA quality	3	8536	463	0.61	0.48 to 0.78	0.36
	SA dosage	3	1223	10	0.22	0.05 to 1.01	0.84
Occult bleed	MA	0					
Total drop-outs	MA	16	24967	9510	0.82	0.73 to 0.92	<0.001
	SA quality	15	24312	9348	0.83	0.74 to 0.93	<0.001
	SA dosage	14	8235	2315	0.79	0.67 to 0.93	<0.001
Drop-outs due to GI symptoms	MA	14	23506	2171	0.69	0.57 to 0.83	0.02
	SA quality	13	22851	2102	0.74	0.63 to 0.87	0.12
	SA dosage	12	7244	338	0.64	0.46 to 0.89	0.03

NR, not relevant (e.g. tests of heterogeneity when only one study is included in the analysis).

of serious GI events). Serious GI events were seen in 114 of 21,454 participants (0.5%). The RR of developing a serious GI event was 0.55 (95% CI 0.38 to 0.80) in the Cox-2 coxibs compared with those on Cox-1 NSAIDs, with no suggestion of heterogeneity ($p = 0.75$). SA (excluding the studies or arms with a high summary risk of bias) did not materially alter the size or significance of the effect, but removing studies with higher than recommended drug doses left few events and the significance of the effect was lost.

Symptomatic ulcers were reported in 281 of the 21,722 participants (1.3%) in 11 studies. The RR of developing a symptomatic ulcer was 0.49 (95% CI 0.38 to 0.62) in those on Cox-2 (coxibs) compared with a Cox-1 NSAID, with no suggestion of heterogeneity ($p = 0.78$). SAs did not materially alter the size or significance of the effect.

Serious cardiovascular or renal illness was reported in 241 of the 19,295 participants in eight

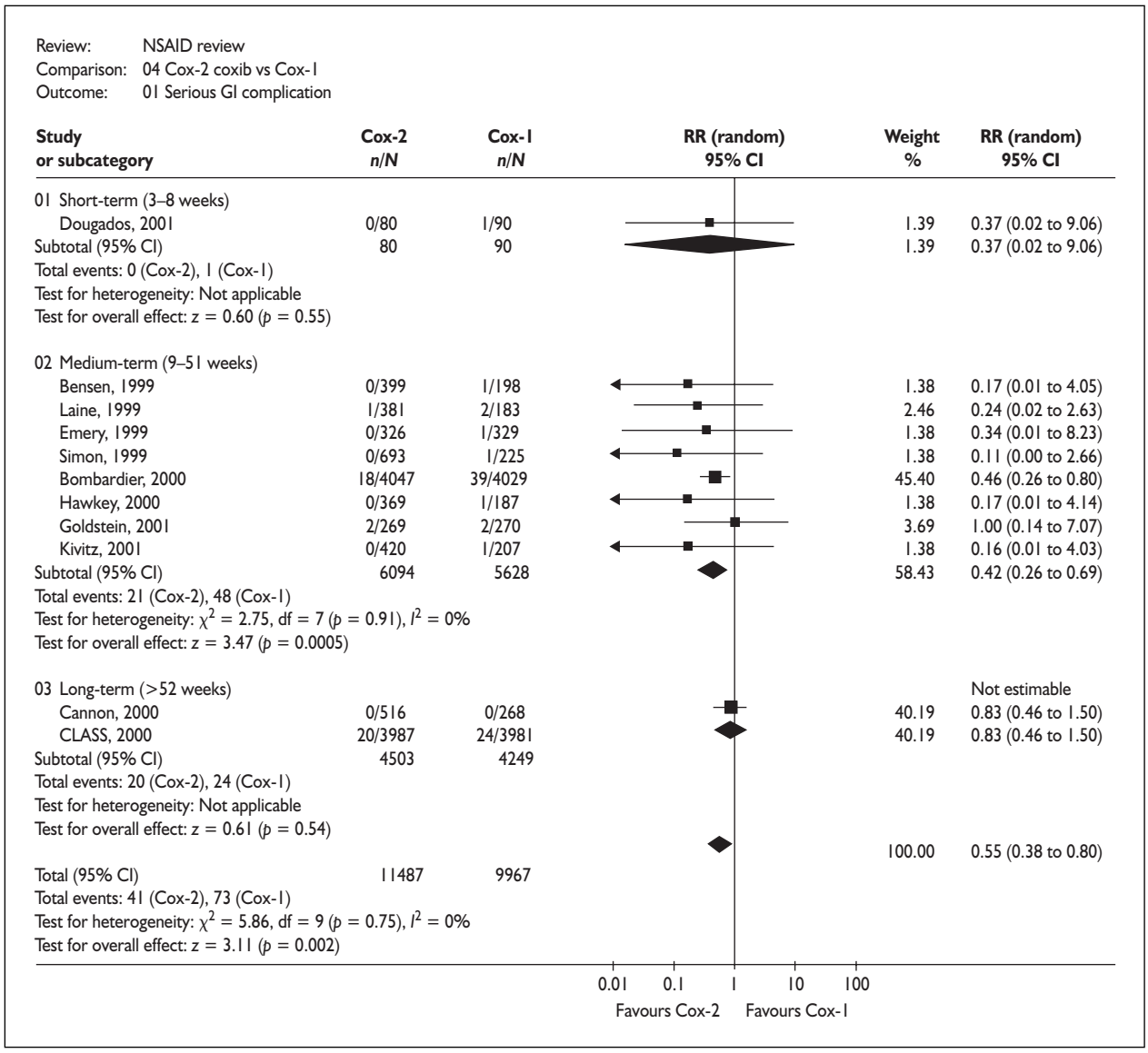

FIGURE 29 *Forest plot of Cox-2 coxib NSAID versus Cox-1 NSAID, outcome serious GI complications*

studies. The RR of developing a serious cardiovascular or renal illness in participants prescribed Cox-2 (coxibs) compared with Cox-1 drugs was 1.19 (95% CI 0.80 to 1.75), with no evidence of heterogeneity ($p = 0.27$). No SA (including removal of studies where the Cox-1 used was naproxen) materially altered the results.

One study provided data on QoL, but without standard deviations. See Appendix 10b for further details.

Deaths due to any cause were reported in six trials (one of which reported no). There were 78 deaths in 18,113 (0.4%) participants. Deaths occurred with equal frequency in the Cox-2 groups and the Cox-1 groups (RR 1.02, 95% CI 0.55 to 1.92), with no evidence of heterogeneity, ($p = 0.26$). No SA materially altered the results.

Secondary outcomes

GI symptoms were reported by 5184 of 12,738 participants (41%) in nine studies. The RR of developing GI symptoms was 0.81 (95% CI 0.74 to 0.89) in the Cox-2 (coxibs) compared with those on Cox-1 NSAIDs, with borderline heterogeneity ($p = 0.10$). The RR remained significant and the heterogeneity reduced with both SAs.

Endoscopic ulcers occurred in 522 of 3343 participants in six studies. The RR of developing an endoscopic ulcer was 0.25 (95% CI 0.21 to 0.30) in the Cox-2 (coxibs) groups compared with the Cox-1 groups, with no evidence of

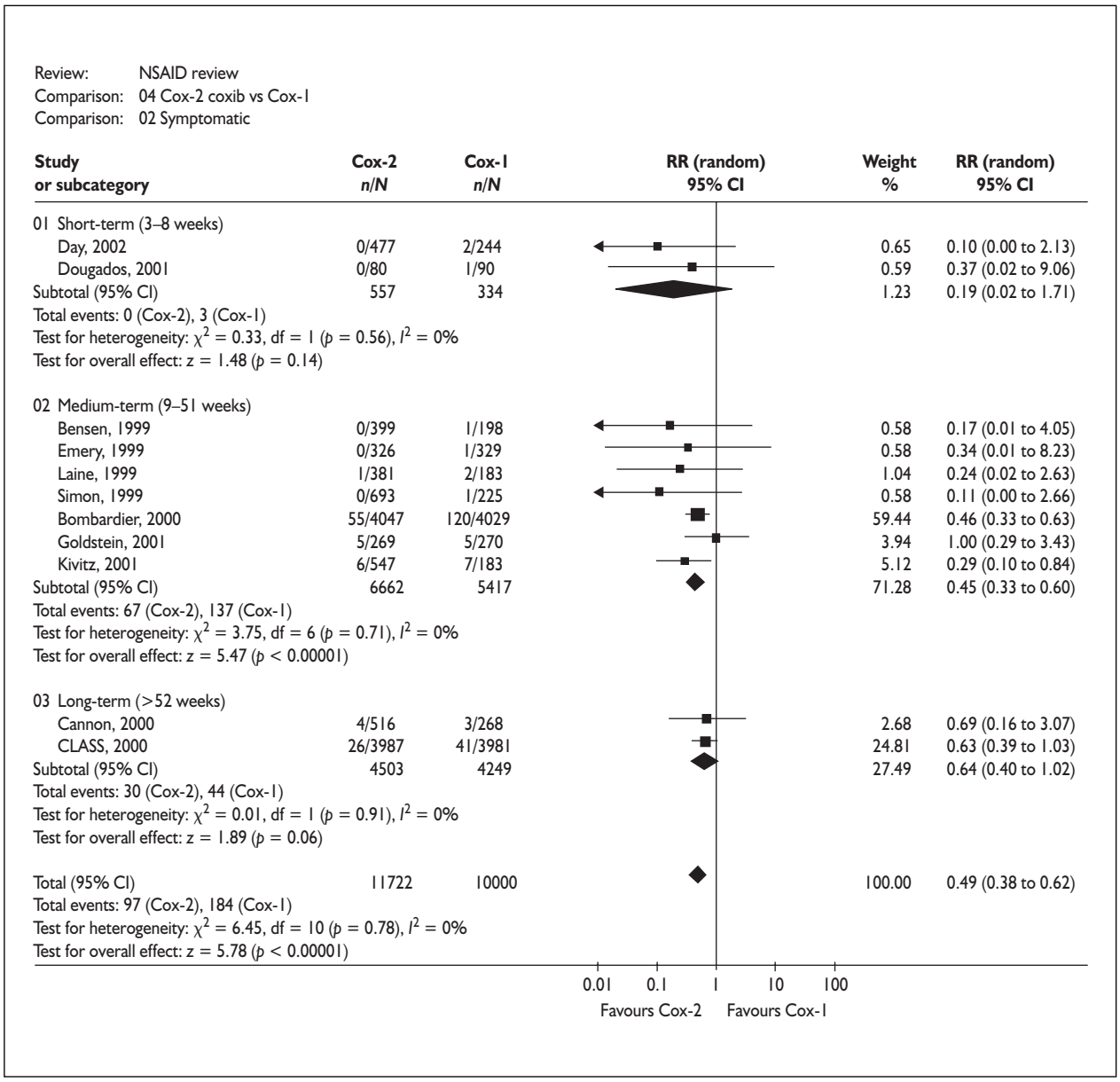

FIGURE 30 *Forest plot of Cox-2 coxib NSAID versus Cox-1 NSAID, outcome symptomatic ulcers*

heterogeneity ($p = 0.66$). SA did not alter the size or significance of this relationship.

Anaemia was reported in 464 of the 9191 participants in four studies. The RR of developing anaemia was 0.62 (95% CI 0.51 to 0.74) in the Cox-2 groups compared with the Cox-1 groups, with no evidence of heterogeneity ($p = 0.54$). SA, removing studies at high risk of bias, did not alter the results of the meta-analysis, but removing arms with a high dose of NSAIDs removed most events and significance was lost.

Occult bleeding was not reported in any study.

Total drop-outs were calculable or reported in 16 studies; 9510 of 24,967 participants dropped out before the end of a trial (38%). The RR of dropping out was 0.82 (95% CI 0.73 to 0.92) in the Cox-2 (coxibs) group compared with the Cox-1 group, with significant heterogeneity ($p < 0.0001$). Heterogeneity did not alter as a result of SAs.

Drop-outs due to GI symptoms were reported in 14 studies in 2171 of 23,506 participants (9%). The RR of dropping out due to GI symptoms was 0.69 (95% CI 0.57 to 0.83) in the Cox-2 group compared with the Cox-1 group, but there was

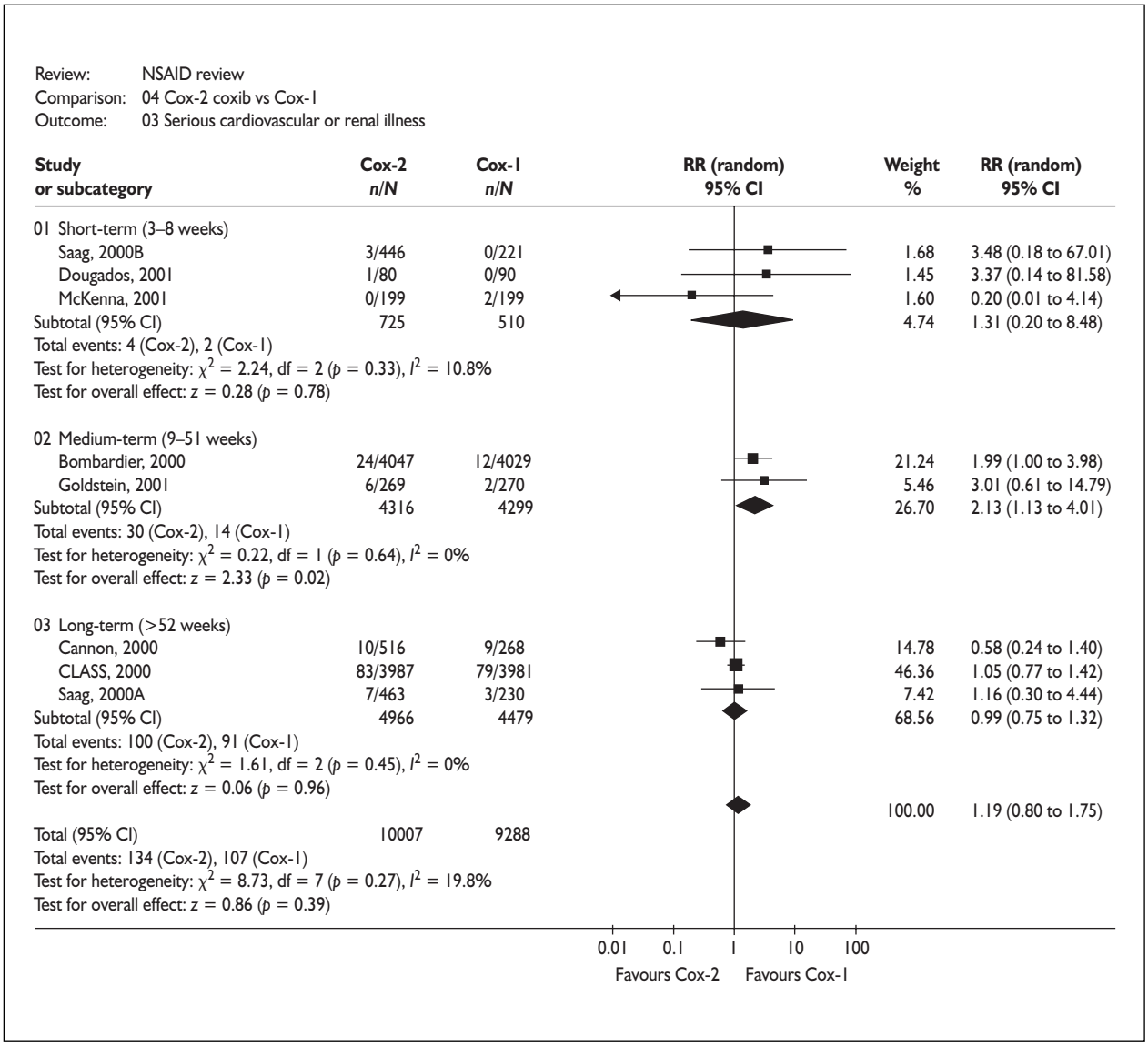

FIGURE 31 *Forest plot of Cox-2 coxib NSAID versus Cox-1 NSAID, outcome serious cardiovascular or renal illness*

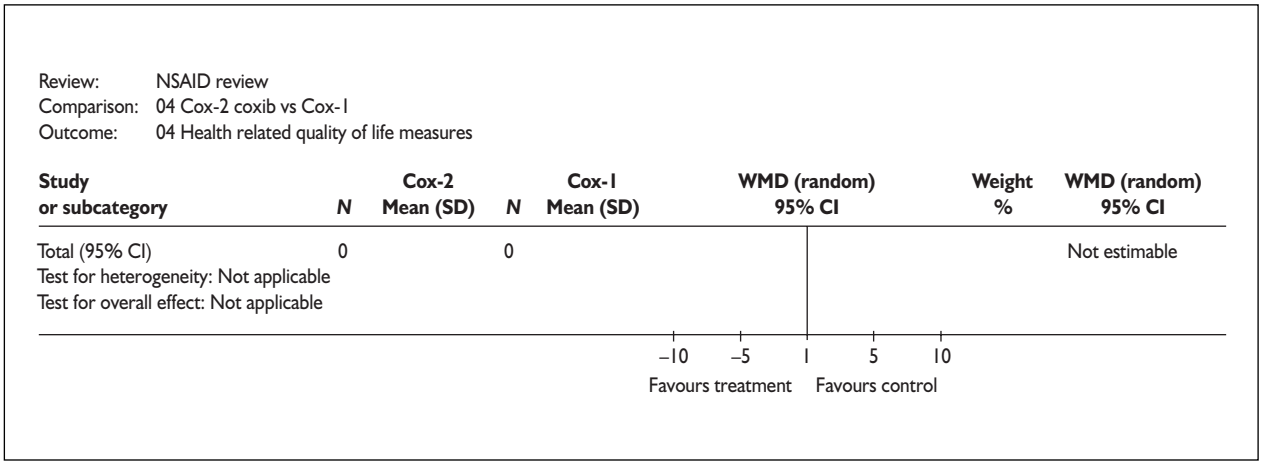

FIGURE 32 *Forest plot of Cox-2 coxib NSAID versus Cox-1 NSAID, outcome quality of life*

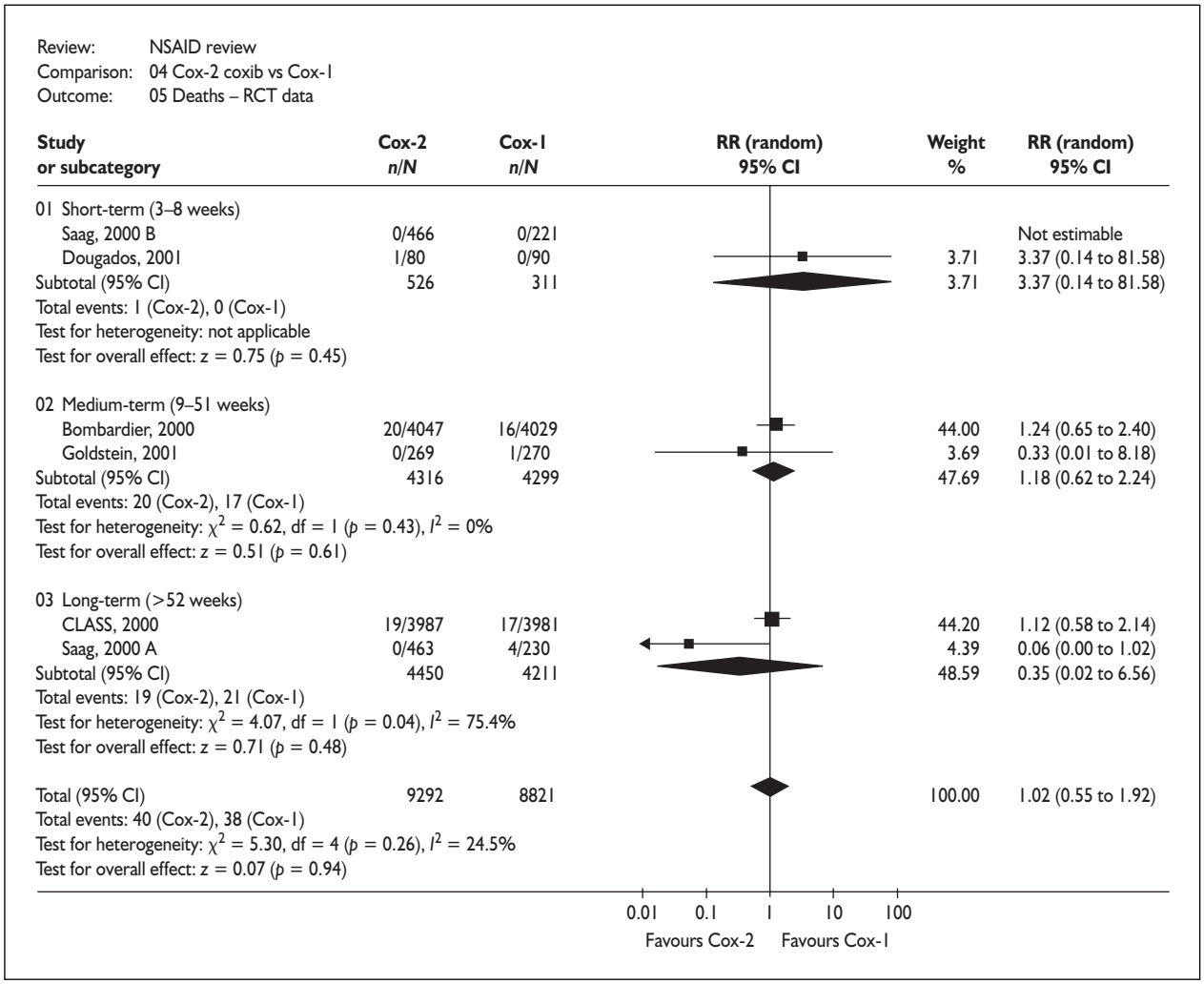

FIGURE 33 *Forest plot of Cox-2 coxib NSAID versus Cox-1 NSAID, outcome deaths*

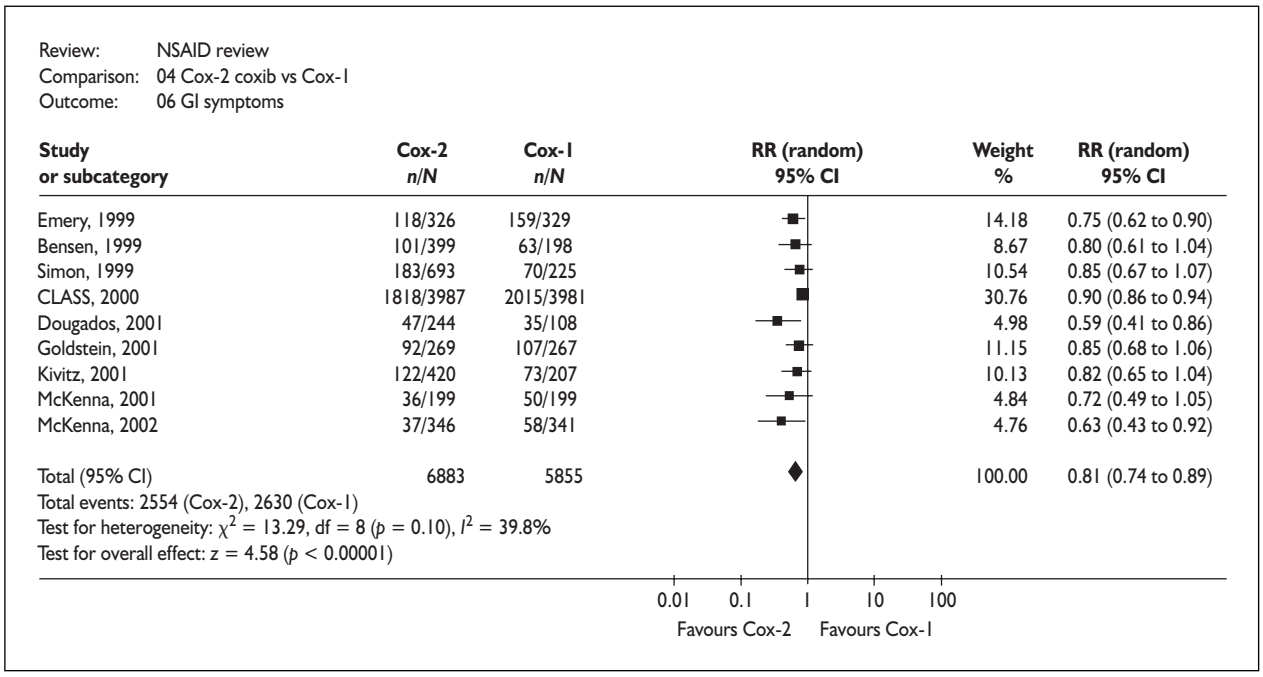

FIGURE 34 *Forest plot of Cox-2 coxib NSAID versus Cox-1 NSAID, outcome GI symptoms*

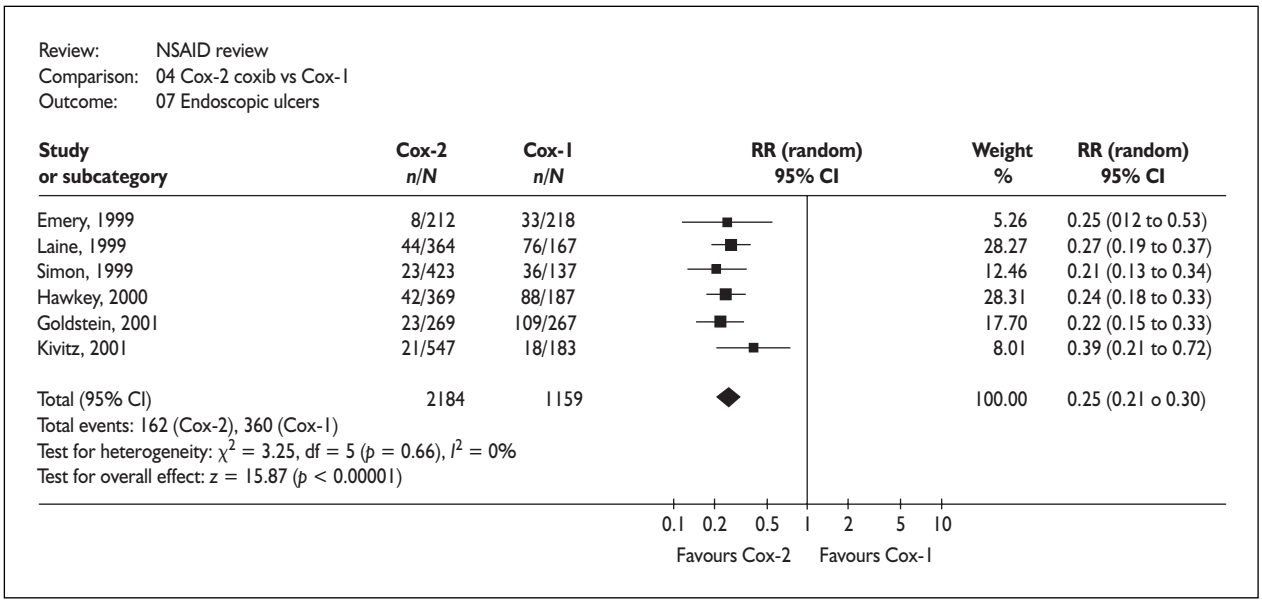

FIGURE 35 *Forest plot of Cox-2 coxib NSAID versus Cox-1 NSAID, outcome endoscopic ulcers*

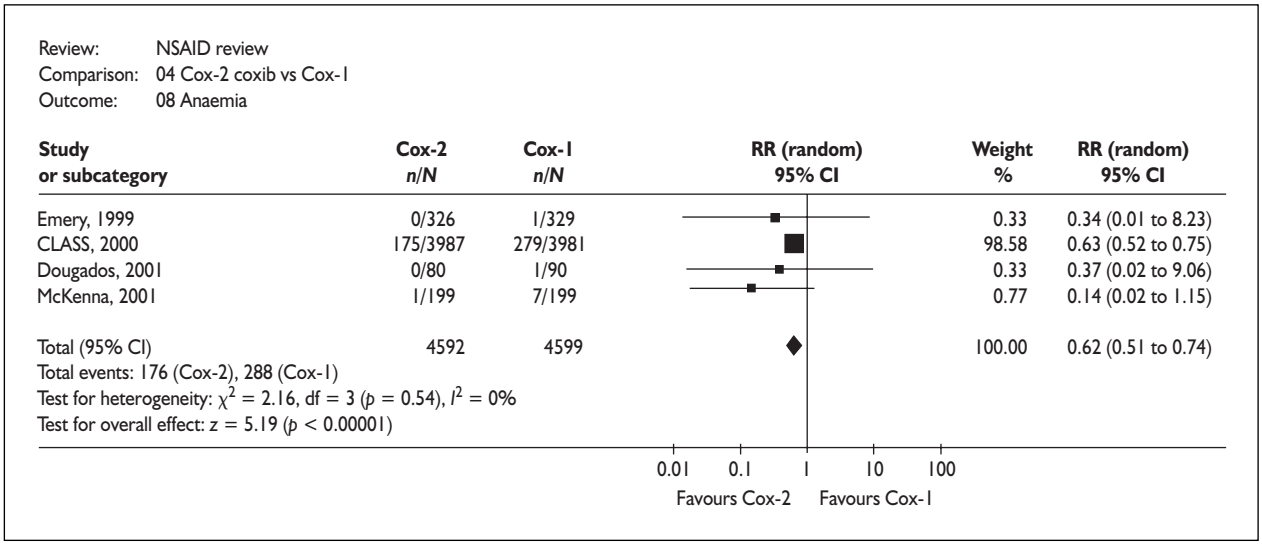

FIGURE 36 *Forest plot of Cox-2 coxib NSAID versus Cox-1 NSAID, outcome anaemia*

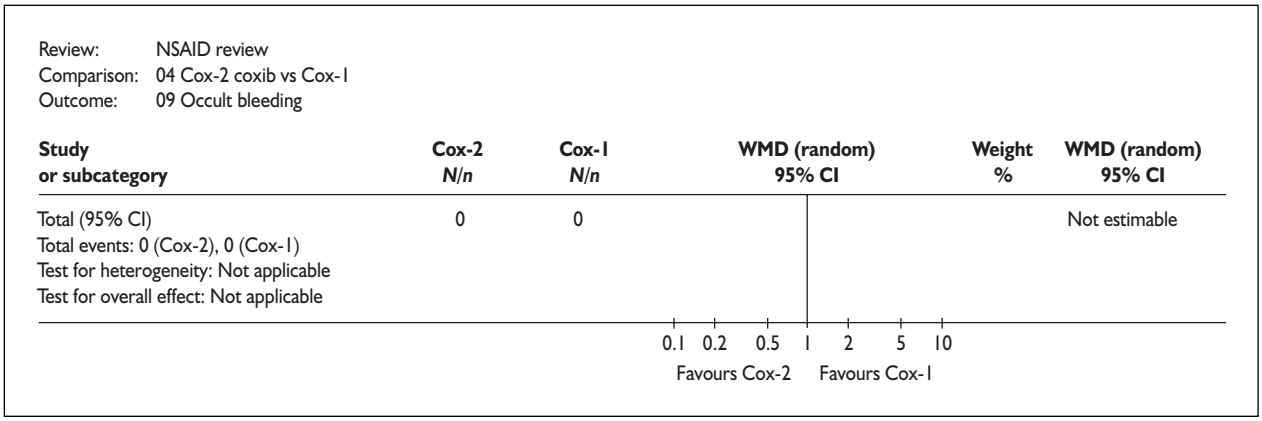

FIGURE 37 *Forest plot of Cox-2 coxib NSAID versus Cox-1 NSAID, outcome occult bleeding*

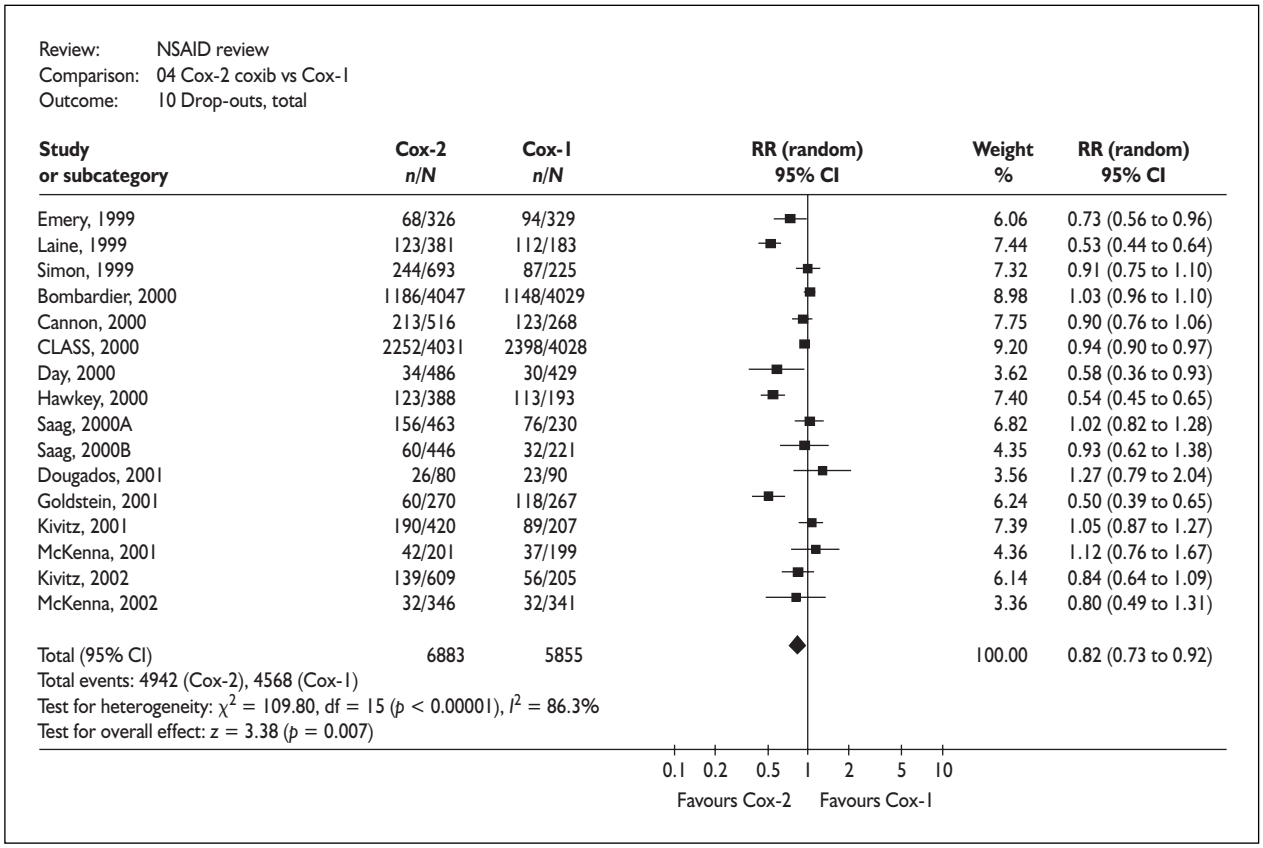

FIGURE 38 *Forest plot of Cox-2 coxib NSAID versus Cox-1 NSAID, outcome total drop-outs*

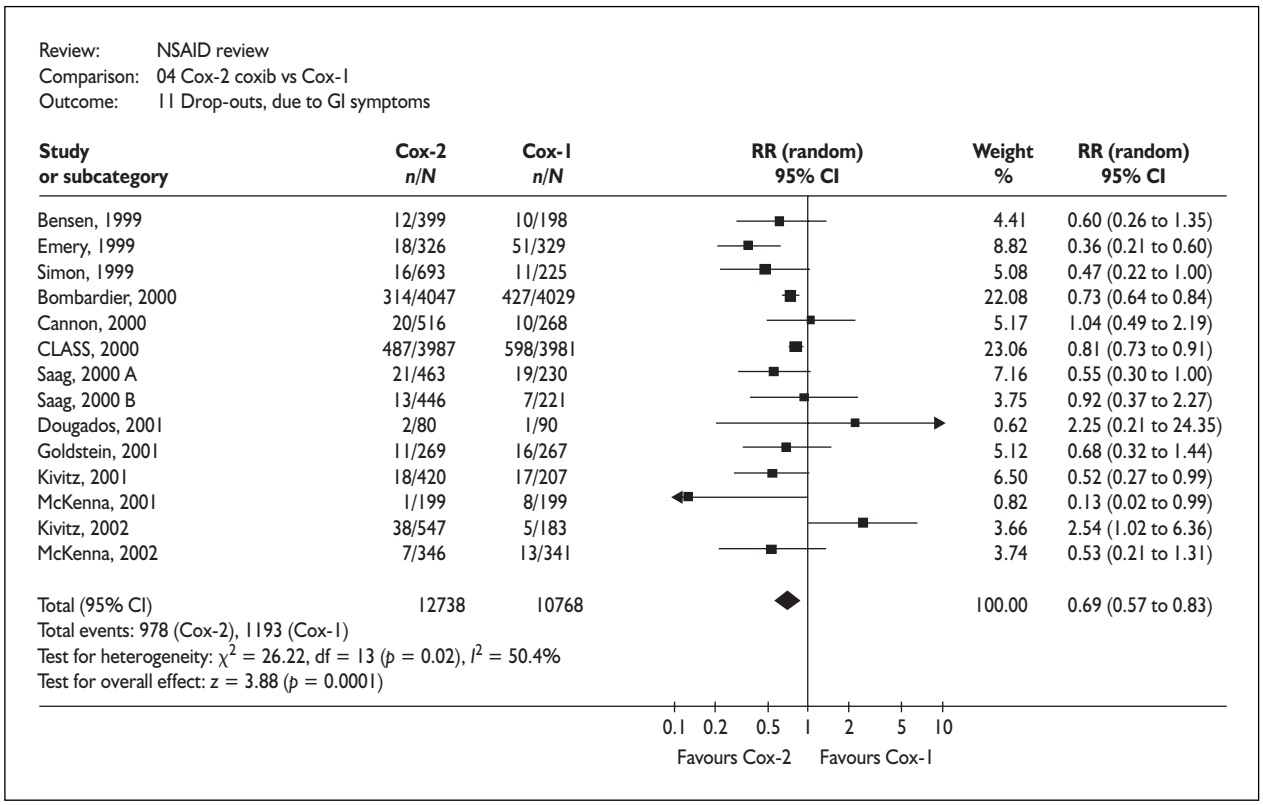

FIGURE 39 *Forest plot of Cox-2 coxib NSAID versus Cox-1 NSAID, outcome drop-outs due to GI symptoms*

statistical heterogeneity ($p = 0.02$). Heterogeneity was reduced (becoming insignificant) with SA removing studies at high risk of bias, but not with arms at high dosages.

Meta-regressions and subgrouping

Subgrouping by study duration was carried out for all primary analyses (see figures). For serious GI complications and symptomatic ulcers, the short-term studies gave the highest estimate of the relative efficacy of Cox-2 (coxibs) versus Cox 1s. However, the differences were not large. The medium-term data also gave a significant RR (0.42) (95% CI 0.26 to 0.69) (*Figure 29*) but the long-term data did not (RR 0.83, 95% CI 0.46 to 1.50). The same pattern was seen with symptomatic ulcers.

Meta-regressions were carried out to explore the relationship between ln RR of symptomatic ulcers and study duration, baseline GI status (quantified by the percentage of participants with a history of ulcers or bleeds) and mean age at baseline. No statistically significant relationships were seen. See Appendix 8 for further details.

ARRs were calculated for the economic analysis (Appendix 9a). We attempted to subgroup ARRs for serious GI events, symptomatic ulcers and endoscopic ulcers by baseline GI status and by age. However, the only studies which provided usable data were in baseline GI risk category 2 (some participants normal, others have some erosions and/or haemorrhages on endoscopy, but no frank ulcers). All studies had a mean age of less than 65 years, so no meaningful subgrouping was possible. See Appendix 9b for further details.

Summary

Seventeen RCTs were included in this comparison. Studies usually included participants with either OA or RA, not both. Mean ages ranged from 38 to 64 years. Baseline GI status was unclear in many studies as baseline endoscopies were usually not performed. Five study arms provided Cox-2 coxibs at doses above the current recommended levels. Study duration ranged from 3 to over 52 weeks.

The summary risk of bias was calculated as being 'low' in three studies, 'moderate' in 13 studies and 'high' in one study. Only three studies had 'adequate' allocation concealment and 14 studies were judged as having comparable baseline characteristics. Pharmaceutical funding was used in all 17 studies. Publication bias was not apparent.

The development of serious GI complications and symptomatic ulcers appeared to be significantly reduced in participants randomised to take Cox-2 coxib drugs compared with Cox-1 drugs. These results were generally robust to SA and without apparent heterogeneity. Serious cardiovascular or renal illness and total deaths were not significantly different between Cox-2 coxibs and Cox-1 groups. There were no usable data to allow conclusions to be drawn regarding QoL.

Total GI symptoms, endoscopic ulcers and anaemia were significantly less common in participants randomised to receive Cox-2 coxib drugs compared with Cox-1 drugs, and these results were stable to SA. Total drop-outs and drop-outs due to GI symptoms also appeared to be significantly less in the Cox-2 groups. However, there was evidence of heterogeneity in these analyses. No studies reported data on occult bleeding.

Chapter 9

Cox-2 preferential NSAID versus Cox-1 NSAID: systematic review – included studies, results, analysis and robustness

Included studies

Table 11 summarises the included studies. For a complete table of characteristics of included studies, see Appendix 6e.

Characteristics of studies

Fifty-one RCTs were included in this comparison, randomising 28,178 participants (65% women) to arms relevant to this comparison. Studies varied in size from 10 participants per arm[107,116] to 5051 per arm.[40]

Nineteen studies were conducted in more than one country, 12 studies were multicentre studies conducted in single countries and 20 studies were carried out in a single centre. Seventeen studies included at least some participants in the UK. Studies were conducted in Europe, South America, North America, New Zealand, Australia, Africa and Asia.

Publication dates were from 1989 to 2002. Six studies were interim reports where no further report was published and three studies required translation into English.[107,116,122] Authors of five studies provided additional information on outcomes when contacted.[37,38,40,42,44]

Participants

Thirty-eight studies included only adults with OA and nine studies included only adults with RA. Two studies included participants with 'degenerative joint disease', one study included participants with both OA and RA and one study only recruited participants with AS.[132]

Only 19 of the 51 studies reported duration of arthritis. One study only recruited patients with OA for less than 1 year.[131] The maximum mean duration of arthritis (actually AS) reported in any arm was 12 years.[132]

The mean age of participants ranged from 38[132] to 72 years.[98] The majority reported a mean age in the 50s or 60s (mean age not stated in three studies).

Only five studies reported performing an endoscopy at baseline. In two of these, people were excluded if they had active GI ulcers. In two studies, people were excluded if they had erosions or ulcers and, in the last, if they had three or more erosions or any ulcers. In the studies where endoscopy was not reported, 11 studies excluded participants with active GI ulcers, 16 excluded people with active ulcers or bleeds or a history of ulcers or bleeds (over varying time spans), one excluded people only if they had a history of GI bleeds and one excluded on the basis of 'serious symptomatic disease'. The remaining 17 studies did not provide details.

Interventions

Twenty-five studies assessed etodolac, 11 studies nimesulide, 14 studies meloxicam and one study nabumetone with arms of the following doses:

- 600 mg etodolac (22 arms)
- 800 mg etodolac (2 arm[120,127])
- 1000 mg etodolac (1 arm[129])
- 200 mg nimesulide (11 arms)
- 7.5 mg meloxicam (7 arms)
- 15 mg meloxicam (8 arms)
- 7.5 or 15 mg meloxicam (1 arm)
- 22.5 mg meloxicam (2 arms[138,139])
- 1000 mg nabumetone (1 arm).

Five studies prescribed Cox-2 preferential NSAIDs at doses above those recommended in at least one arm. Nimesulide has no set maximum dose in the UK. The control arms were prescribed the following Cox-1 NSAIDs; piroxicam (18 studies), diclofenac (16 studies), naproxen (11 studies), ibuprofen (two studies), tenoxicam (two studies), indomethacin and ketoprofen (one study each).

The duration of the trials ranged from 3 weeks[114,119,122] to 3 years.[129] Thirty-nine studies were short term (3–8 weeks), nine medium term (9–51 weeks) and three long term (52 weeks or longer).

Patient education was not mentioned in any study.

TABLE 11 *Brief characteristics of Cox-2 preferentials versus Cox-1 included studies*

Study	*N*	Participants	Interventions
Fossaluzza, 1989[98] **Summary risk of bias:** moderate	**Allocated:** a 20, b 20	**Baseline GI status:** no baseline endoscopy but those with active peptic ulcer were excluded **Type of arthritis:** OA	**Comparison:** nimesulide (b) vs naproxen (a) **Duration:** 28 days
Platt, 1989A[99] **Summary risk of bias:** moderate	**Allocated:** a 47, b 38	**Baseline GI status:** no baseline endoscopy but those with peptic ulcer disease or history of GI bleed in the last 5 years were excluded **Type of arthritis:** OA	**Comparison:** etodolac (b) vs diclofenac (a) **Duration:** 8 weeks
Platt, 1989B[99] **Summary risk of bias:** moderate	**Allocated:** a 19, b 18	**Baseline GI status:** no baseline endoscopy but those with peptic ulcer disease or history of GI bleed in the last 5 years were excluded **Type of arthritis:** OA	**Comparison:** etodolac (b) vs naproxen (a) **Duration:** 6 weeks
Platt, 1989C[99] **Summary risk of bias:** moderate	**Allocated:** a 77, b 80	**Baseline GI status:** no baseline endoscopy but those with peptic ulcer disease or history of GI bleed in the last 5 years were excluded **Type of arthritis:** OA	**Comparison:** etodolac (b) vs piroxicam (a) **Duration:** 12 weeks
Freitas, 1990[100] **Summary risk of bias:** moderate	**Allocated:** a 32, b 33	**Baseline GI status:** no baseline endoscopy, no further details **Type of arthritis:** OA	**Comparison:** etodolac (b) vs piroxicam (a) **Duration:** 8 weeks
Taha, 1990[101] **Summary risk of bias:** high	**Allocated:** 32 in total	**Baseline GI status:** baseline endoscopy performed and definite or presumptive peptic ulceration excluded **Type of arthritis:** RA	**Comparison:** etodolac (b) vs naproxen (a) **Duration:** 4 weeks
Astorga Paulsen, 1991[102] **Summary risk of bias:** moderate	**Allocated:** a 108, b 112	**Baseline GI status:** no baseline endoscopy, no further details **Type of arthritis:** OA	**Comparison:** etodolac (b) vs piroxicam (a) **Duration:** 8 weeks
Braseur, 1991[103] **Summary risk of bias:** moderate	**Allocated:** a 29, b 32	**Baseline GI status:** no baseline endoscopy, no further details **Type of arthritis:** OA	**Comparison:** etodolac (b) vs diclofenac SR (a) **Duration:** 6 weeks
Karbowski, 1991[104] **Summary risk of bias:** moderate	**Allocated:** a 33, b 31	**Baseline GI status:** no baseline endoscopy, no further details **Type of arthritis:** OA	**Comparison:** etodolac (b) vs indomethacin (a) **Duration:** 6 weeks
Palferman, 1991[105] **Summary risk of bias:** moderate	**Allocated:** a 27, b 29	**Baseline GI status:** no baseline endoscopy but excluded if GI bleeding or peptic ulcer disease **Type of arthritis:** OA	**Comparison:** etodolac (b) vs naproxen (a) **Duration:** 6 weeks
Pena, 1991[106] **Summary risk of bias:** moderate	**Allocated:** a 31, b 31	**Baseline GI status:** no baseline endoscopy, no further details **Type of arthritis:** OA	**Comparison:** etodolac (b) vs naproxen (a) **Duration:** 8 weeks
Perpignano, 1991[107] **Summary risk of bias:** high	**Allocated:** a 10, b 10	**Baseline GI status:** baseline endoscopy performed and patients without erosions (or worse) were included **Type of arthritis:** OA	**Comparison:** etodolac (b) vs naproxen (a) **Duration:** 4 weeks

continued

TABLE 11 *Brief characteristics of Cox-2 Preferentials vs Cox-1 included studies (cont'd)*

Study	*N*	Participants	Interventions
Dick, 1992[108] **Summary risk of bias:** high	**Allocated:** a 59, b 57	**Baseline GI status:** no baseline endoscopy but excluded serious symptomatic disease **Type of arthritis:** degenerative joint disease	**Comparison:** etodolac (b) vs piroxicam (a) **Duration:** 6 weeks
Grisanti, 1992[109] **Summary risk of bias:** moderate	**Allocated:** a 87, b 85	**Baseline GI status:** no baseline endoscopy but excluded patients with a history of peptic ulcer disease or GI bleed in the last 5 years **Type of arthritis:** OA	**Comparison:** etodolac (b) vs diclofenac (a) **Duration:** 8 weeks
Jubb, 1992[110] **Summary risk of bias:** moderate	**Allocated:** a 25, b 24	**Baseline GI status:** no baseline endoscopy but excluded history of gastric ulcer or haemorrhage **Type of arthritis:** RA	**Comparison:** etodolac SR (b) vs piroxicam (a) **Duration:** 4 weeks
Khan, 1992[111] **Summary risk of bias:** moderate	**Allocated:** a ?32, b ?32	**Baseline GI status:** no baseline endoscopy but excluded patients with active peptic ulcer or haemorrhage **Type of arthritis:** degenerative joint disease	**Comparison:** etodolac SR (b) vs diclofenac SR (a) **Duration:** 4 weeks
Waterworth, 1992[112] **Summary risk of bias:** high	**Allocated:** a 29, b 28	**Baseline GI status:** no baseline endoscopy but excluded patients with definite peptic ulcer disease in the last 5 years **Type of arthritis:** OA	**Comparison:** etodolac (b) vs piroxicam (a) **Duration:** 6 weeks
Burssens, 1993[113] **Summary risk of bias:** high	**Allocated:** a 36, b 37	**Baseline GI status:** no baseline endoscopy but excluded patients with history of active peptic ulcer and GI haemorrhage **Type of arthritis:** OA	**Comparison:** etodolac SR (b) vs tenoxicam (a) **Duration:** 4 weeks
Dreiser, 1993A[114] **Summary risk of bias:** high	**Allocated:** a 30, b 29	**Baseline GI status:** no baseline endoscopy but excluded patients with active ulcer **Type of arthritis:** OA	**Comparison:** nimesulide (b) vs piroxicam (a) **Duration:** 3 weeks
Dreiser, 1993B[114] **Summary risk of bias:** high	**Allocated:** a ?27, b ?28	**Baseline GI status:** no baseline endoscopy but excluded patients with active ulcer **Type of arthritis:** OA	**Comparison:** nimesulide (b) vs ketoprofen (a) **Duration:** 8 weeks
Eisenkolb, 1993[115] **Summary risk of bias:** high	**Allocated:** a 69, b 66	**Baseline GI status:** no baseline endoscopy, no further details **Type of arthritis:** OA	**Comparison:** etodolac (b) vs diclofenac (a) **Duration:** 6 weeks
Estevez, 1993[116] **Summary risk of bias:** high	**Allocated:** a 10, b 10	**Baseline GI status:** no baseline endoscopy, no further details **Type of arthritis:** OA	**Comparison:** nimesulide (b) vs diclofenac (a) **Duration:** 12 weeks
Porzio, 1993[117] **Summary risk of bias:** high	**Allocated:** a 41, b 50	**Baseline GI status:** no baseline endoscopy but excluded patients with active peptic ulcer, history of GI ulcer or haemorrhage **Type of arthritis:** RA	**Comparison:** etodolac SR (b) vs diclofenac SR (a) **Duration:** 4 weeks
Roth, 1993[78] **Summary risk of bias:** High	**Allocated:** a 58, b 53	**Baseline GI status:** no more than 3 erosions at baseline endoscopy Normal endoscopy: a 17, b 18 Hyperaemia: a 24, b 20 3 or less erosion: a 17, b 15 **Type of arthritis:** OA	**Comparison:** ibuprofen (b) vs nabumetone (a) **Duration:** 12 weeks

continued

TABLE 11 *Brief characteristics of Cox-2 Preferentials vs Cox-1 included studies (cont'd)*

Study	*N*	Participants	Interventions
Perpignano, 1994[118] **Summary risk of bias:** moderate	**Allocated:** a 60, b 60	**Baseline GI status:** no baseline endoscopy but excluded patients with active peptic ulcer, history of GI ulcer or haemorrhage either associated with NSAID use or in the last 3 years **Type of arthritis:** OA	**Comparison:** etodolac SR (b) vs tenoxicam (a) **Duration:** 8 weeks
Carrabba, 1995[119] **Summary risk of bias:** moderate	**Allocated:** a 109, b 216	**Baseline GI status:** no baseline endoscopy, participants excluded if evidence of active peptic ulcer in previous 6 months **Type of arthritis:** OA	**Comparison:** meloxicam suppositories (b) vs piroxicam suppositories (a) **Duration:** 3 weeks
Dore, 1995[120] **Summary risk of bias:** moderate	**Allocated:** a 82, b 86	**Baseline GI status:** no baseline endoscopy but excluded patients with history of GI bleed **Type of arthritis:** OA	**Comparison:** etodolac (b) vs naproxen (a) **Duration:** 4 weeks
Quattrini, 1995[121] **Summary risk of bias:** moderate	**Allocated:** a 60, b 60	**Baseline GI status:** no baseline endoscopy performed, but history of peptic ulceration or GI bleeding in previous 12 months excluded **Type of arthritis:** OA	**Comparison:** nimesulide (b) vs naproxen (a) **Duration:** 4 weeks
Degner, 1996[122] [abstract] **Summary risk of bias:** moderate	**Allocated:** a 135, b 141	**Baseline GI status:** no baseline endoscopy, no further details **Type of arthritis:** RA	**Comparison:** meloxicam (b) vs piroxicam (a) **Duration:** 3 weeks
Hosie, 1996[123] **Summary risk of bias:** high	**Allocated:** a 167, b 169	**Baseline GI status:** no baseline endoscopy performed, patients excluded if evidence of active peptic ulceration in previous 6 months **Type of arthritis:** RA	**Comparison:** meloxicam (b) vs eiclofenac sodium SR (a) **Duration:** 6 months
Linden, 1996[42] **Summary risk of bias:** moderate	**Allocated:** a 127, b 129	**Baseline GI status:** no baseline endoscopy performed **Type of arthritis:** OA	**Comparison:** meloxicam (b) vs piroxicam (a) **Duration:** 6 weeks
Wojtulewski, 1996[124] **Summary risk of bias:** moderate	**Allocated:** a 180, b 199	**Baseline GI status:** participants excluded with clinical evidence of peptic ulceration **Type of arthritis:** RA	**Comparison:** meloxicam (b) vs naproxen (a) **Duration:** 26 weeks
Goei The, 1997[125] **Summary risk of bias:** moderate	**Allocated:** a 130, b 128	**Baseline GI status:** no baseline endoscopy **Type of arthritis:** OA	**Comparison:** meloxicam (b) vs diclofenac SR (a) **Duration:** 6 weeks
Hosie, 1997[126] **Summary risk of bias:** moderate	**Allocated:** a 149, b 306	**Baseline GI status:** no baseline endoscopy but patients excluded if had clinical evidence of peptic ulceration during the last 6 months **Type of arthritis:** OA	**Comparison:** meloxicam (b) vs piroxicam (a) **Duration:** 6 weeks
Jennings, 1997[127] **Summary risk of bias:** high	**Allocated:** a 31, b 29	**Baseline GI status:** no baseline endoscopy but excluded patients with stomach ulcer **Type of arthritis:** OA of the foot	**Comparison:** etodolac (b) vs naproxen (a) **Duration:** 5 weeks
Lightfoot, 1997[128] **Summary risk of bias:** moderate	**Allocated:** a 139, b 147	**Baseline GI status:** no baseline endoscopy performed, no further details **Type of arthritis:** RA	**Comparison:** etodolac (b) vs piroxicam (a) **Duration:** 12 weeks

continued

TABLE 11 *Brief characteristics of Cox-2 Preferentials vs Cox-1 included studies (cont'd)*

Study	*N*	Participants	Interventions
Neustadt, 1997[129] **Summary risk of bias:** moderate	**Allocated:** a 417, b 409	**Baseline GI status:** no baseline endoscopy performed, no further details **Type of arthritis:** RA	**Comparison:** etodolac (b) vs Ibuprofen (a) **Duration:** 3 years
Rogind, 1997[130] **Summary risk of bias:** moderate	**Allocated:** a 133, b 138	**Baseline GI status:** no baseline endoscopy but excluded patients with history of GI bleed or peptic ulcer disease **Type of arthritis:** OA	**Comparison:** etodolac (b) vs piroxicam(a) **Duration:** 8 weeks
Dequeker, 1998[38] **Summary risk of bias:** moderate	**Allocated:** a 4641, b 4645	**Baseline GI status:** participants with active peptic ulcer were excluded but no baseline endoscopy **Type of arthritis:** OA	**Comparison:** meloxicam (b) vs piroxicam (a) **Duration:** 28 days
Hawkey, 1998[40] MELISSA **Summary risk of bias:** moderate	**Allocated:** a 5051, b 5000	**Baseline GI status:** participants with active peptic ulcer were excluded but no baseline endoscopy was performed **Type of arthritis:** OA	**Comparison:** meloxicam (b) vs diclofenac (a) **Duration:** 28 days
Porto, 1998[131] **Summary risk of bias:** moderate	**Allocated:** a 45, b 44	**Baseline GI status:** patients only included in study if baseline endoscopy showed normal mucosa or 10 petechiae or less **Type of arthritis:** OA	**Comparison:** nimesulide (b) vs diclofenac (a) **Duration:** 30 days
Dougados, 1999[132] **Summary risk of bias:** moderate	**Allocated:** a 108, b 120, c 124	**Baseline GI status:** no baseline endoscopy **Type of arthritis:** AS	**Comparison:** meloxicam (b, c) vs piroxicam (a) **Duration:** 52 weeks
Huskisson, 1999[133] **Summary risk of bias:** moderate	**Allocated:** a 144, b 135	**Baseline GI status:** no baseline endoscopy performed, patients excluded if history or symptoms of gastric or duodenal ulcer **Type of arthritis:** OA	**Comparison:** nimesulide (b) vs diclofenac (a) **Duration:** 24 weeks
Roy, 1999[134] **Summary risk of bias:** high	**Allocated:** a 49, b 41	**Baseline GI status:** no baseline endoscopy performed, but active peptic ulcer excluded **Type of arthritis:** OA	**Comparison:** nimesulide (b) vs piroxicam (a) **Duration:** 8 weeks
Sharma, 1999[44] **Summary risk of bias:** high	**Allocated:** a 40, b 25	**Baseline GI status:** no baseline endoscopy performed **Type of arthritis:** OA	**Comparison:** nimesulide (b) vs piroxicam (a) **Duration:** 8 weeks
Zgradie, 1999[135] **Summary risk of bias:** moderate	**Allocated:** a 90, b 90	**Baseline GI status:** no baseline endoscopy **Type of arthritis:** OA	**Comparison:** nimesulide (b) vs diclofenac sodium (a) **Duration:** 4 weeks
Patel, 2000[136] **Summary risk of bias:** high	**Allocated:** unclear (assessed: a 66, b 61)	**Baseline GI status:** no baseline endoscopy performed, no further details **Type of arthritis:** RA: a 16, b 15. OA: a 24, b 22	**Comparison:** meloxicam (b) vs diclofenac substudy CR (a) **Duration:** 28 days
Yocum, 2000[137] **Summary risk of bias:** high	**Allocated:** a 153, b 154, c 156 (5 participants missing from 5 arms)	**Baseline GI status:** participants excluded if UGI perforations, ulcers or peptic ulcer bleeding in 6 months prior to enrolment **Type of arthritis:** OA	**Comparison:** meloxicam (b, c) vs diclofenac (a) **Duration:** 12 weeks

continued

TABLE 11 *Brief characteristics of Cox-2 Preferentials vs Cox-1 included studies (cont'd)*

Study	*N*	Participants	Interventions
Chang, 2001[37] **Summary risk of bias:** moderate	**Allocated:** a 36, b 36	**Baseline GI status:** baseline endoscopy performed and excluded participants with peptic ulcers **Type of arthritis:** OA	**Comparison:** meloxicam (b) vs piroxicam (a) **Duration:** 4 weeks
Kriegel, 2001[138] **Summary risk of bias:** moderate	**Allocated:** a 187, b 183	**Baseline GI status:** no baseline endoscopy performed, but active GI disease excluded **Type of arthritis:** OA	**Comparison:** nimesulide (b) vs naproxen (a) **Duration:** 52 weeks
Furst, 2002[139] **Summary risk of bias:** moderate	**Allocated:** a 181, b 175, c 184, d 177	**Baseline GI status:** no baseline endoscopy **Type of arthritis:** RA	**Comparison:** meloxicam (b, c, d) vs diclofenac (a) **Duration:** 12 weeks

Study quality

The summary risk of bias was 'low' for none of the studies, 'moderate' for 34 studies and 'high' for 17 studies.

Twelve studies reported some detail about randomisation (more than the word 'randomised' or 'randomly allocated'). Three trials reported using 'sealed envelopes'.[38,40,42]

Only two trials reported using a method of randomisation where allocation concealment was assessed by the reviewers as 'adequate'. One study reported that "the code for each medication package was supplied in a sealed envelope and opened at the end of the trial"[121] and one that computer allocation was centralised and used centralised personnel.[37]

Baseline characteristics appeared comparable in 10 studies, unclear in 23 and not comparable in 18. Studies were assessed as 'unclear' because insufficient information was provided regarding age, sex and type and duration of arthritis.

Forty-four trials reported using a 'double-blind' method or 'double-dummy' technique for medication prescribing and so, in these trials, participants were assessed as being blind to the intervention they received. Another six trials failed to report if participants had been blinded to the treatment and so blinding of participants was assessed as 'unclear' in these trials. Participants in one trial were not blinded to treatment. The authors explicitly reported that the meloxicam and piroxicam suppositories prescribed to the participants "differed in shape and colour and may have been recognised by some patients".[119]

In 43 studies which were labelled by the trialists as 'double-blind', but did not provide any further information, it was not clear whether the outcome assessors and/or healthcare providers were blinded in addition to the participants. Therefore, outcome assessor blinding was graded as 'unclear'. In three trials the authors reported explicitly that the outcome assessors were blinded to which treatment participants had received. In five trials the authors explicitly reported that only the participants and the healthcare providers had been blinded to treatment.[38,40,42,44,119]

A priori sample size calculations were performed in 14 studies and not mentioned in the remainder. Fifteen studies analysed their primary outcome data using the ITT principle. Eighteen studies did not (as they excluded randomised participants from analysis) and in 18 studies it was unclear whether an ITT method had been applied. A method of assessing compliance was reported in 13 studies, but only five studies reported the results of an assessment.

Pharmaceutical companies were stated as funding 28 studies. There was a strong suggestion of pharmaceutical funding in 12 further studies (where one or more author or crucial trial personnel were paid by a pharmaceutical company). In 10 studies funding was unclear. One study reported independent funding, except that the drugs were provided by Boehringer Ingelheim.[37]

Publication bias

There were sufficient included studies (16 studies) with data on symptomatic ulcers to use these trials for assessment of publication bias. The funnel plot

TABLE 12 *Cox-2 preferentials versus Cox-1 meta-analysis (MA) and sensitivity analysis (SA) results*

Outcome	Analysis	No. of Included RCTs	No. of participants	No. of events	RR (random effects)	95% CI	Heterogeneity *p*-value
Serious GI events	MA	19	22725	43	0.61	0.34 to 1.10	0.99
	SA quality	15	21820	39	0.59	0.32 to 1.10	0.95
	SA dosage	18	22256	42	0.65	0.36 to 1.18	0.98
Symptomatic ulcers	MA	16	21371	82	0.41	0.26 to 0.65	1.00
	SA quality	13	20769	66	0.40	0.24 to 0.67	0.99
	SA dosage	16	21070	80	0.41	0.26 to 0.66	1.00
Serious CV or renal events	MA	11	19556	48	0.95	0.55 to 1.66	0.87
	SA quality	7	18651	44	1.02	0.57 to 1.83	0.78
	SA dosage	11	19556	48	0.95	0.55 to 1.66	0.87
	SA naproxen	11	19556	48	0.95	0.55 to 1.66	0.87
QoL	MA	1	335		WMD –0.10	–0.95 to 0.75	NR
	SA quality	0					
	SA dosage	1	335		WMD –0.10	–0.95 to 0.75	NR
Deaths	MA	14	20582	19	0.68	0.28 to 1.64	0.71
	SA quality	9	19647	15	0.90	0.33 to 2.50	0.54
	SA dosage	14	20405	19	0.68	0.28 to 1.64	0.71
	SA naproxen	13	20552	17	0.76	0.30 to 1.93	0.70
GI symptoms	MA	30	23659	3894	0.73	0.68 to 0.79	0.33
	SA quality	21	22449	3625	0.70	0.66 to 0.75	0.48
	SA dosage	29	23190	3772	0.71	0.67 to 0.75	0.67
Endoscopic ulcers	MA	6	367	24	0.41	0.16 to 1.05	0.49
	SA quality	3	208	13	0.51	0.15 to 1.67	0.50
	SA dosage	6	367	24	0.41	0.16 to 1.05	0.49
Anaemia	MA	4	1027	6	0.30	0.07 to 1.30	1.00
	SA quality	3	970	5	0.29	0.06 to 1.51	0.98
	SA dosage	4	1027	6	0.30	0.07 to 1.30	1.00
Occult bleed	MA	4	1039	17	0.86	0.33 to 2.24	0.83
	SA quality	4	1039	17	0.86	0.33 to 2.24	0.83
	SA dosage	4	862	16	0.86	0.33 to 2.25	0.82
Total drop-outs	MA	44	26967	4274	0.93	0.89 to 0.97	0.59
	SA quality	30	25275	3868	0.93	0.89 to 0.98	0.96
	SA dosage	41	25612	3440	0.92	0.87 to 0.98	0.53
Drop-outs due to GI symptoms	MA	32	23776	1174	0.63	0.56 to 0.71	0.68
	SA quality	21	22275	1068	0.61	0.54 to 0.69	0.76
	SA dosage	32	23599	1165	0.63	0.56 to 0.71	0.69

NR, not relevant (e.g. tests of heterogeneity when only one study is included in the analysis)

was not interpretable, but the analyses using tests by Egger and colleagues[35] ($p = 0.19$) or Begg and Mazumdar[36] ($p = 0.56$) (see Appendix 7e) did not suggest the presence of publication bias.

Results

Results are summarised in *Table 12* and forest plots are shown in *Figures 40–50*.

Primary outcomes

Information on serious GI events was provided by 19 studies (of which four reported a total absence of serious GI events). Forty-three events occurred in 22,725 participants (0.2%). The RR of developing a serious GI event was 0.61 (95% CI 0.34 to 1.10) in those on Cox-2 preferentials compared with those on Cox-1 NSAIDs, with no suggestion of heterogeneity ($p = 0.99$). SAs (excluding the arms or studies with a high

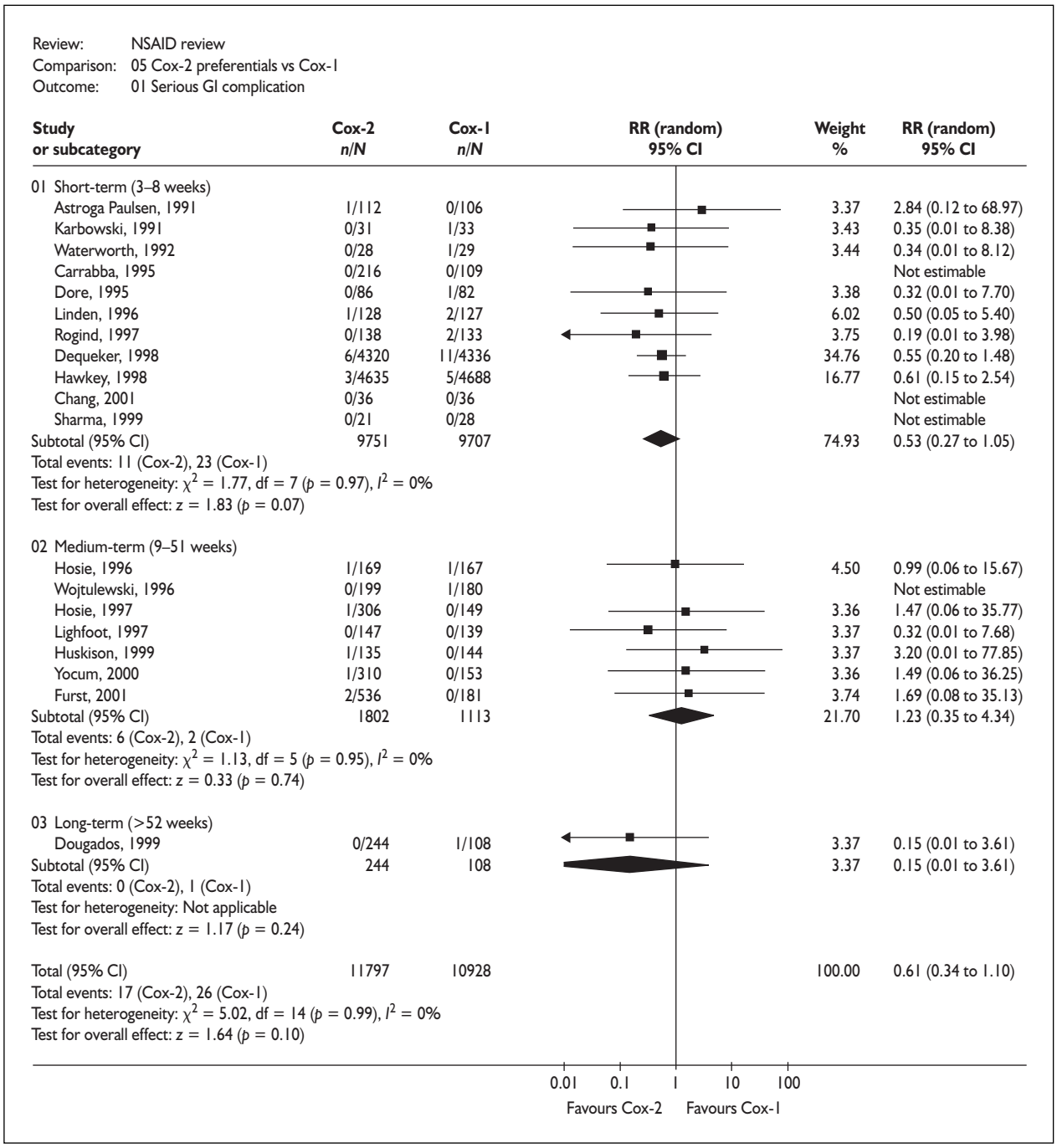

FIGURE 40 *Forest plot of Cox-2 preferential NSAID versus Cox-1 NSAID, outcome serious GI complications*

summary risk of bias or a higher than maximum recommended daily dose of Cox-2 preferentials) did not alter the size or significance of the effect.

Symptomatic ulcers were reported in 16 studies (of which two reported an absence of symptomatic ulcers). They occurred in 82 of the 21,371 participants (0.4%). The RR of developing a symptomatic ulcer was 0.41 (95% CI 0.26 to 0.65) in the Cox-2 preferential groups compared with those on Cox-1 NSAIDs, with no suggestion of heterogeneity ($p = 1.0$). SAs did not materially alter the size or significance of the effect.

Eleven studies reported serious cardiovascular or renal illness in 48 of the 19,556 participants. The risk of developing a serious cardiovascular or renal illness was not significantly different in participants prescribed Cox-2 preferentials compared with Cox-1s (RR 0.95, 95% CI 0.55 to

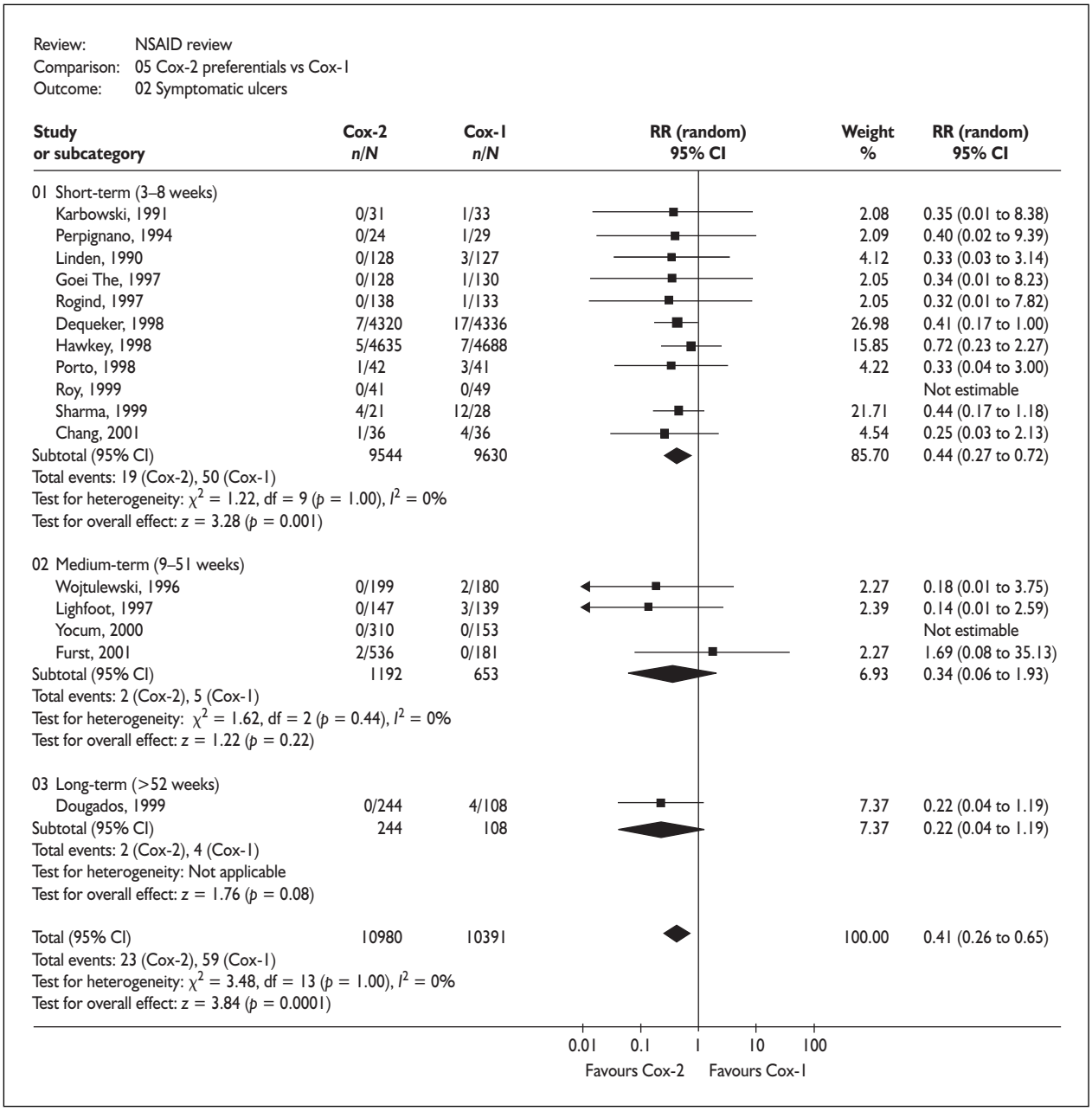

FIGURE 41 *Forest plot of Cox-2 preferential NSAID versus Cox-1 NSAID, outcome symptomatic ulcers*

1.66, with no evidence of heterogeneity, $p = 0.87$). No SA materially altered the results.

Three studies provided data on QoL. Only one study reported health-related QoL measures with standard deviations, so that they could be meta-analysed.[120] At 6 months there was no significant difference between the meloxicam and the diclofenac groups in the mean change in the QoL measure assessed using the NHP. Both groups improved (WMD –0.10, 95% CI –0.95 to 0.75). See Appendix 10c for further details.

Deaths due to any cause were reported in 14 trials (five of these trials reported that there were no deaths). There were 19 deaths in 20,582 participants (0.1%). Deaths occurred with equal frequency in the Cox-2 and the Cox-1 groups (RR 0.68, 95% CI 0.28 to 1.64, with no evidence of heterogeneity, $p = 0.71$). No SA materially altered the results.

Secondary outcomes

Thirty studies, involving 23,659 participants, provided data on total numbers of people with GI

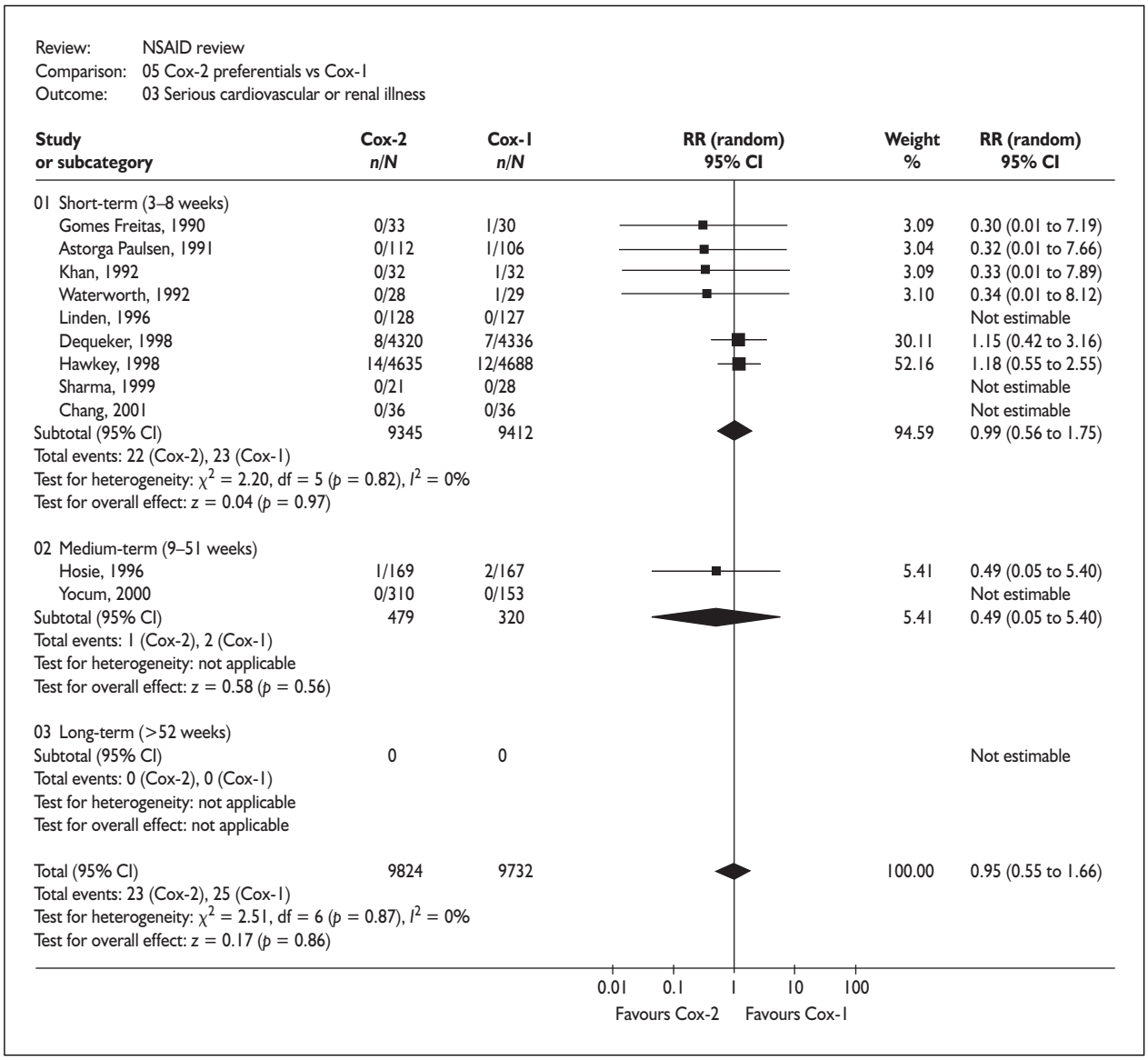

FIGURE 42 *Forest plot of Cox-2 preferential NSAID versus Cox-1 NSAID, outcome serious cardiovascular or renal illness*

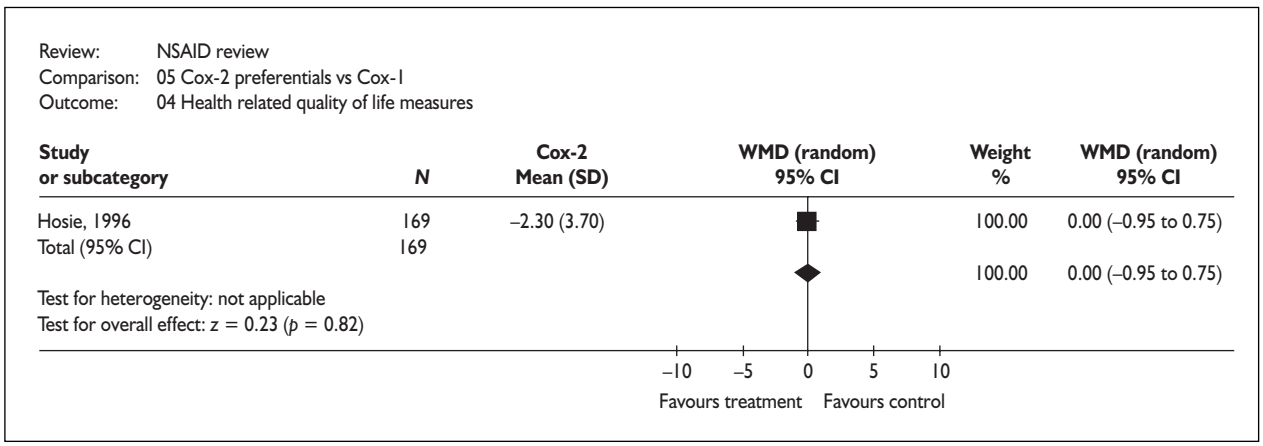

FIGURE 43 *Forest plot of Cox-2 preferential NSAID versus Cox-1 NSAID, outcome quality of life*

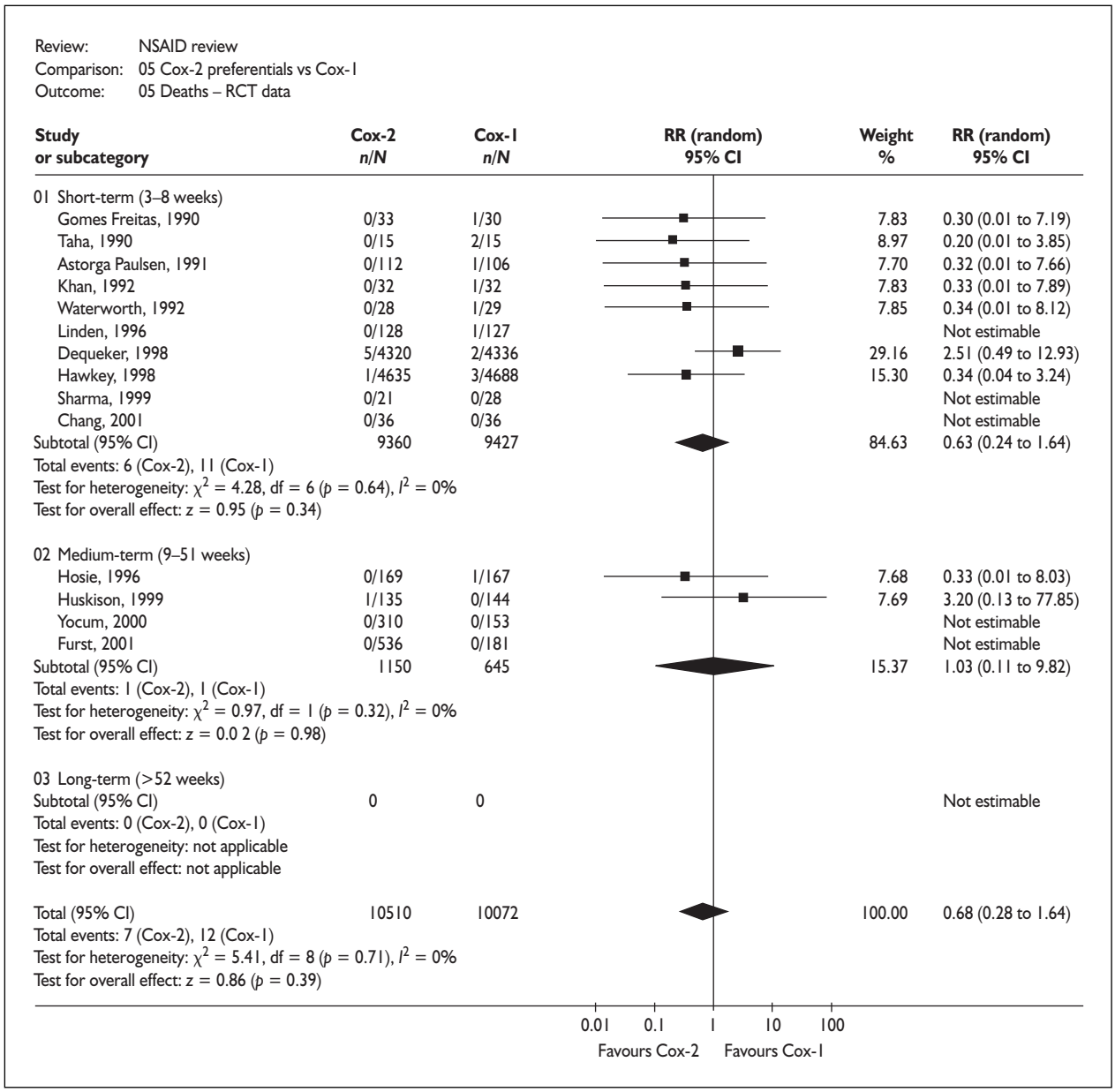

FIGURE 44 *Forest plot of Cox-2 preferential NSAID versus Cox-1 NSAID, outcome deaths*

symptoms. GI symptoms were noted in 3894 (16%). The RR of developing GI symptoms was 0.73 (95% CI 0.68 to 0.79) in the Cox-2 preferentials compared with those on Cox-1 NSAIDs, with no evidence of heterogeneity ($p = 0.33$). No SA materially altered the results.

Six studies including 367 participants provided data on endoscopic ulcers. Endoscopic ulcers were seen in 24 participants and the RR of developing an endoscopic ulcer was 0.41 (95% CI 0.16 to 1.05) in the Cox-2 preferentials compared with the Cox-1 groups, with no evidence of heterogeneity ($p = 0.49$). SAs did not materially alter the size or significance of this relationship.

Anaemia was reported in four studies and occurred in six of the 1027 participants. The RR of developing anaemia was 0.30 (95% CI 0.07 to 1.30) in the Cox-2 preferential groups compared with the Cox-1 groups with no evidence of heterogeneity ($p = 1.00$). SA did not materially alter the results of the MA.

Occult bleeding was reported in four studies and occurred in 17 of the 1039 participants. MA

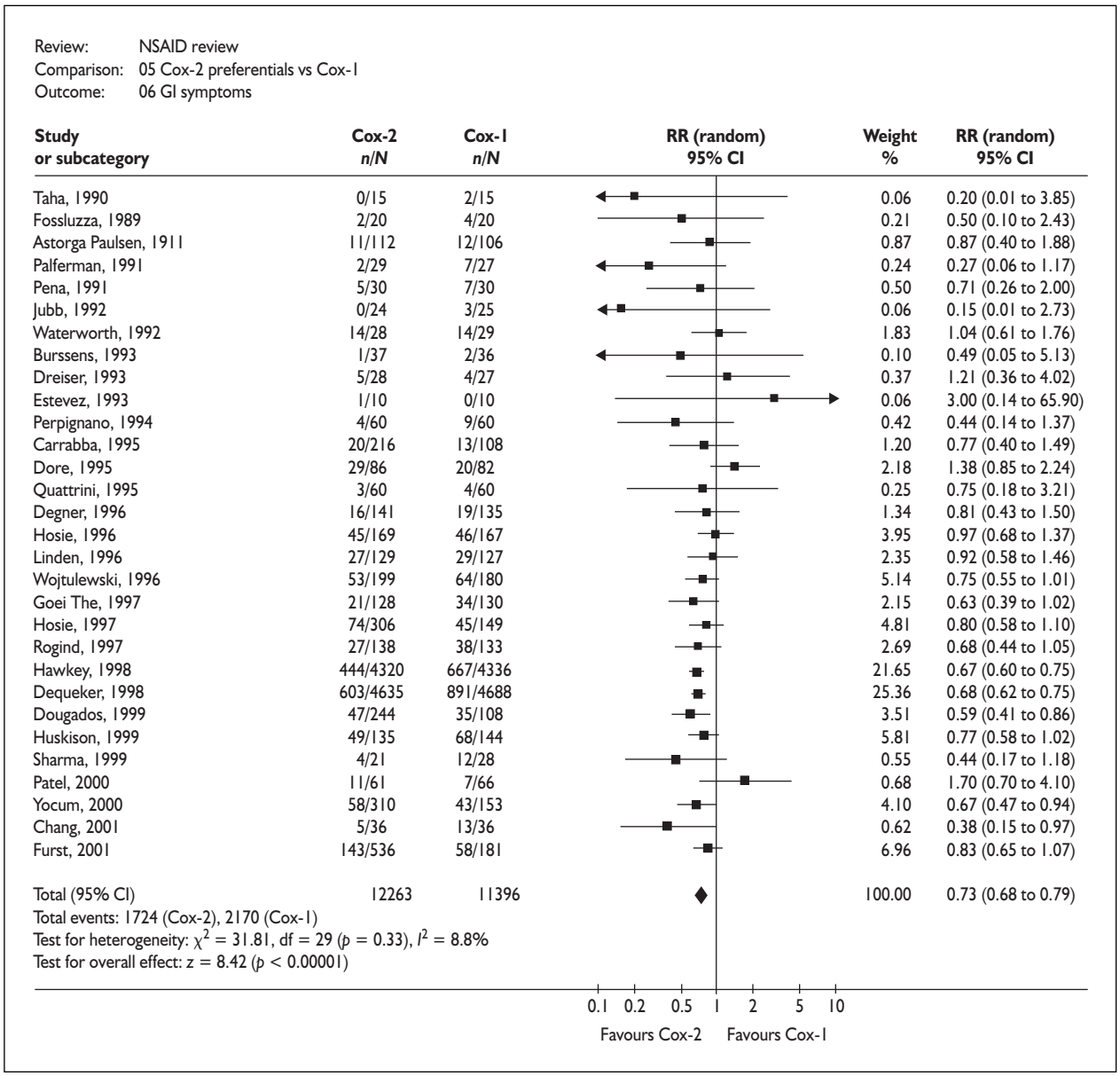

FIGURE 45 *Forest plot of Cox-2 preferential NSAID versus Cox-1 NSAID, outcome GI symptoms*

showed no significant difference in the occurrence of occult bleeding between the Cox- 2 preferential and Cox-1 groups (RR 0.86, 95% CI 0.33 to 2.24, with no evidence of heterogeneity, $p = 0.83$). This was not altered in SAs.

Total drop-outs were calculable or reported in 44 studies; 4274 of 26,967 participants dropped out before the end of a trial (16%). The RR of dropping out was 0.93 (95% CI 0.89 to 0.97) in the Cox-2 preferential group compared with the Cox-1 group, with no evidence of heterogeneity ($p = 0.59$). SAs did not alter these results.

Numbers of drop-outs due to GI symptoms were reported in 32 studies and occurred in 1174 of the 23776 participants (5%). The RR of dropping out due to GI symptoms was 0.63 (95% CI 0.56 to 0.71) in the Cox-2 group compared with the Cox-1 group, with no evidence of heterogeneity ($p = 0.68$). SAs did not alter these results.

Meta-regressions and subgrouping

Subgrouping by study duration was carried out for all primary analyses (see figures). As most of the events for all of the primary outcomes occurred in the short-term studies, it is difficult to draw any conclusions about differential effects over time.

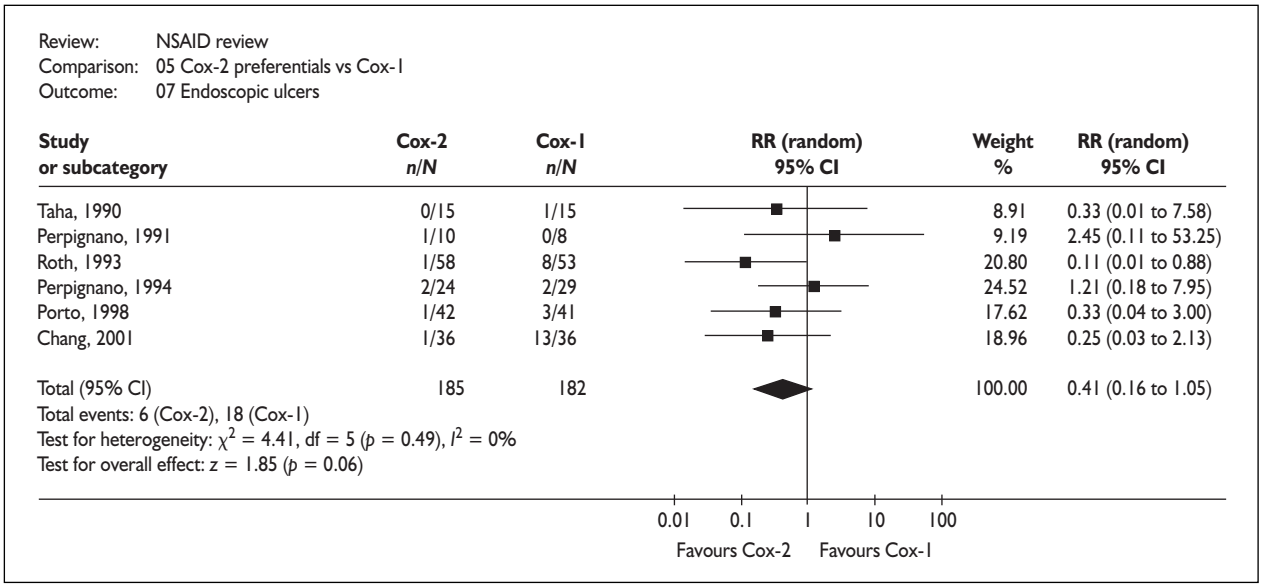

FIGURE 46 *Forest plot of Cox-2 preferential NSAID versus Cox-1 NSAID, outcome endoscopic ulcers*

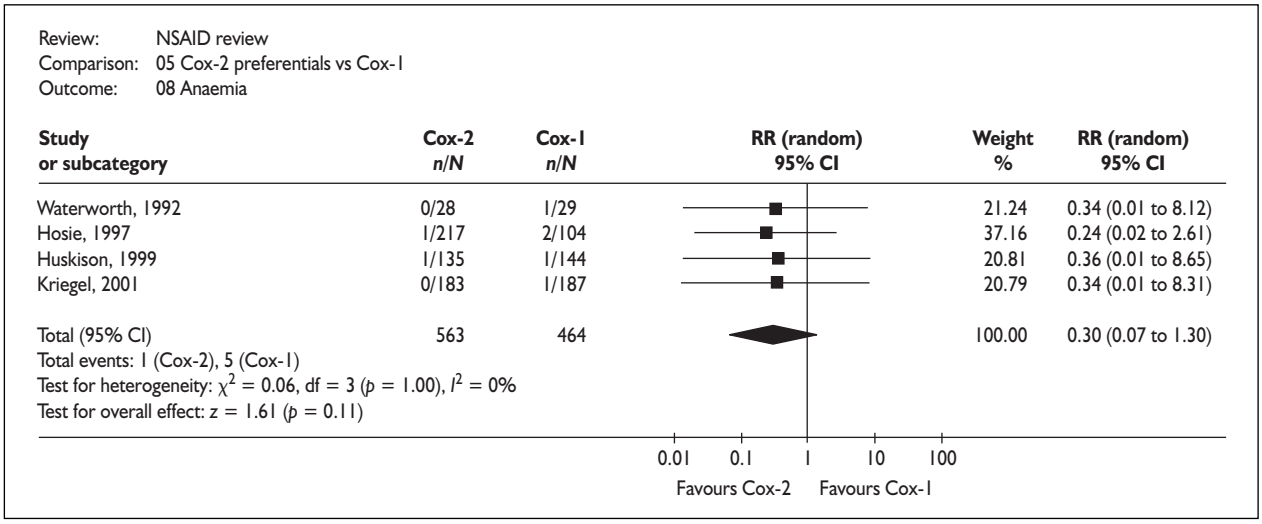

FIGURE 47 *Forest plot of Cox-2 preferential NSAID versus Cox-1 NSAID, outcome anaemia*

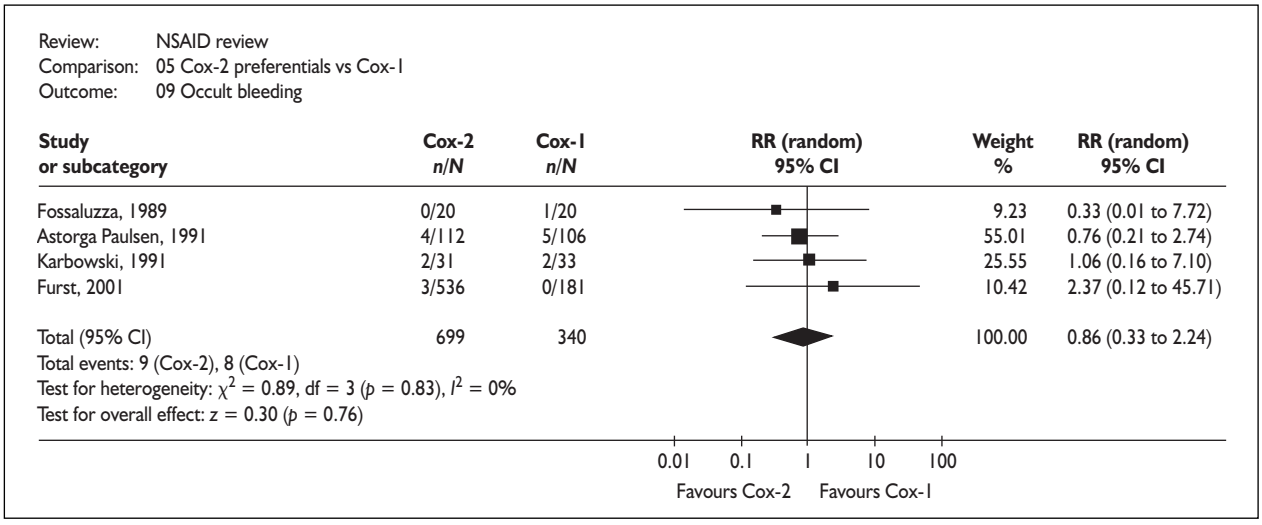

FIGURE 48 *Forest plot of Cox-2 preferential NSAID versus Cox-1 NSAID, outcome occult bleeding*

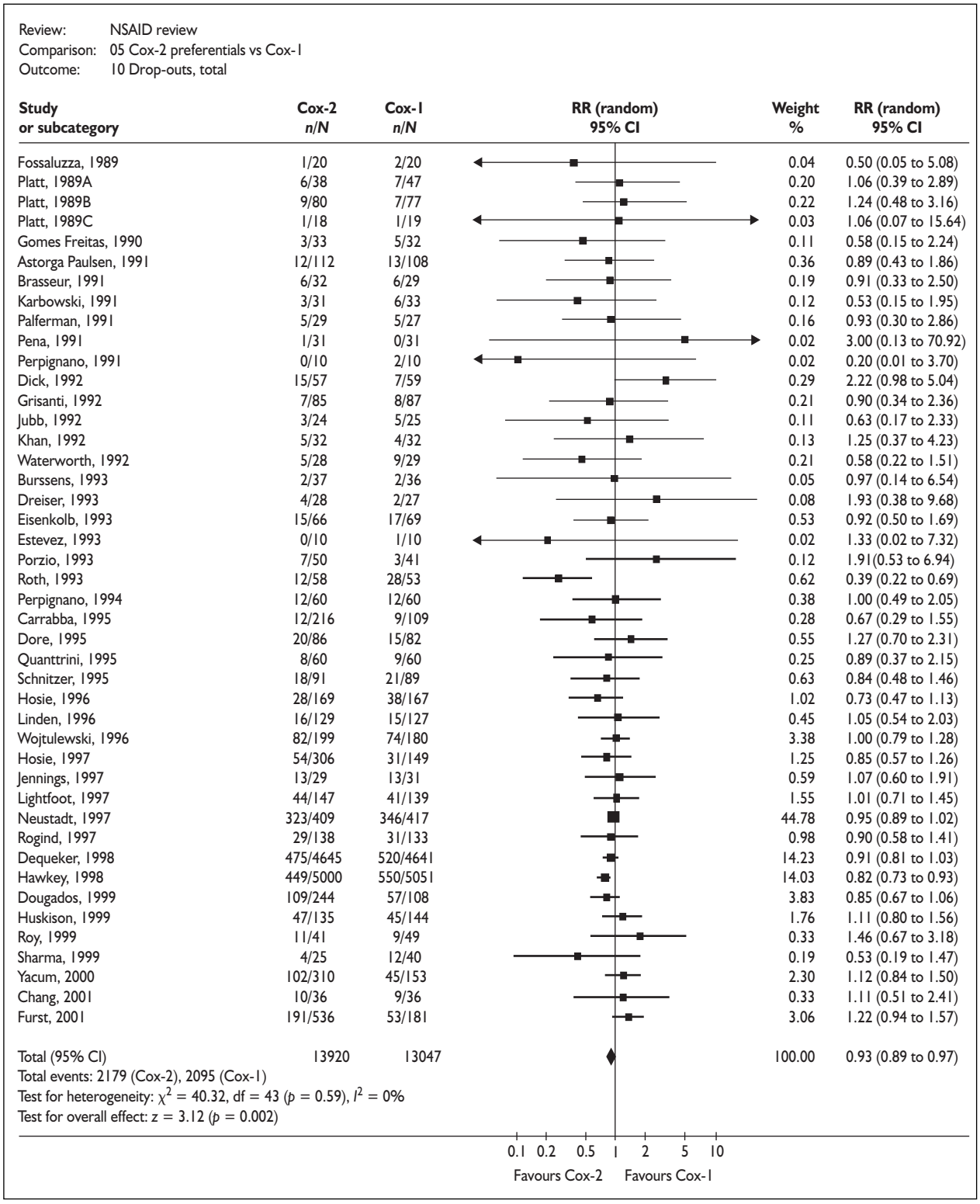

FIGURE 49 *Forest plot of Cox-2 preferential NSAID versus Cox-1 NSAID, outcome total drop-outs*

Meta-regressions were carried out to explore the relationship between ln (RR) of symptomatic ulcers and study duration, baseline GI status (quantified by the percentage of participants with a history of ulcers or bleeds) and mean age at baseline. No statistically significant relationships were seen. See Appendix 8 for further details.

Absolute RRs were calculated for the economic analysis (Appendix 9a). The authors attempted to

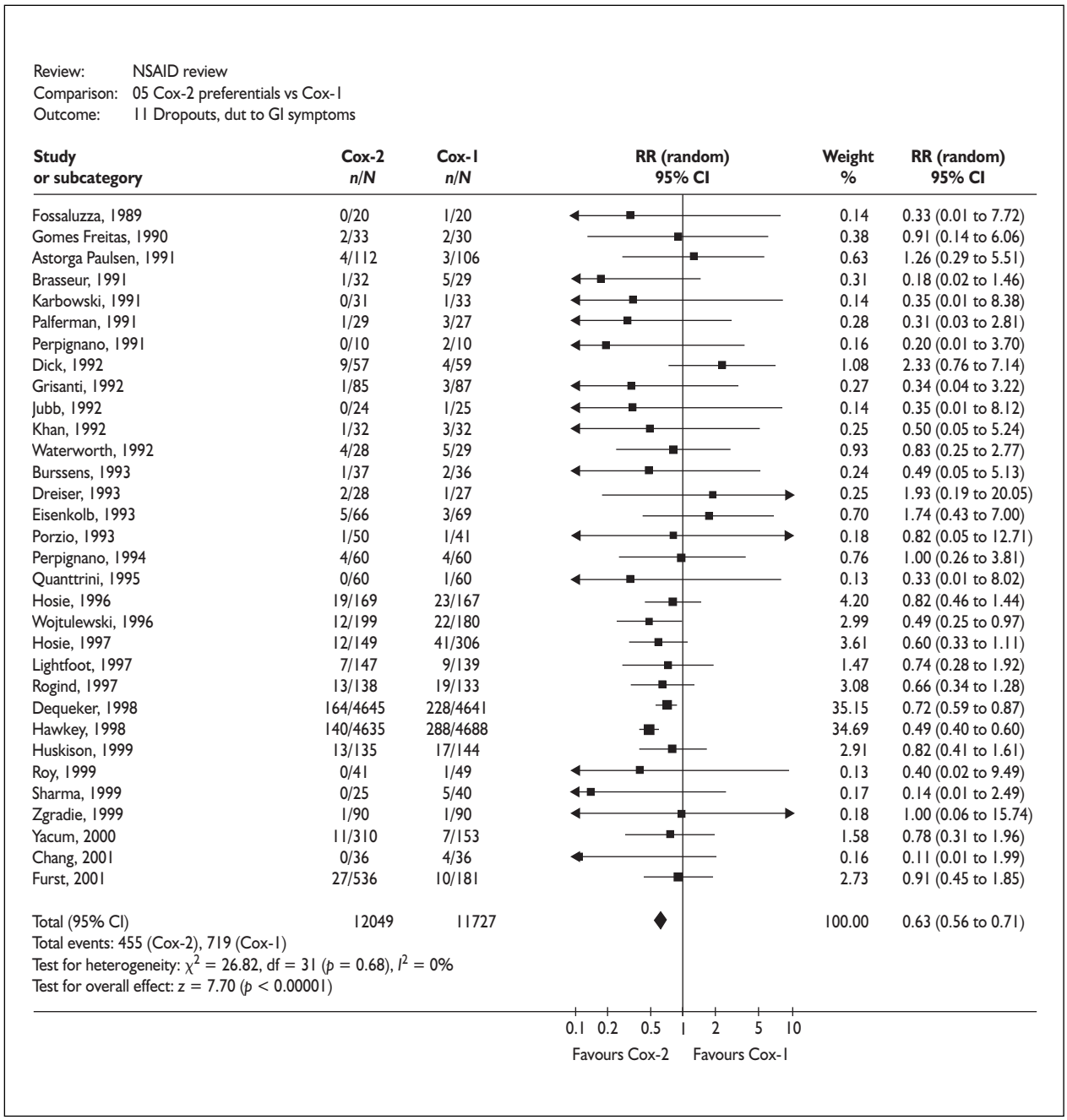

FIGURE 50 *Forest plot of Cox-2 preferential NSAID versus Cox-1 NSAID, outcome drop-outs due to GI symptoms*

subgroup ARRs for serious GI events, symptomatic ulcers and endoscopic ulcers by baseline GI status and by age. All studies which could be categorised by baseline GI risk fell in category 2 (some participants normal, others have some erosions and/or haemorrhages on endoscopy, but no frank ulcers). Subgrouping by age reduced the heterogeneity apparent in the ARR calculation on endoscopic ulcers, but no clear differences in effect were seen in the age subgroups on any of the outcomes. See Appendix 9b for further details.

Summary

Fifty-one RCTs were included in this comparison. All four drugs (etodolac, nimesulide, meloxicam and nabumetone) were studied. Studies usually included either participants with OA or with RA, not both, and mean ages ranged from 38 to 72 years. Baseline GI status was unclear in many studies as baseline endoscopies were usually not carried out. Five study arms provided Cox-2 preferential doses above the current recommended levels. Study duration ranged from 3 weeks to 3 years.

The summary risk of bias was calculated as being 'low' in no studies, 'moderate' in 34 and 'high' in 17. Only two studies had 'adequate' allocation concealment, and 10 studies were judged as having comparable baseline characteristics. Pharmaceutical funding was used in 40 studies. Publication bias was not apparent.

The development of symptomatic ulcers, GI symptoms, total drop-outs and drop-outs due to GI symptoms all appear to be significantly reduced in participants randomised to take Cox-2 preferential drugs compared with Cox-1 drugs, and these results are robust to SA and without apparent heterogeneity. Serious GI complications, serious cardiovascular or renal illness, QoL, total deaths and endoscopic ulcers were not significantly different between Cox-2 preferential and Cox-1 groups, but the numbers of people with these outcomes were low.

Chapter 10

H_2RA plus NSAID versus PPI plus NSAID: systematic review – included studies, results, analysis and robustness

Included studies

Table 13 summarises the included studies. For a complete table of characteristics of included studies, see Appendix 6f.

Characteristics of study

One RCT, by Yeomans and colleagues[140] the ASTRONAUT study, was included in this comparison, randomising 425 participants (69% female). The study was performed in 73 centres in 15 countries including the UK. No additional data were received from the authors.

Participants

The study recruited participants with RA, OA, psoriatic arthritis, AS or a combination of any of these (or other types of arthritis which were not stated). Mean duration of arthritis was not stated. Mean age of participants was 56 years.

All participants had undergone treatment for ulcers and/or erosions. Endoscopy was then performed and participants were excluded if the endoscopy failed to show treatment success. Successful treatment was defined as the disappearance of ulcer and the presence of fewer than five erosions in the stomach, fewer than five erosions in the duodenum and not more than mild dyspeptic symptoms.

Interventions

Yeomans and colleagues[140] compared ranitidine (an H_2RA) with omeprazole (a PPI), both prescribed within the recommended daily dosage.[23] All participants also took various NSAIDs (naproxen 16%, indomethacin 23%, diclofenac 29%).

The maximum duration of intervention was 26 weeks. Patient education and details of other medication prescribed during the study were not mentioned.

Study quality

The summary risk of bias was 'moderate'. The study reported that participants were 'randomly assigned' but did not give further details and so allocation concealment was assessed as 'unclear'. Participants appeared comparable at baseline and were blinded to treatment. It was unclear whether the outcome assessor was blinded to treatment.

A priori sample size calculations were performed. The authors did not analyse their primary outcome data using the ITT principle. Compliance was reported as assessed by tablet count but the result was not reported. Astra Hassle pharmaceutical company funded the study and the contact author serves as a consultant for Searle Australia.

Publication bias

There were insufficient included studies to assess publication bias.

TABLE 13 *Brief characteristics of included H_2RA versus PPI studies*

Study	*N*	Participants	Interventions
Yeomans, 1998[140] ASTRONAUT **Summary risk of bias:** moderate	**Allocated:** unclear (assessed: b 210, c 215)	**Baseline GI status:** endoscopy performed following healing phase for ulcers had to show treatment success **Type of arthritis:** OA and RA	**Comparison:** omeprazole plus mixed NSAIDs (b) vs ranitidine plus mixed NSAIDs (c) **Duration:** 26 weeks

TABLE 14 *Indirect comparisons, H_2RA versus PPI displayed with relevant direct comparisons, and the data on which the indirect comparisons are based*

Outcome	RR, direct (95% CI), events	RR, indirect (95% CI)	RR, H_2RA vs placebo (95% CI), events	RR, PPI vs placebo (95% CI), events
Serious GI complications	0.33 (0.01 to 7.95), 1	0.72 (0.02 to 33.22)	0.33 (0.01 to 8.14), 1	0.46 (0.07 to 2.92), 3
Symptomatic ulcers	0.33 (0.01 to 7.95), 1	16.22 (0.46 to 570.93)	1.46 (0.06 to 35.53), 1	0.09 (0.02 to 0.47), 18
Serious CV or renal events	0.68 (0.04 to 11.15)	0.53 (0.08 to 3.46), 5		0.78 (0.10 to 6.26), 3
Deaths		17.65 (0.23 to 1351.18)	3.00 (0.13 to 68.26), 1	0.17 (0.01 to 4.05), 1
GI symptoms		1.67 (0.89 to 3.14)	0.72 (0.56 to 0.92), 201	0.43 (0.24 to 0.76), 45
Endoscopic ulcers	3.11 (1.62 to 5.95), 46	1.49 (1.08 to 2.04)	0.55 (0.44 to 0.70), 250	0.37 (0.30 to 0.46), 281
Anaemia			3.00 (0.12 to 73.29), 1	
Occult bleeding				
Drop-outs, total	0.94 (0.59 to 1.52), 59	0.99 (0.62 to 1.59)	0.97 (0.84 to 1.12), 362	0.98 (0.62 to 1.53), 116
Drop-outs, due to GI symptoms		1.58 (0.74 to 3.35)	0.71 (0.43 to 1.20), 57	0.45 (0.26 to 0.78), 48

Results

Results are summarised in *Table 14* and forest plots are shown in *Figures 51–54*. For SAs, see Appendix 11a.

Direct comparisons

Primary outcomes

One serious GI event occurred in the PPI group, a bleeding duodenal ulcer requiring hospitalisation. The same event was also recorded as a symptomatic ulcer.

Serious cardiovascular or renal illness, health-related QoL measures and deaths were not reported.

Secondary outcomes

Endoscopic ulcers were seen in 46 of 425 participants. The RR of developing at least one gastroduodenal ulcer was 3.11 (95% CI 1.62 to 5.95) in the H_2RA group compared with the PPI group. SAs did not remove this study or alter the results.

Fifty-nine of 425 participants dropped out of the study. Drop-out occurred with equal frequency in the H_2RA group and the PPI group (RR 0.94, 95% CI 0.59 to 1.52). SAs did not remove this study or alter the results.

Total GI symptoms, anaemia, occult bleeding and numbers of drop-outs due to GI symptoms were not reported.

Indirect comparisons

Indirect comparisons use the results of the MA of H_2RA plus NSAIDs versus NSAIDs alone and the results of the MA of PPI plus NSAIDs versus NSAIDs alone to estimate the effect of H_2RA plus NSAIDs versus a PPI plus NSAIDs. They provide lower quality evidence than studies which directly compare H_2RA plus NSAIDs versus a PPI plus NSAIDs.

Primary outcomes

No significant effects were seen for any primary outcome (all had very wide CIs).

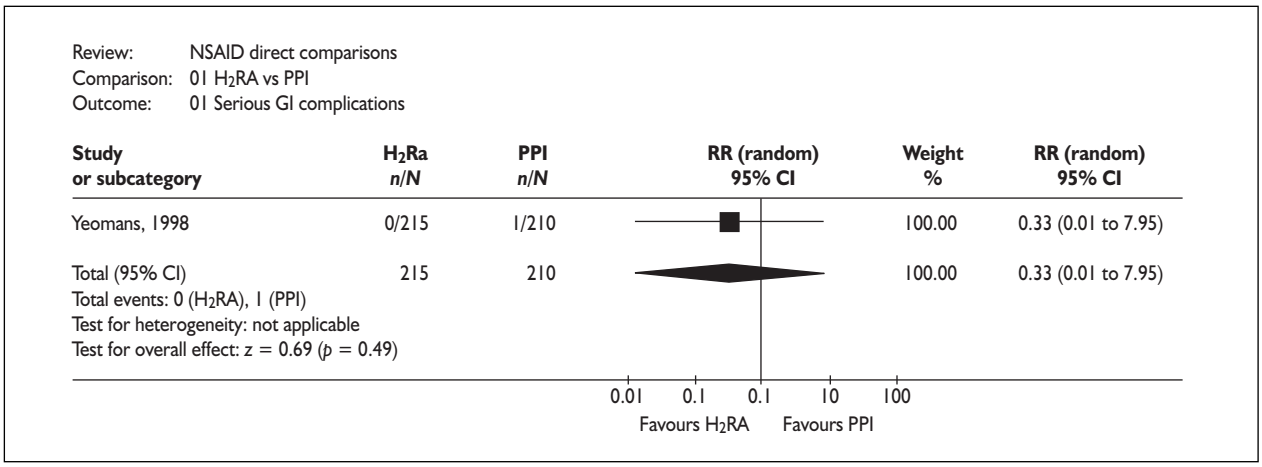

FIGURE 51 *Forest plot of H_2RA plus NSAID versus PPI plus NSAID, outcome serious GI events*

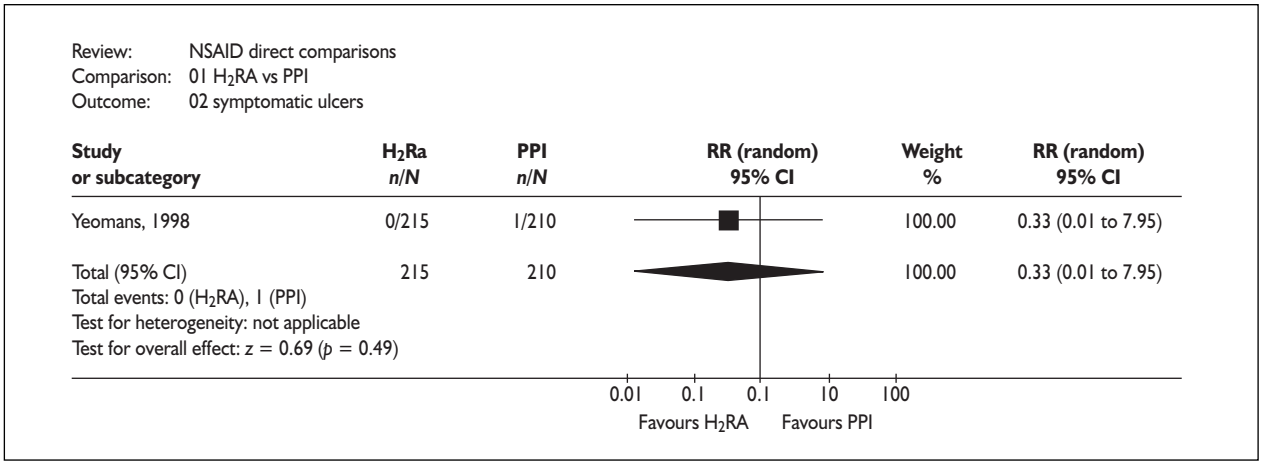

FIGURE 52 *Forest plot of H_2RA plus NSAID versus PPI plus NSAID, outcome symptomatic ulcers*

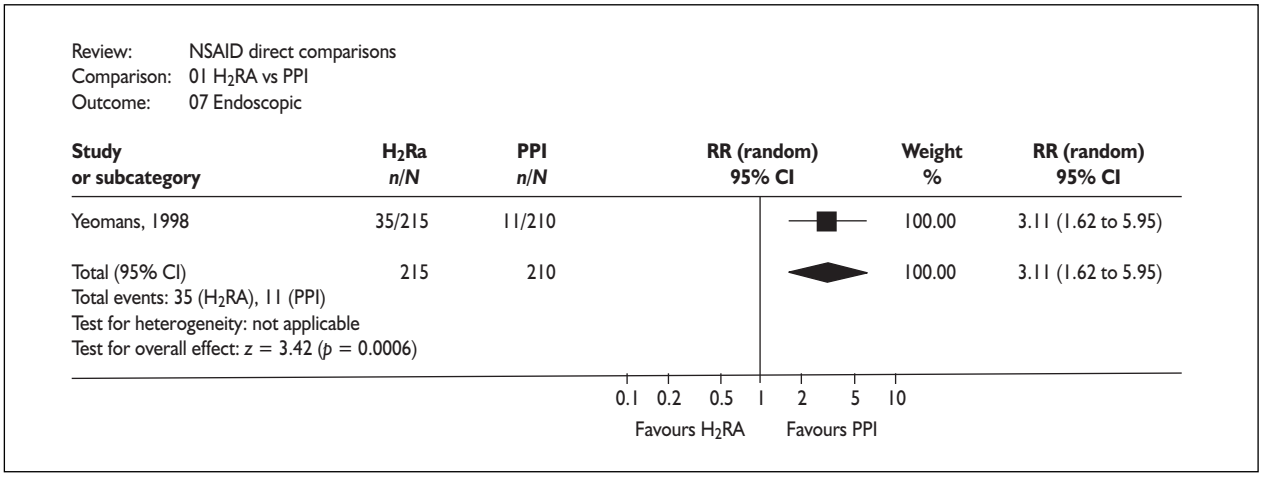

FIGURE 53 *Forest plot of H_2RA plus NSAID versus PPI plus NSAID, outcome endoscopic ulcers*

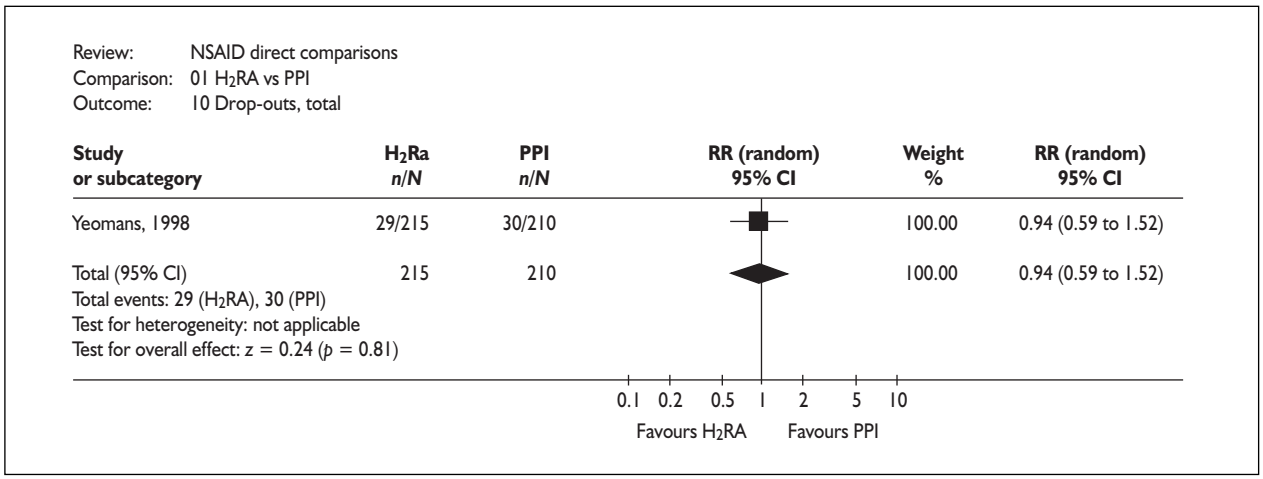

FIGURE 54 *Forest plot of H_2RA plus NSAID versus PPI plus NSAID, outcome total drop-outs*

Secondary outcomes

Outcomes were not calculable for anaemia and occult bleeding. No statistically significant effects were seen for any secondary outcome, except endoscopic ulcers ($RR_{indirect}$ 1.49, 95% CI 1.08 to 2.04), suggesting more endoscopic ulcers in the participants taking H_2RA, compared with those taking PPIs.

Summary

Only one study directly compared the efficacy of an H_2RA plus NSAIDs versus a PPI plus NSAIDs. It included 425 participants with OA, RA and other types of arthritis, and a mean age of 56 years. All participants had undergone treatment of ulcers or erosions. Drugs were all prescribed at appropriate doses and follow-up was 26 weeks.

The summary risk of bias was 'moderate', with unclear allocation concealment and apparent comparability at baseline. A pharmaceutical company funded the study.

There were insufficient data to assess any primary outcomes in the included study, and indirect comparisons did not suggest any significant relationships.

Endoscopic ulcers were significantly more likely in participants on H_2RAs rather than PPIs in the included (direct comparison) study. This finding was supported by the indirect comparison data. There was no significant difference in total drop-outs in either direct or indirect comparisons. No other secondary outcomes were reported in the direct comparison RCT and no significant results were seen for GI symptoms, drop-outs or drop-outs due to GI symptoms in the indirect comparisons.

Chapter 11

H_2RA plus NSAID versus misoprostol plus NSAID: systematic review – included studies, results, analysis and robustness

Included studies

Table 15 summarises the included studies. For a complete table of characteristics of included studies, see Appendix 6g.

Characteristics of studies

Three RCTs directly compared H_2RA with misoprostol, randomising 631 participants (55% female). The studies varied in size from at least 16 participants per arm[143] to 269 participants per arm.[142] The studies were performed in Italy,[141] USA[142] and Turkey.[143] Publication dates were from 1995 to 1996. One study was published in Turkish[143] and only the English abstract and table of results were data extracted. No additional outcome data were received from authors of the included studies.

Participants

Valentini and colleagues[141] recruited patients with cancer and Raskin and colleagues[142] recruited participants with OA, RA, a combination and other types of arthritis (not stated). Yildiz and colleagues[143] reported recruiting participants with 'rheumatic symptoms'. Mean duration of cancer pain or arthritis was not stated. Mean age of participants ranged from 37[143] to 61 years.[142]

The baseline GI status of participants varied greatly between studies. All three studies performed baseline endoscopy. Valentini and colleagues[141] excluded participants with more than one petechia or area of haemorrhage or erosion and with a history of peptic ulcer disease. Raskin and colleagues[142] excluded patients with evidence of an ulcer and a history of recurrent peptic ulcer

TABLE 15 *Brief characteristics of included H_2RA versus misoprostol studies*

Study	*N*	Participants	Interventions
Valentini, 1995[141] **Summary risk of bias:** moderate	**Allocated:** a 31, b 30	**Baseline GI status:** baseline endoscopy performed, excluded patients with more than 1 petechia or area of haemorrhage or erosion; also excluded patients with history of peptic ulcer disease **Type of arthritis:** not applicable – cancer patients	**Comparison:** misoprostol plus diclofenac (b) vs ranitidine plus diclofenac (a) **Duration:** 4 weeks
Raskin, 1996[142] **Summary risk of bias:** moderate	**Allocated:** a 269, b 269	**Baseline GI status:** all experiencing UGI pain thought to be related to their NSAID therapy, baseline endoscopy excluded patients with evidence of an ulcer of the gastric or duodenal mucosa or with history of recurrent peptic ulcer disease **Type of arthritis:** OA, RA, both and other	**Comparison:** misoprostol plus mixed NSAIDs (b) vs ranitidine plus mixed NSAIDs (a) **Duration:** 8 weeks
Yildiz, 1996[143] **Summary risk of bias:** moderate	**Allocated:** unclear (completed: a 16, b 16)	**Baseline GI status:** baseline endoscopy performed and did not exclude any endoscopic score (1 person in each group had ulcer at baseline and excluded from analyses by reviewers) **Type arthritis:** 'Rheumatic symptoms', no further details	**Comparison:** famotidine plus naproxen sodium and indomethacin (b) vs misoprostol plus naproxen sodium and indomethacin (a) **Duration:** 2 months

disease in the previous 12 months but participants had to be experiencing UGI pain thought to be related to NSAID treatment and 22% had a history of ulcers. Yildiz and colleagues[143] did not exclude any endoscopic score (one person in each group had an ulcer at baseline but were excluded from analyses for this systematic review).

Interventions

Two studies compared ranitidine with misoprostol. One study compared famotidine with misoprostol. The daily dose of famotidine prescribed was twice the recommended daily dosage according to the BNF.[143] All participants in the Valentini study[141] complained of cancer pain and were prescribed a dose of diclofenac above that recommended in arthritis. All participants in the Raskin study[142] took various NSAIDs including ibuprofen, naproxen, piroxicam and sulindac. All participants in the Yildiz study[143] took naproxen sodium and indomethacin suppositories.

The maximum duration of intervention ranged from 4[141] to 8 weeks. Patient education was not mentioned in any study. Details of other medication prescribed during the study were not stated in one study.[143] Valentini and colleagues[141] reported that chemotherapy, radiation, corticosteroids and antineoplastics were allowed throughout the study. Raskin and colleagues[142] reported that antacids were permitted during the initial week only, other anti-ulcer medications, antineoplastics, anticoagulants, prednisone >7.5 mg/ day, cyclophosphamide and methotrexate were all excluded.

Study quality

The summary risk of bias was 'moderate' for all three studies with method of randomisation described as 'randomised' and participants 'divided randomly'. Allocation concealment was unclear for all three studies.

Baseline comparability was unclear for two studies owing to insufficient information. The participants with cancer were not blinded to treatment. Participants were blinded in the study by Raskin and colleagues[142] and blinding was unclear in Yildiz and colleagues.[143] The outcome assessor was blinded to the treatment of the participants with cancer and it was unclear whether the outcome assessor was blinded in the other two studies.

A priori sample size calculations were performed in the study with cancer patients[141] but it was not stated in the other two studies. Two studies did not analyse their primary outcome data using the ITT principle and it was unclear in the other study.[143] Measurement of compliance was not stated in any of the three studies.

The pharmaceutical company Searle funded one study[142] and employed one of the authors. Searle employed at least one of the authors in another study[141] and the source of funding was not stated in the third.[143]

Publication bias

There were insufficient included studies to assess publication bias.

Results

Results are summarised in *Table 16* and forest plots are shown in *Figures 55–59*. For SAs see Appendix 11b.

Primary outcomes

One study reported an absence of any serious GI events, any serious cardiovascular or renal illness and any deaths in either group.[142] Valentini and colleagues[141] reported one symptomatic ulcer in the H_2RA group. Health-related QoL measures were not reported in any study.

Secondary outcomes

Total GI symptoms were reported in 345 of 587 participants (59%). The RR of developing a GI symptom was 0.85 (95% CI 0.74 to 0.97) in the H_2RA group compared with the misoprostol group, with no evidence of heterogeneity between the two studies (p = 0.46). Significance was retained in all SAs. This result suggests that participants randomised to receive H_2RA have a significantly decreased risk of developing GI symptoms-compared with participants taking misoprostol. This result is derived from only two studies.

Three studies reported on endoscopic ulcers (including one study that reported an absence of endoscopic ulcers).[143] Endoscopic ulcers were seen in 23 of 454 participants (5%). The RR of developing at least one gastroduodenal ulcer was 4.35 (95% CI 1.51 to 12.55) in the H_2RA group compared with the misoprostol group. Significance was retained in all SAs.

TABLE 16 *Indirect comparisons, H_2RA versus misoprostol displayed with relevant direct comparisons, and the data on which the indirect comparisons are based*

Outcome	RR, direct (95% CI), events	RR, indirect (95% CI)	RR, H_2RA vs placebo (95% CI), events	RR, misoprostol vs placebo (95% CI), events
Serious GI complications		0.58 (0.02 to 17.05)	0.33 (0.01 to 8.14), 1	0.57 (0.36 to 0.91), 75
Symptomatic ulcers	2.67 (0.11 to 62.42), 1	4.06 (0.16 to 104.45)	1.46 (0.06 to 35.53), 1	0.36 (0.20 to 0.67), 44
Serious CV or renal events		0.30 (0.02 to 4.38)	0.53 (0.08 to 3.46), 5	1.78 (0.26 to 12.07), 4
Deaths		3.37 (0.14 to 82.83)	3.00 (0.13 to 68.26), 1	0.89 (0.46 to 1.74), 35
GI symptoms	0.85 (0.74 to 0.97), 345	0.74 (0.49 to 1.12)	0.72 (0.56 to 0.92), 201	0.97 (0.70 to 1.35), 1218
Endoscopic ulcers	4.35 (1.51 to 12.55), 23	1.67 (1.22 to 2.28)	0.55 (0.44 to 0.70), 250	0.33 (0.27 to 0.41), 658
Anaemia		1.13 (0.01 to 103.35)	3.00 (0.12 to 73.29), 1	2.66 (0.11 to 63.84), 1
Occult bleeding				0.46 (0.16 to 1.32), 16
Drop-outs, total	0.78 (0.57 to 1.07), 125	0.87 (0.73 to 1.04)	0.97 (0.84 to 1.12), 362	1.11 (1.00 to 1.23), 4772
Drop-outs, due to GI symptoms	0.40 (0.22 to 0.74), 46	0.52 (0.31 to 0.88)	0.71 (0.43 to 1.20), 57	1.36 (1.26 to 1.46), 2332

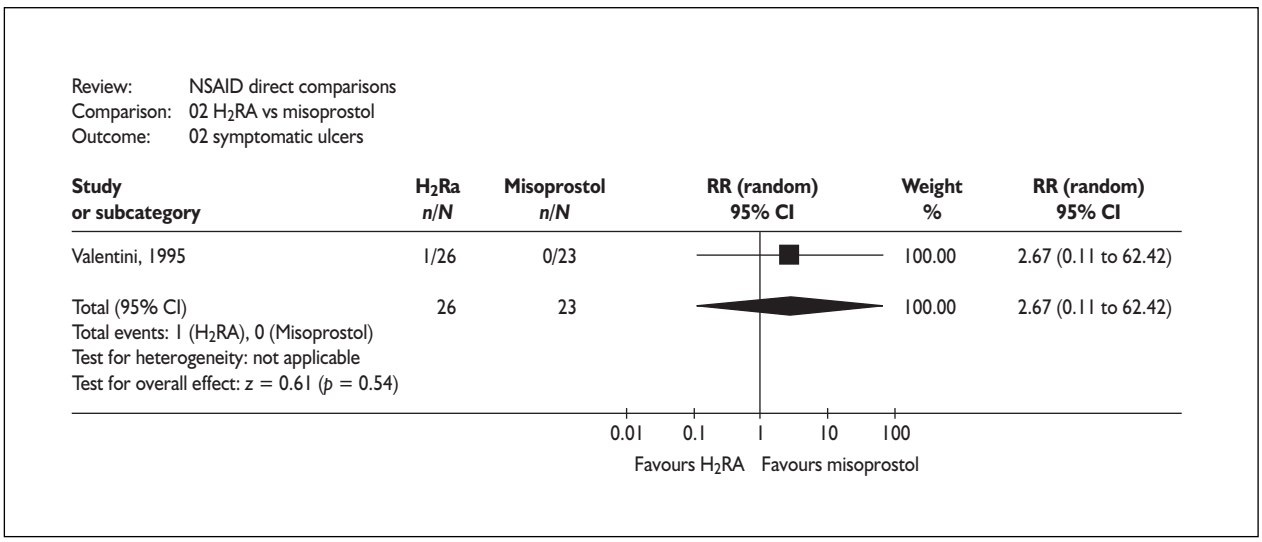

FIGURE 55 *Forest plot of H_2RA plus NSAID versus misoprostol plus NSAID, outcome symptomatic ulcers*

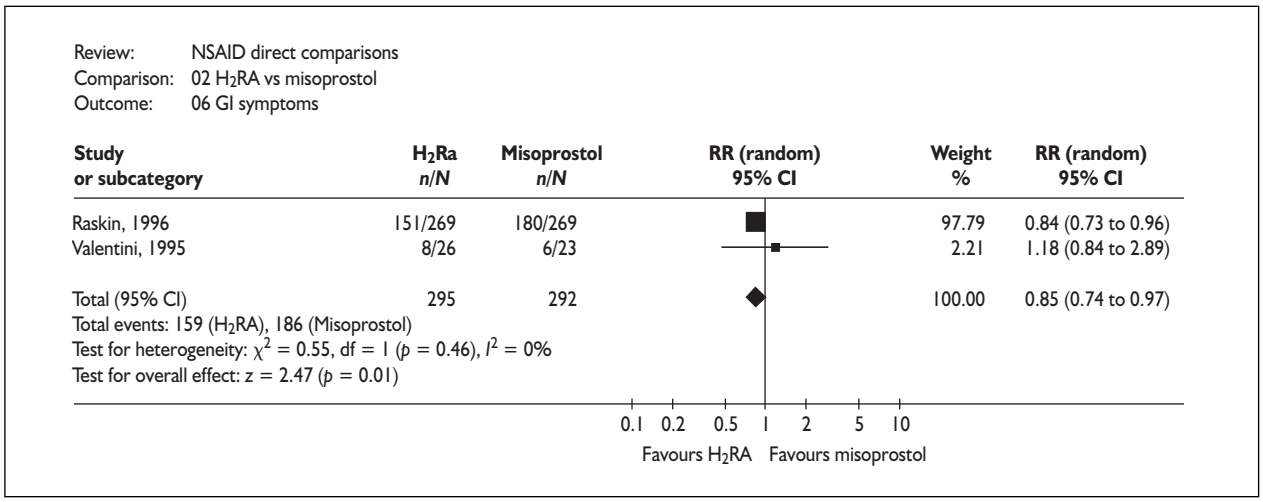

FIGURE 56 *Forest plot of H_2RA plus NSAID versus misoprostol plus NSAID, outcome GI symptoms*

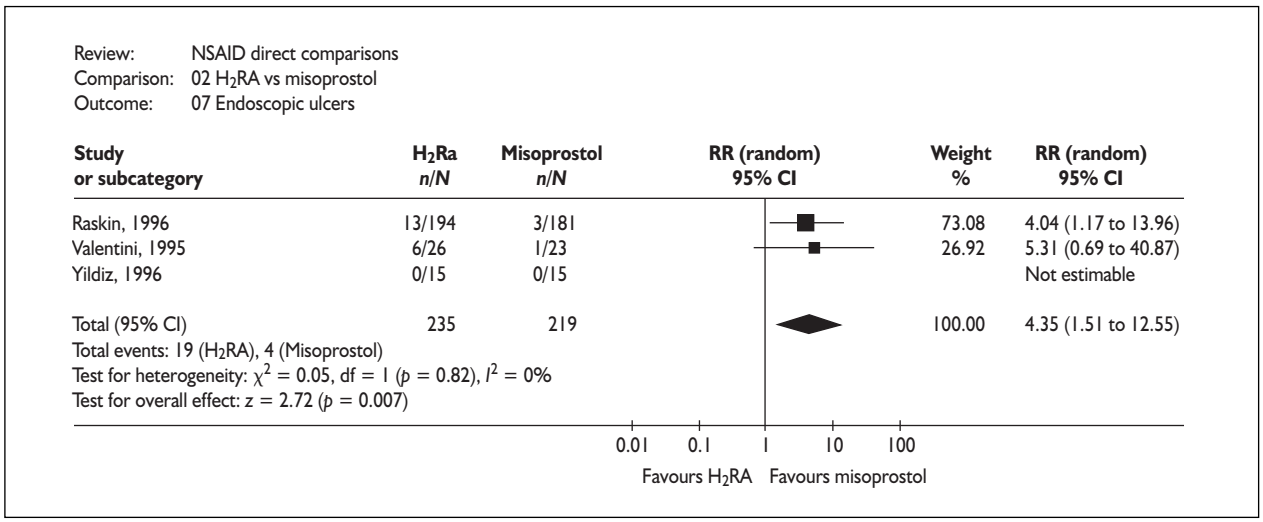

FIGURE 57 *Forest plot of H_2RA plus NSAID versus misoprostol plus NSAID, outcome endoscopic ulcers*

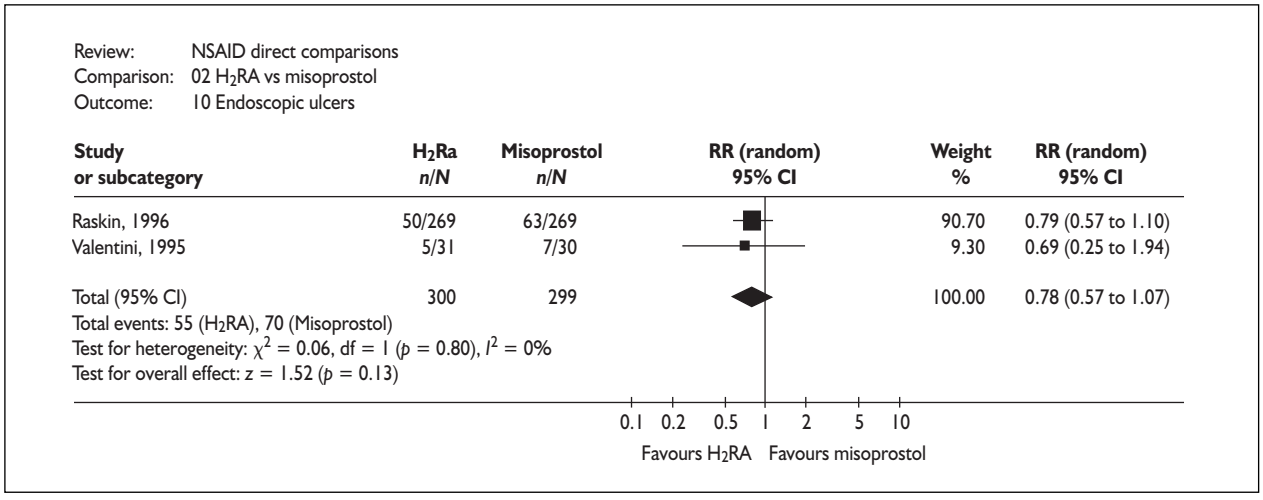

FIGURE 58 *Forest plot of H_2RA plus NSAID versus misoprostol plus NSAID, outcome total drop-outs*

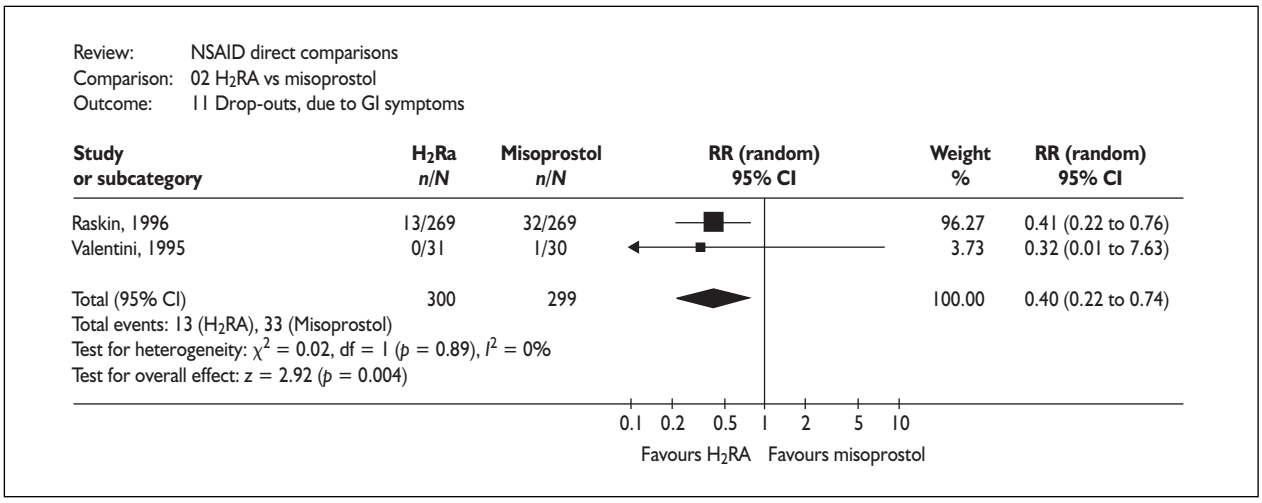

FIGURE 59 *Forest plot of H_2RA plus NSAID vs misoprostol plus NSAID, outcome drop-outs due to GI symptoms*

Drop-outs due to GI symptoms were significantly less common in the H_2RA group than the misoprostol group (RR 0.40, 95% CI 0.22 to 0.74). Significance was retained in all SAs. Total drop-outs were similar in number in the H_2RA and misoprostol groups. Anaemia and occult bleeding were not reported.

Indirect comparisons, H_2RA versus misoprostol

Indirect comparisons use the results of the MA of H_2RA plus NSAIDs versus NSAIDs alone and the results of the MA of misoprostol plus NSAIDs versus NSAIDs alone to estimate the effect of H_2RA plus NSAIDs versus misoprostol plus NSAIDs. They provide lower quality evidence than studies which directly compare H_2RA plus NSAIDs versus misoprostol plus NSAIDs.

Primary outcomes

Significant results were not seen for any primary outcomes and CIs were very wide.

Secondary outcomes

Significant results for secondary outcomes were only seen for endoscopic ulcers and drop-outs due to GI symptoms. Those treated with H_2RAs had a higher risk of endoscopic ulcers than those treated with misoprostol ($RR_{indirect}$ 1.67, 95% CI 1.22 to 2.28), but a lower risk of dropping out due to GI symptoms ($RR_{indirect}$ 0.52, 95% CI 0.31 to 0.88).

Summary

Three studies directly compared the efficacy of a H_2RA versus misoprostol, including participants with cancer pain, OA and RA, and aged 37–61 years on average. Baseline GI status was variable. Two studies prescribed either the H_2RA or NSAIDs at higher than recommended doses. Duration was from 4 to 8 weeks.

The summary risk of bias was 'moderate' for all three studies, with allocation concealment unclear in all and baseline comparability unclear in two. At least two of the studies were funded by a pharmaceutical company.

Comparability of primary outcomes could not be assessed by direct or indirect comparisons.

Endoscopic ulcers were significantly more common in those on H_2RAs compared with those on misoprostol according to both direct (RR 4.35, 95% CI 1.51 to 12.55, robust to SA) and indirect methods of assessment. Conversely, GI symptoms were less likely in those on H_2RAs (RR 0.85, 95% CI 0.74 to 0.97, robust to SA but not supported by indirect comparisons). The included direct comparisons suggested that drop-outs due to GI symptoms were less likely in those randomised to H_2RAs compared with misoprostol (RR 0.40, 95% CI 0.22 to 0.74, robust to SA), and again this was confirmed by indirect comparisons. No other secondary outcomes suggested significant differences in effect in either direct or indirect comparisons.

Chapter 12

H_2RA plus NSAID versus Cox-2 coxib NSAID: systematic review – included studies, results, analysis and robustness

Included studies

No studies were found that directly assessed this comparison. Only indirect comparisons can inform our understanding.

Publication bias

Publication bias could not be assessed in the absence of direct comparison studies.

Results

Direct comparisons, H_2RAs versus Cox-2 coxib

Results are summarised in *Table 17*. No studies were included that directly compared H_2RAs with Cox-2 coxib NSAIDs.

Indirect comparisons

Indirect comparisons use the results of the MA of H_2RA plus NSAIDs versus NSAIDs alone and the results of the MA of Cox-2 coxibs vs NSAIDs alone to estimate the effect of H_2RA plus NSAIDs versus Cox-2 coxibs. They provide lower quality evidence than studies which directly compare H_2RA plus NSAIDs versus Cox-2 coxibs.

Primary outcomes

No significant differences were seen between H_2RAs with Cox-1 NSAIDs and NSAIDs Cox-2s for any primary outcomes.

Secondary outcomes

No significant differences were seen between H_2RAs with Cox-1 NSAIDs and Cox-2 NSAIDs for any secondary outcome except endoscopic ulcers. Indirect comparisons suggest that endoscopic ulcers are more common in participants randomised to H_2RAs plus Cox-1 NSAIDs than in those randomised to Cox-2 coxib NSAIDs (RRindirect 2.20, 95% CI 1.64 to 2.95).

Summary

There were no included RCTs that directly compared the effects of H_2RA plus NSAID versus Cox-2 NSAID. Indirect comparison only suggests that endoscopic ulcers are more common in those on H_2RAs and a Cox-1 NSAID than in those on Cox-2 coxib NSAIDs.

TABLE 17 *Indirect comparisons, H_2RA versus Cox-2 coxibs displayed with relevant direct comparisons, and the data on which the indirect comparisons are based*

Outcome	RR, indirect (95% CI)	RR, H_2RA vs placebo (95% CI), events	RR, Cox-2 coxibs vs placebo (95% CI), events
Serious GI complications	0.60 (0.02 to 17.47)	0.33 (0.01 to 8.14), 1	0.55 (0.38 to 0.80), 114
Symptomatic ulcers	2.98 (0.12 to 73.19)	1.46 (0.06 to 35.53), 1	0.49 (0.38 to 0.62), 281
Serious CV or renal events	0.45 (0.07 to 3.05)	0.53 (0.08 to 3.46), 5	1.19 (0.80 to 1.75), 241
Deaths	2.94 (0.12 to 71.69)	3.00 (0.13 to 68.26), 1	1.02 (0.55 to 1.92), 78
GI symptoms	0.89 (0.68 to 1.16)	0.72 (0.56 to 0.92), 201	0.81 (0.74 to 0.89), 5184
Endoscopic ulcers	2.20 (1.64 to 2.95)	0.55 (0.44 to 0.70), 250	0.25 (0.21 to 0.30), 522
Anaemia	4.84 (0.19 to 120.23)	3.00 (0.12 to 73.29), 1	0.62 (0.51 to 0.74), 464
Occult bleeding			
Drop-outs, total	1.18 (0.98 to 1.42)	0.97 (0.84 to 1.12), 362	0.82 (0.73 to 0.92), 9510
Drop-outs, due to GI symptoms	1.03 (0.60 to 1.78)	0.71 (0.43 to 1.20), 57	0.69 (0.57 to 0.83), 2171

Chapter 13

PPI plus NSAID versus misoprostol plus NSAID: systematic review – included studies, results, analysis and robustness

Included studies

Table 18 summarises the included studies. For a complete table of characteristics of included studies, see Appendix 6h.

Two RCTs directly compared PPI with misoprostol, randomising 973 participants (64% female) to relevant study arms. The studies varied in size from 133 participants per arm[64] to 296 participants per arm.[62] The study by Graham and colleagues[64] was performed in 63 centres in North America and the Omnium trial conducted by Hawkey and colleagues[62] was performed in 93 centres in 14 countries including the UK and the USA. No additional outcome data were provided by authors of these included studies.

Participants

Hawkey and colleagues[62] recruited patients with OA, RA, combination and other types of arthritis. Graham and colleagues[64] did not report any details of type or duration of arthritis. Mean age of participants ranged from 57[62] to 62 years.[64]

In the Omnium trial,[62] two-thirds of all participants had just received treatment for ulcers and the remaining one-third had received the same treatment for more than 10 erosions. All participants in the Graham trial[64] had a history of ulcers with two-thirds of participants having previously completed a healing trial. Both studies excluded participants with an ulcer on baseline endoscopy. Graham and colleagues[64] defined an ulcer as a crater at least 5 mm in diameter.

Interventions

One study compared lansoprazole with misoprostol[64] and the other compared omeprazole with misoprostol.[62] The daily doses of NSAIDs and PPIs prescribed were within the recommended daily dosage according to the BNF.[23] OMNIUM[62] used 400 µg/day misoprostol (the minimum recommended daily dose) and Graham and colleagues[64] used 800 µg/day misoprostol (the

TABLE 18 *Brief characteristics of included PPI versus misoprostol studies*

Study	*N*	Participants	Interventions
Hawkey, 1998[62] OMNIUM **Summary risk of bias:** moderate	**Allocated:** b 274, c 296 (7 participants unaccounted for)	**Baseline GI status:** endoscopy performed and excluded participants without treatment success following 4–8 weeks healing phase **Type of arthritis:** OA, RA, other and combination	**Comparison:** misoprostol plus mixed NSAIDs (c) vs omeprazole plus mixed NSAIDs (b) **Duration:** 6 months
Graham, 2002[64] **Summary risk of bias:** low	**Allocated:** b 134, c 136, d 133	**Baseline GI status:** baseline endoscopy performed, patients had to have history of endoscopically documented gastric ulcer with or without coexisting duodenal ulcer or GI bleeding (2/3 participants had previously completed a healing trial for NSAID-associated gastric ulcer) **Type of arthritis:** no details	**Comparison:** lansoprazole (c, d) plus mixed NSAIDs vs misoprostol (b) plus mixed NSAIDs **Duration:** 12 weeks

maximum recommended daily dose). All participants took various NSAIDs including diclofenac and naproxen.

Aspirin use was not stated in OMNIUM[62] and was permitted at low dose for cardiovascular protection in Graham and colleagues.[64] Use of glucocorticoids was permitted in OMNIUM[63] and antacids were allowed in Graham and colleagues.[64]

The maximum duration of intervention was 12 weeks in Graham and colleagues[64] and 6 months in OMNIUM.[62] Patient education was not mentioned in either study.

Study quality

The summary risk of bias was 'moderate' for one study[62] and 'low' for the other.[64]

Allocation was described as 'randomly assigned' in OMNIUM[62] but the randomisation phase was not formally balanced (allocation was to a previous healing phase and not the participants who continued the study). Allocation concealment was unclear. The authors of the study by Graham and colleagues[64] supplied additional information that the "randomisation schedule was generated by a statistical specialist who was not involved in the trial design and that the randomisation was coded and stored in sealed envelopes". Allocation concealment was considered adequate.

Participants appeared comparable at baseline in both studies. All participants were blinded to treatment, with the exception of the participants in the misoprostol arm of Graham and colleagues.[64] It was unclear whether the outcome assessor was blinded in the OMNIUM trial.[62] Graham and colleagues[64] supplied extra information that stated that the outcome assessor was blinded.

A priori sample size calculations were performed in both studies. Neither study used the ITT principle. Participants were discontinued and excluded from analysis in one of the studies if they developed more than 10 erosions or more than moderate dyspepsia and adverse events.[62]

The pharmaceutical company Astra Hassle funded the OMNIUM trial[62] and one of the authors served as a consultant for Searle. TAP Pharmaceutical Products funded the trial by Graham and colleagues[64] and employed two of the authors.

Publication bias

There were insufficient included studies to assess publication bias.

Results

Results are summarised in *Table 19* and forest plots are shown in *Figures 60–64*. For SAs see Appendix 11c.

Primary outcomes

The OMNIUM trial[62] reported an absence of serious GI events in any arm and the other study reported one serious GI event in the PPI group.[64]

Symptomatic ulcers were not reported in either study.

One study reported two serious cardiovascular or renal illnesses in each arm.[65]

One study[62] (reported in Yeomans and colleagues[65]) provided data on health-related QoL measures. This study followed the NHP and the PGWB during a healing phase and then a follow-on prevention phase (the phase included here). During the prevention phase, "the health-related QoL assessed by the NHP was preserved". No further data, or data by intervention group, were presented. Similarly, the PGWB index was maintained at "the same level" as after healing. See Appendix 10a for further details on QoL outcomes.

One study reported one death in the misoprostol arm.[65]

Secondary outcomes

Endoscopic ulcers were reported in 160 of 972 participants (16%) and occurred with equal frequency in the PPI group and the misoprostol group (RR 1.08, 95% CI 0.50 to 2.32), with significant heterogeneity ($p = 0.02$). A total of 139 of 973 participants (14%) dropped out; the RR of dropping out was 0.71 (95% CI 0.52 to 0.98), with no evidence of heterogeneity ($p = 0.99$). This lower risk of drop-outs in the PPI arm compared with misoprostol was not altered by SA. Total GI symptoms, anaemia, occult bleeding and numbers of drop-outs due to GI symptoms were not reported in either trial.

Indirect comparisons

Indirect comparisons use the results of the MA of H_2RA plus NSAIDs versus NSAIDs alone and the

TABLE 19 *Indirect comparisons, PPI versus misoprostol displayed with relevant direct comparisons, and the data on which the indirect comparisons are based*

Outcome	RR, direct (95% CI), events	RR, indirect (95% CI)	RR, PPI vs placebo (95% CI), events	RR misoprostol vs placebo (95% CI), events
Serious GI complications	1.51 (0.06 to 36.71), 1	0.81 (0.12 to 5.52)	0.46 (0.07 to 2.92), 3	0.57 (0.36 to 0.91), 75
Symptomatic ulcers		0.25 (0.05 to 1.36)	0.09 (0.02 to 0.47), 18	0.36 (0.20 to 0.67), 44
Serious CV or renal events	0.50 (0.07 to 3.51), 4	0.44 (0.03 to 7.36)	0.78 (0.10 to 6.26), 3	1.78 (0.26 to 12.07), 4
Deaths	0.17 (0.01 to 4.08), 1	0.19 (0.01 to 4.13)	0.17 (0.01 to 4.05), 1	0.89 (0.46 to 1.74), 35
GI symptoms		0.44 (0.23 to 0.86)	0.43 (0.24 to 0.76), 45	0.97 (0.70 to 1.35), 1218
Endoscopic ulcers	1.08 (0.50 to 2.32), 160	1.12 (0.83 to 1.51)	0.37 (0.30 to 0.46), 281	0.33 (0.27 to 0.41), 658
Anaemia				2.66 (0.11 to 63.84), 1
Occult bleeding				0.46 (0.16 to 1.32), 16
Drop-outs, total	0.71 (0.52 to 0.98), 139	0.88 (0.56 to 1.40)	0.98 (0.62 to 1.53), 116	1.11 (1.00 to 1.23), 4772
Drop-outs, due to GI symptoms		0.33 (0.19 to 0.58)	0.45 (0.26 to 0.78), 48	1.36 (1.26 to 1.46), 2332

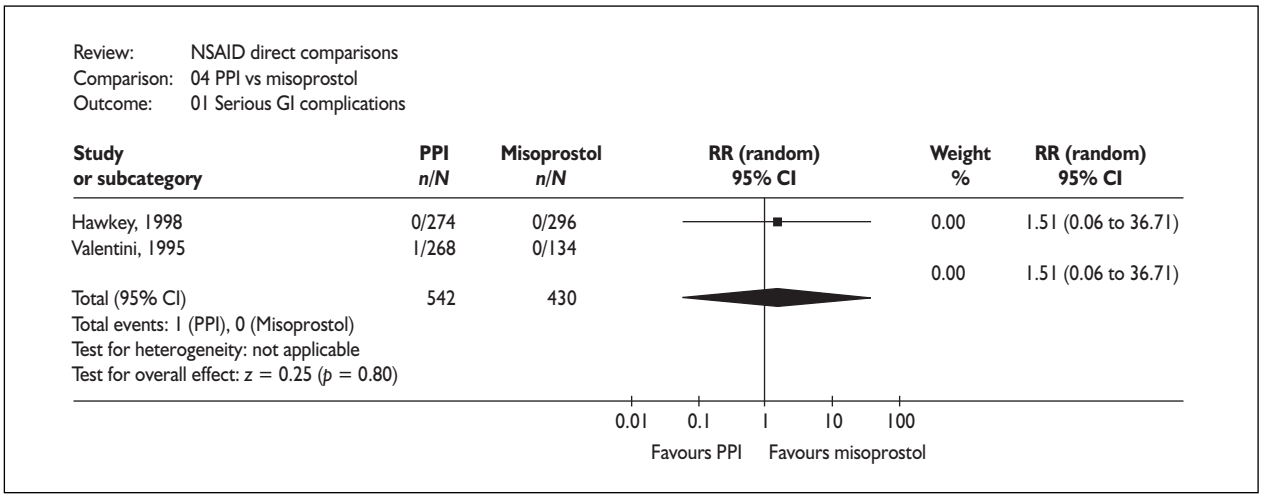

FIGURE 60 *Forest plot of PPI plus NSAID versus misoprostol plus NSAID, outcome serious GI events*

results of the MA of PPI plus NSAIDs versus NSAIDs alone to estimate the effect of H_2RA plus NSAIDs versus a PPI plus NSAIDs. They provide lower quality evidence than studies which directly compare H_2RA plus NSAIDs versus a PPI plus NSAIDs.

Primary outcomes

No significant differences were seen between the use of PPIs with NSAIDs versus misoprostol with NSAIDs for any primary outcomes, and 95% CIs were very wide.

Secondary outcomes

No significant differences were seen between use of PPIs with NSAIDs versus misoprostol with NSAIDs for any secondary outcome except GI symptoms and drop-outs due to GI symptoms. Indirect comparisons suggest that GI symptoms are less common in participants randomised to PPIs

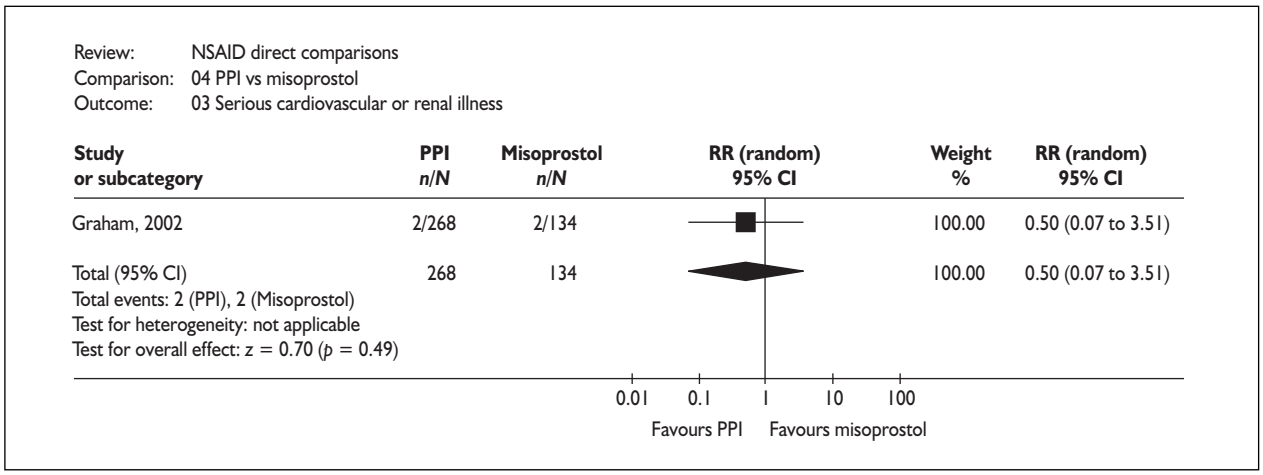

FIGURE 61 *Forest plot of PPI plus NSAID versus misoprostol plus NSAID, outcome serious cardiovascular or renal events*

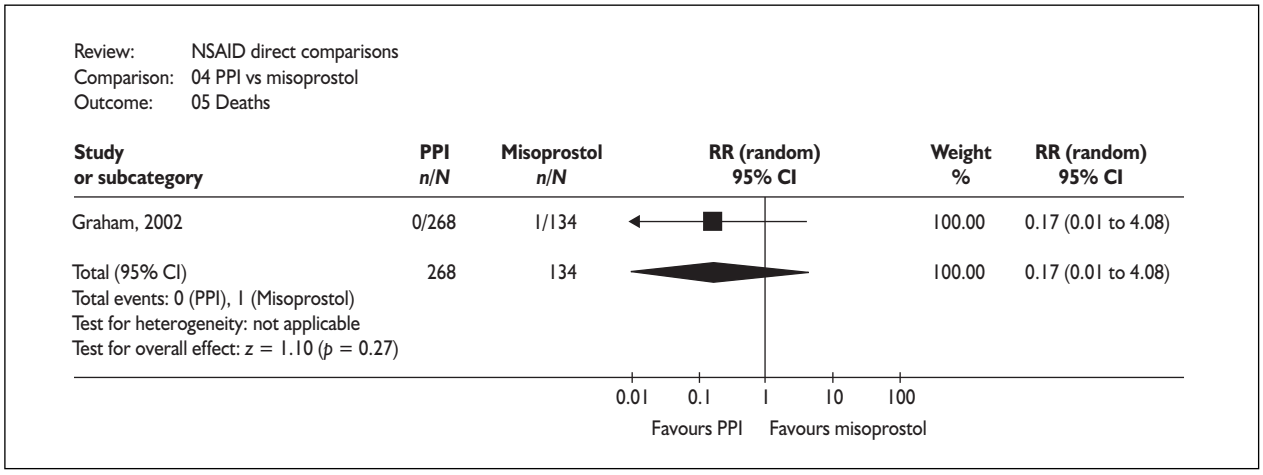

FIGURE 62 *Forest plot of PPI plus NSAID versus misoprostol plus NSAID, outcome deaths*

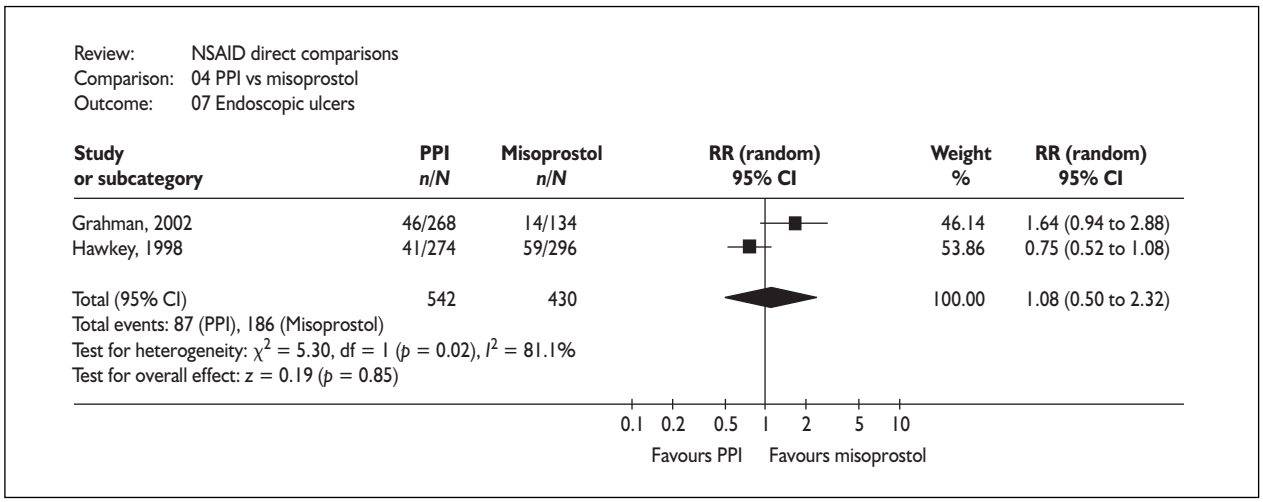

FIGURE 63 *Forest plot of PPI plus NSAID versus misoprostol plus NSAID, outcome endoscopic ulcers*

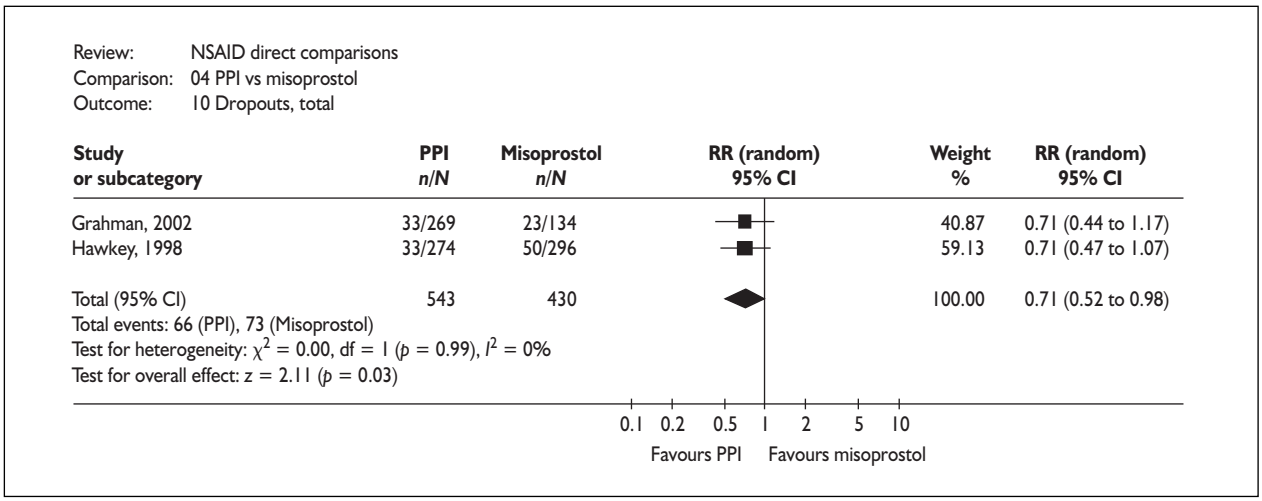

FIGURE 64 *Forest plot of PPI plus NSAID versus misoprostol plus NSAID, outcome total drop-outs*

than in those randomised to misoprostol ($RR_{indirect}$ 0.44, 95% CI 0.23 to 0.86). Similarly, drop-outs due to GI symptoms appear less common in those randomised to PPIs compared with misoprostol ($RR_{indirect}$ 0.33, 95% CI 0.19 to 0.58).

Summary

Two RCTs directly compared PPI with misoprostol. Participants had OA and RA, were middle aged and all had previously had ulcers or erosions. Lansoprazole and omeprazole were compared with misoprostol, all within current recommended doses. Duration was 12–26 weeks.

One study was assessed as being of moderate risk of bias and the other of low risk of bias. Allocation concealment was adequate in one study and unclear in the other and baseline comparability was adequate in both studies. It was not possible to assess publication bias.

There were no significant differences between those on PPIs and misoprostol as regards any primary outcomes, from direct or indirect comparisons.

Total drop-outs were significantly less frequent in those on PPIs than those on misoprostol in direct comparisons (RR 0.71, 95% CI 0.52 to 0.98), but there were no significant differences in indirect comparisons. GI symptoms and drop-outs due to GI symptoms were not reported in the direct comparisons, but indirect comparisons suggest significantly fewer GI symptoms and drop-outs due to GI symptoms in those on PPIs compared with those on misoprostol. Endoscopic ulcers occurred to similar degrees in those on PPIs and misoprostol according to both the direct and indirect comparisons. Anaemia and occult bleeding were not reported in the direct comparisons, and did not show significant differences in the indirect comparisons.

Chapter 14

PPI plus NSAID versus Cox-2 coxib NSAID: systematic review – included studies, results, analysis and robustness

Included studies

Table 20 summarises the included studies. For a complete table of characteristics of included studies, see Appendix 6i.

One study[22] directly compared PPIs with Cox-2 coxibs, randomising 287 participants (56% female). The study was performed in Hong Kong, China. No additional outcome data were provided by authors of this study.

Participants

The study recruited patients with OA, RA and other types of arthritis and did not state duration of arthritis. Mean age of participants was 68.8 years in the PPI arm and 66.5 years in the Cox-2 arm. All participants were required to present with ulcer healing on baseline endoscopy after healing treatment following initial presentation with bleeding ulcers.

Interventions

The study compared omeprazole plus diclofenac with celecoxib. The daily doses of NSAIDs and PPIs prescribed were within the recommended daily dosage according to the BNF. The maximum duration of intervention was 6 months. Aspirin use was permitted at low dose and antacids, non-NSAID analgesics and disease-modifying anti-rheumatic drugs (DMARDs) were also permitted. Patient education was not mentioned. Compliance was assessed by tablet count and "92% of participants in each arm took at least 70% of the study medication".

Study quality

The summary risk of bias was 'low'. The method of randomisation was described as 'randomly assigned' with a computer-generated list of random numbers and independent staff who assigned treatments according to consecutive numbers in sealed envelopes. Allocation concealment was 'adequate'. Participants appeared comparable at baseline. All participants and outcome assessors were blinded to treatment. An *a priori* sample size calculation was performed. The study did not use the ITT principle to assess the primary outcome. The Chinese University of Hong Kong and Health Services Research Centre of Hong Kong funded the study.

Publication bias

There were insufficient included studies to assess publication bias.

Results

The results are summarised in *Table 21* and forest plots are shown in *Figures 65–72*. For SAs, see Appendix 11d.

TABLE 20 *Brief characteristics of included PPI versus Cox-2 coxib studies*

Study	*N*	Participants	Interventions
Chan, 2002[22] **Summary risk of bias:** low	**Allocated:** a 143, b 144	**Baseline GI status:** baseline endoscopy performed, included those who presented with ulcer bleeding, with ulcer healing confirmed by follow-up endoscopy **Type of arthritis:** OA and RA	**Comparison:** celecoxib (b) vs omeprazole plus diclofenac (extended release) (a) **Duration:** 6 months

TABLE 21 *Indirect comparisons, PPI versus Cox-2 coxib displayed with relevant direct comparisons, and the data on which the indirect comparisons are based*

Outcome	RR, direct (95% CI), events	RR, indirect (95% CI)	RR, PPI vs placebo (95% CI), events	RR, Cox-2 coxib vs placebo (95% CI), events
Serious GI complications	2.01 (0.84 to 4.84), 21	0.84 (0.12 to 5.60)	0.46 (0.07 to 2.92), 3	0.55 (0.38 to 0.80), 114
Symptomatic ulcers	1.29 (0.50 to 3.38), 16	0.18 (0.04 to 0.91)	0.09 (0.02 to 0.47), 18	0.49 (0.38 to 0.62), 281
Serious CV or renal events	1.11 (0.49 to 2.53), 21	0.66 (0.08 to 5.38)	0.78 (0.10 to 6.26), 3	1.19 (0.80 to 1.75), 241
Deaths	1.01 (0.06 to 15.94), 2	0.17 (0.01 to 3.58)	0.17 (0.01 to 4.05), 1	1.02 (0.55 to 1.92), 78
GI symptoms	0.61 (0.33 to 1.14), 37	0.53 (0.30 to 0.95)	0.43 (0.24 to 0.76), 45	0.81 (0.74 to 0.89), 5184
Endoscopic ulcers		1.48 (1.12 to 1.96)	0.37 (0.30 to 0.46), 281	0.25 (0.21 to 0.30), 522
Anaemia	9.06 (0.49 to 166.80), 4			0.62 (0.51 to 0.74), 464
Occult bleeding				
Drop-outs, total	0.91 (0.51 to 1.62), 40	1.20 (0.75 to 1.90)	0.98 (0.62 to 1.53), 116	0.82 (0.73 to 0.92), 9510
Drop-outs, due to GI symptoms	0.84 (0.26 to 2.69), 11	0.65 (0.36 to 1.17)	0.45 (0.26 to 0.78), 48	0.69 (0.57 to 0.83), 2171

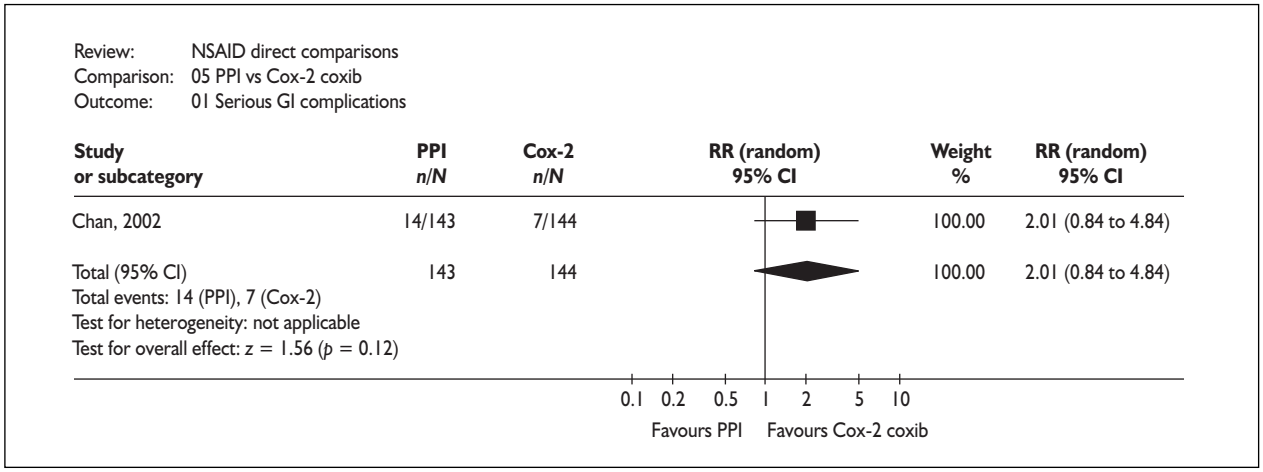

FIGURE 65 *Forest plot of PPI plus NSAID vs Cox-2 coxib NSAID, outcome serious GI events*

Primary outcomes

Chan and colleagues[22] reported 14 serious GI events in the PPI arm and seven serious GI events in the Cox-2 arm (RR 2.01, 95% CI 0.84 to 4.84); nine symptomatic ulcers in the PPI arm and seven in the Cox-2 arm (RR 1.29, 95% CI 0.50 to 3.38); 11 serious cardiovascular or renal illnesses in the PPI arm and 10 in the Cox-2 arm (RR 1.11, 95% CI 0.49 to 2.53); and one death in each arm (RR 1.01, 95% CI 0.06 to 15.95). Health-related QoL was not reported.

Secondary outcomes

Endoscopic ulcers were not reported. Anaemia occurred in four participants in the PPI arm and none of the participants in the Cox-2 arm (RR 9.06, 95% CI 0.49 to 166.81). Forty of 287 participants dropped out (RR 0.91, 95% CI 0.51 to 1.62, PPI vs Cox-2 coxib). Eleven of 287 participants dropped out due to GI symptoms (RR 0.84, 95% CI 0.26 to 2.69, PPI vs Cox-2 coxib). Occult bleeding was not reported.

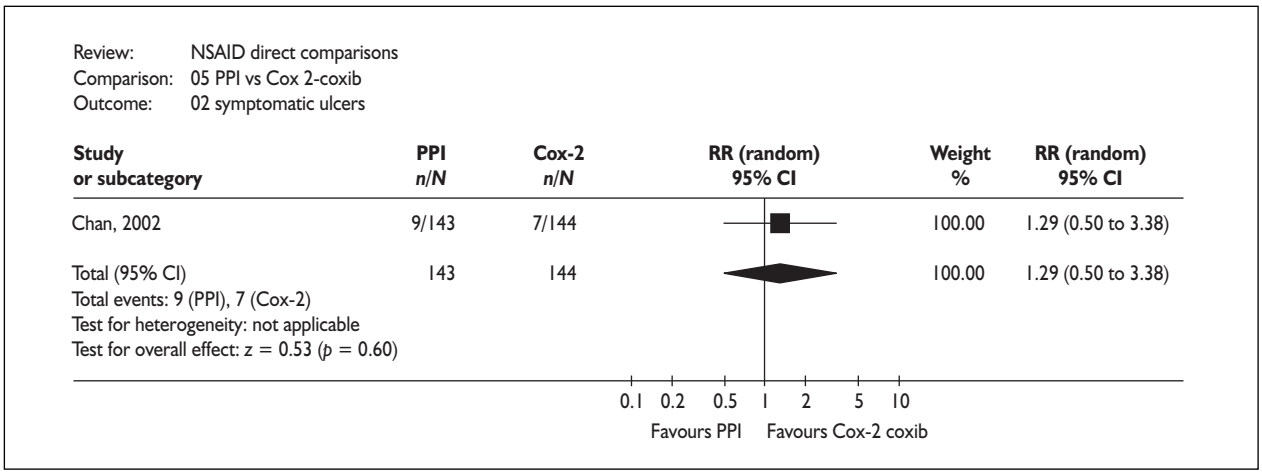

FIGURE 66 *Forest plot of PPI plus NSAID versus Cox-2 coxib NSAID, outcome symptomatic ulcers*

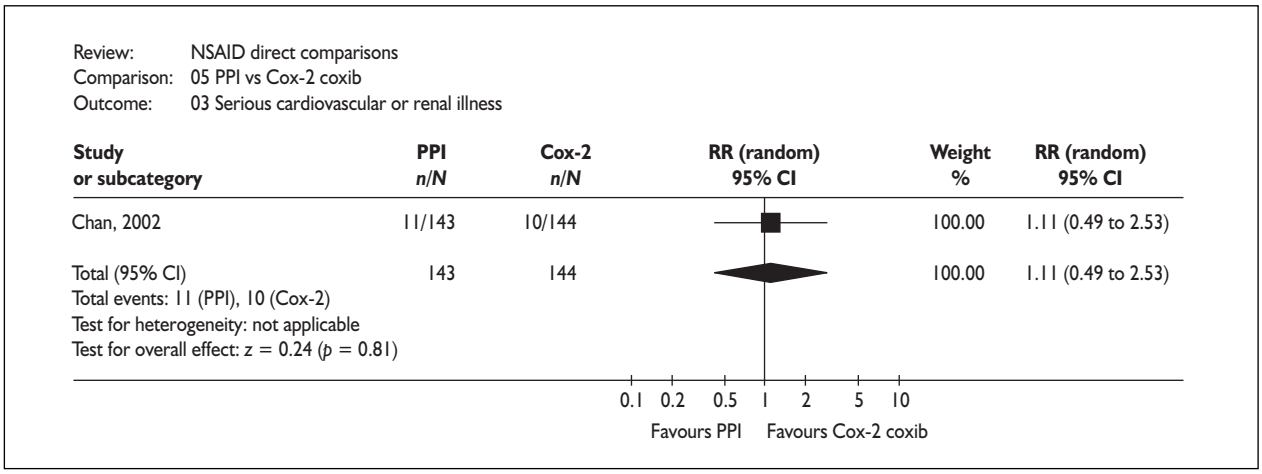

FIGURE 67 *Forest plot of PPI plus NSAID versus Cox-2 coxib NSAID, outcome serious cardiovascular or renal events*

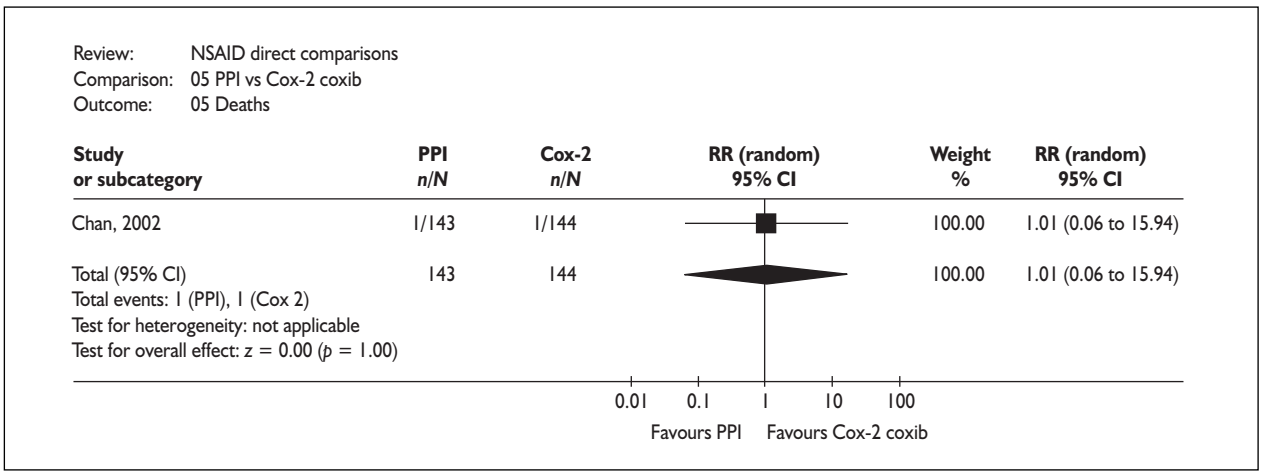

FIGURE 68 *Forest plot of PPI plus NSAID versus Cox-2 coxib NSAID, outcome deaths*

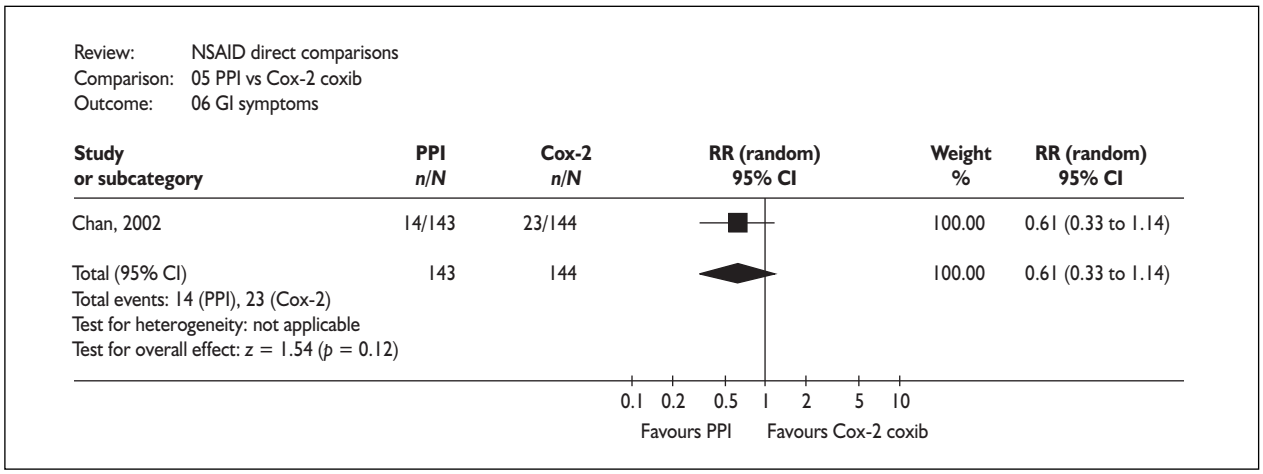

FIGURE 69 *Forest plot of PPI plus NSAID versus Cox-2 coxib NSAID, outcome GI symptoms*

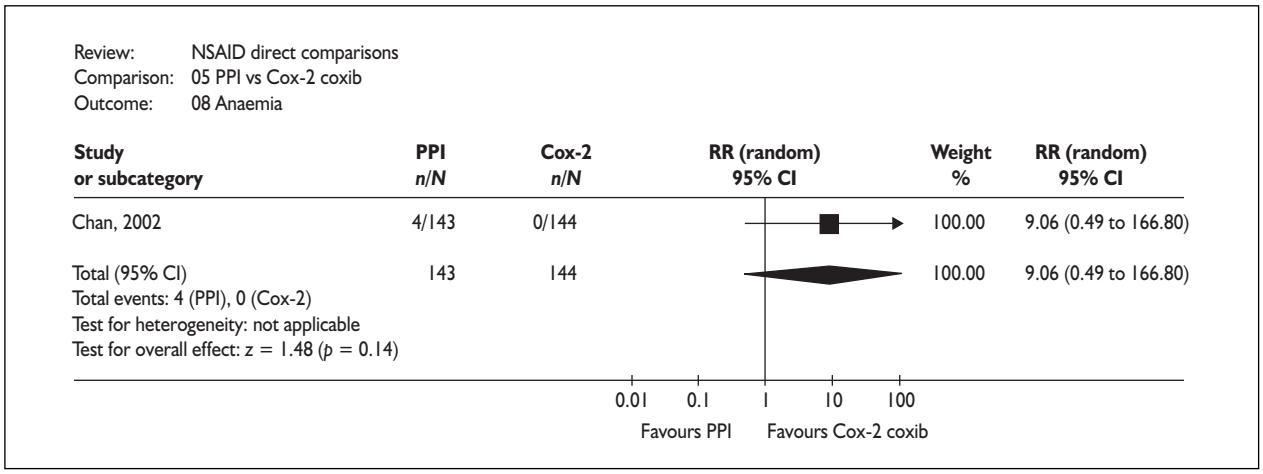

FIGURE 70 *Forest plot of PPI plus NSAID versus Cox-2 coxib NSAID, outcome anaemia*

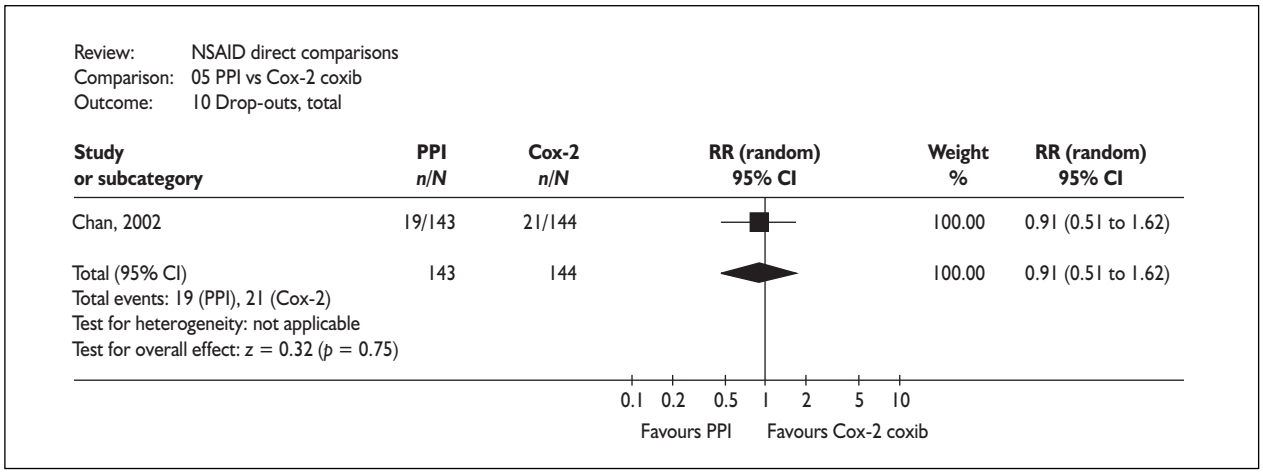

FIGURE 71 *Forest plot of PPI plus NSAID versus Cox-2 coxib NSAID, outcome total drop-outs*

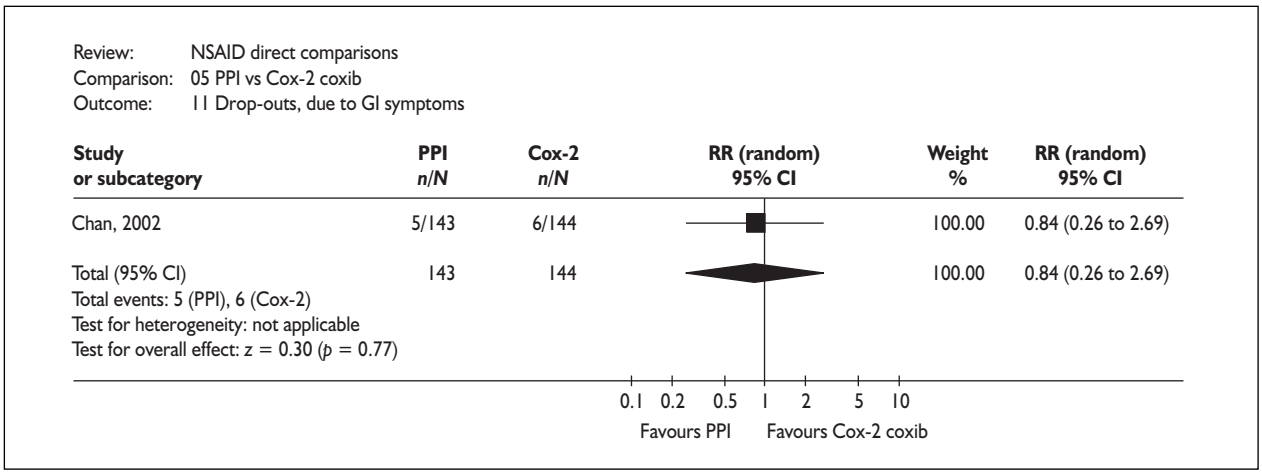

FIGURE 72 *Forest plot of PPI plus NSAID versus Cox-2 coxib NSAID, outcome drop-outs due to GI symptoms*

Indirect comparisons

Indirect comparisons use the results of the MA of PPIs plus NSAIDs versus NSAIDs alone and the results of the MA of Cox-2 coxibs versus NSAIDs alone to estimate the effect of PPIs plus NSAIDs versus Cox-2 coxibs. They provide lower quality evidence than studies which directly compare PPIs plus NSAIDs versus Cox-2 coxibs.

Primary outcomes

No significant differences were seen between the use of PPIs with NSAIDs versus Cox-2 coxib NSAIDs for any primary outcomes, except symptomatic ulcers, which appeared less common in those on PPIs ($RR_{indirect}$ 0.18, 95% CI 0.04 to 0.91).

Secondary outcomes

No significant differences were seen between use of PPIs with NSAIDs versus Cox-2 NSAIDs for occult bleeding or any type of drop-outs. Significantly fewer GI symptoms were seen in those on PPIs ($RR_{indirect}$ 0.53, 95% CI 0.30 to 0.95), but there were significantly more endoscopic ulcers ($RR_{indirect}$ 1.48, 95% CI 1.12 to 1.96). No other significant differences were seen.

Summary

One RCT directly compared PPIs with Cox-2 in 287 participants with OA and RA and a mean age of 68 years, following healing of bleeding ulcers. Omeprazole plus diclofenac was compared with celecoxib at doses within the recommended ranges for 26 weeks.

The summary risk of bias was 'low', with adequate allocation concealment and baseline comparability. Funding was from non-pharmaceutical industry sources.

No significant differences were reported between those on PPIs and Cox-2 coxibs in respect of any primary outcomes in the study directly comparing the two treatments. However, indirect comparisons suggested significantly fewer symptomatic ulcers in those on PPIs compared with Cox-2 coxibs.

Similarly, there were no significant differences in secondary outcomes between the PPI and Cox-2 groups in the direct comparison, but indirect comparisons suggested a significant reduction in GI symptoms in those on PPIs compared with those on Cox-2 coxibs, together with a significant increase in endoscopic ulcers.

Chapter 15

Misoprostol plus NSAID versus Cox-2 coxib NSAID: systematic review – included studies, results, analysis and robustness

Included studies

Table 22 summarises the included studies. For a complete table of characteristics of included studies, see Appendix 6j.

Characteristics of studies

One RCT directly compared misoprostol plus Cox-1 NSAIDs with Cox-2 coxibs,[144] randomising 283 participants (80% female). The study was performed in North and South America. No additional outcome data were provided by the authors of this study.

Participants

All participants had OA. Mean duration of arthritis was 8.5 years in one arm and 6.8 years in the other. Participants' mean age was 62 years. No baseline endoscopy was performed; 7% of both arms had a prior history of GI ulceration or bleeds.

Interventions

The study compared rofecoxib with misoprostol plus diclofenac (Arthrotec). Misoprostol was prescribed at 400 µg/day, rofecoxib at 12.5 mg/day, both within the recommended dosages. The maximum duration of intervention was 6 weeks. Patient education was not mentioned in any study.

Study quality

The summary risk of bias was 'moderate'. Method of randomisation was described as "randomised according to a computer-generated schedule stratified by history of GI ulcer or bleeds". Allocation concealment was unclear, but baseline comparability was good. Participants were blinded, whereas blinding of assessors was unclear.

ITT analyses were undertaken and *a priori* sample size calculations were performed. Compliance was not mentioned. Merck funded the study.

Publication bias

There were insufficient included studies to assess publication bias.

Results

The results are summarised in *Table 23* and forest plots are shown in *Figures 73–76*. For SAs see Appendix 11e.

Primary outcomes

Serious cardiovascular or renal events were the only primary outcome reported. Twenty-four events occurred with no significant difference between misoprostol or Cox-2 coxib arms (RR 0.72, 95% CI 0.32 to 1.58, robust to SA).

Secondary outcomes

Total GI symptoms were reported in 187 participants (39%), with a significantly larger risk in those on misoprostol than in the Cox-2 coxib group (RR 1.68, 95% CI 1.32 to 2.13). Sensitivity SAs did not alter the results.

TABLE 22 *Brief characteristics of included misoprostol versus Cox-2 coxib studies*

Study	*N*	Participants	Interventions
Acevedo, 2001[144] **Summary risk of bias:** moderate	**Allocated:** a 241, b 242	**Baseline GI status:** no baseline endoscopy performed, 7% had prior history of UGI ulceration or bleeding **Type of arthritis:** OA	**Comparison:** rofecoxib (b) vs arthrotec (a) **Duration:** 6 weeks

TABLE 23 *Indirect comparisons, misoprostol versus Cox-2 coxib displayed with relevant direct comparisons, and the data on which the indirect comparisons are based*

Outcome	RR, direct (95% CI), events	RR, indirect (95% CI)	RR, misoprostol vs placebo (95% CI), events	RR, Cox-2 coxib vs placebo (95% CI), events
Serious GI complications		1.04 (0.57 to 1.88)	0.57 (0.36 to 0.91), 75	0.55 (0.38 to 0.80), 114
Symptomatic ulcers		0.73 (0.38 to 1.41)	0.36 (0.20 to 0.67), 44	0.49 (0.38 to 0.62), 281
Serious CV or renal events	0.72 (0.32 to 1.58), 24	1.50 (0.21 to 10.60)	1.78 (0.26 to 12.07), 4	1.19 (0.80 to 1.75), 241
Deaths		0.87 (0.35 to 2.17)	0.89 (0.46 to 1.74), 35	1.02 (0.55 to 1.92), 78
GI symptoms	1.68 (1.32 to 2.13), 187	1.20 (0.85 to 1.68)	0.97 (0.70 to 1.35), 1218	0.81 (0.74 to 0.89), 5184
Endoscopic ulcers		1.32 (1.00 to 1.74)	0.33 (0.27 to 0.41), 658	0.25 (0.21 to 0.30), 522
Anaemia		4.29 (0.18 to 103.92)	2.66 (0.11 to 63.84), 1	0.62 (0.51 to 0.74), 464
Occult bleeding		0.46 (0.16 to 1.32)	0.46 (0.16 to 1.32), 16	
Drop-outs, total	1.54 (0.86 to 2.76), 43	1.35 (1.16 to 1.58)	1.11 (1.00 to 1.23), 4772	0.82 (0.73 to 0.92), 9510
Drop-outs, due to GI symptoms	9.04 (1.15 to 70.78), 10	1.97 (1.61 to 2.41)	1.36 (1.26 to 1.46), 2332	0.69 (0.57 to 0.83), 2171

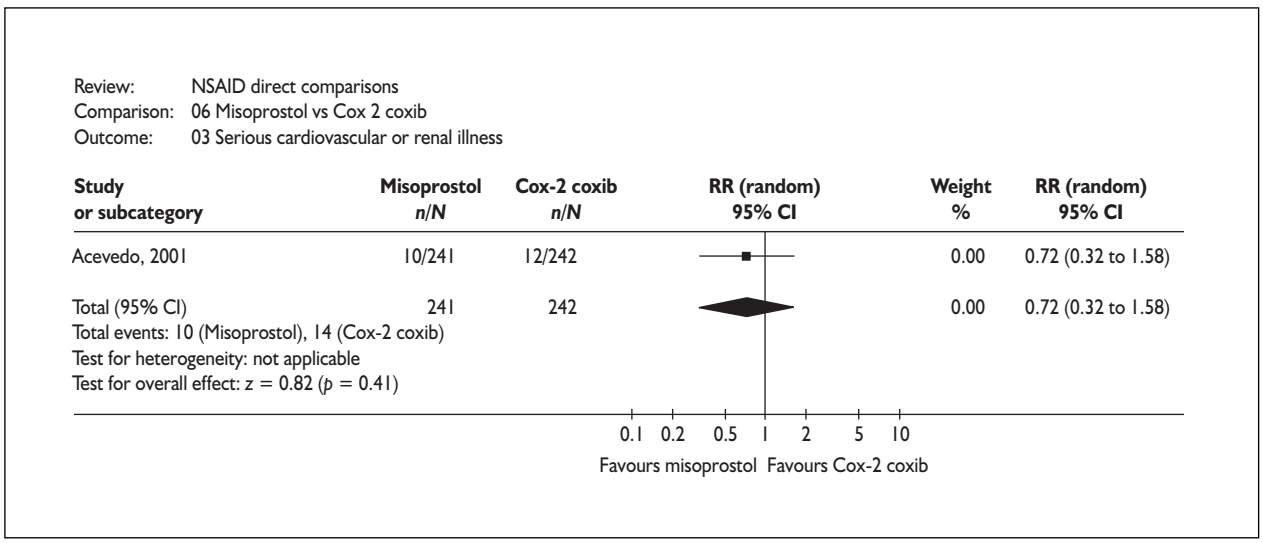

FIGURE 73 *Forest plot of misoprostol plus NSAID versus Cox-2 coxib NSAID, outcome serious cardiovascular or renal illness*

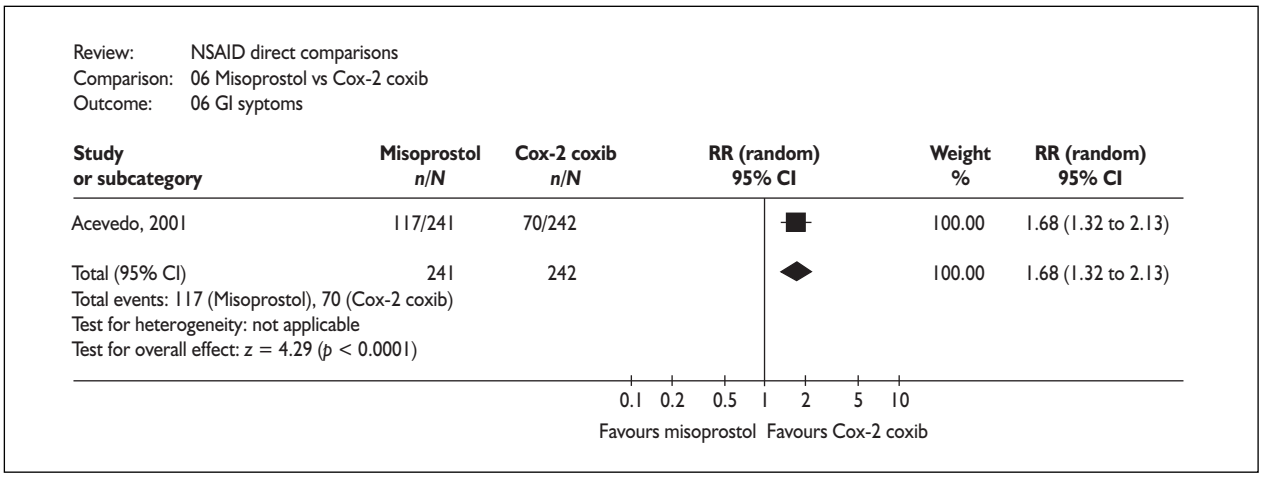

FIGURE 74 *Forest plot of misoprostol plus NSAID versus Cox-2 coxib NSAID, outcome GI symptoms*

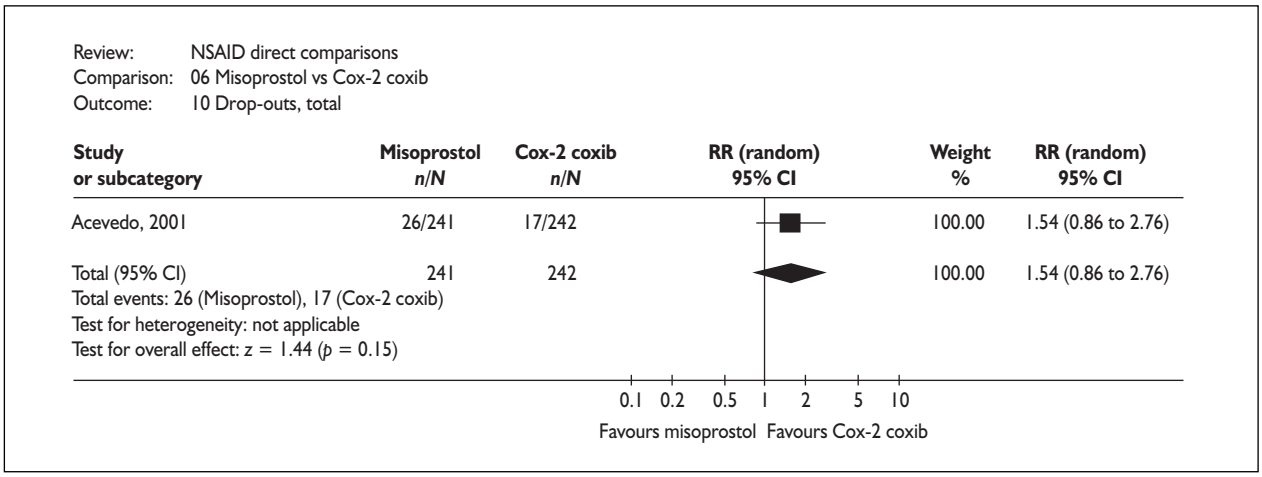

FIGURE 75 *Forest plot of Misoprostol plus NSAID versus Cox-2 coxib NSAID, outcome total drop-outs*

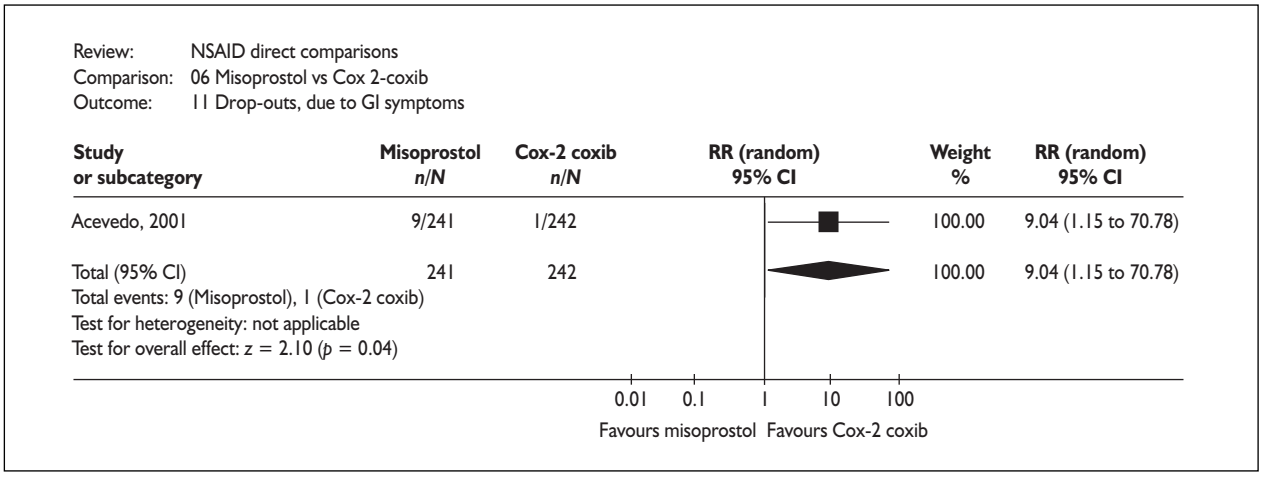

FIGURE 76 *Forest plot of Misoprostol plus NSAID versus Cox-2 coxib NSAID, outcome drop-outs due to GI symptoms*

Total drop-outs were not significantly different between the misoprostol and Cox-2 coxib arms (RR 1.54, 95% CI 0.86 to 2.76), whereas drop-outs due to GI symptoms were significantly more likely in the misoprostol than the Cox-2 coxib arms (RR 9.04, 95% CI 1.15 to 70.8, stable to SAs). No other outcomes were reported.

Indirect comparisons

Indirect comparisons use the results of the MA of misoprostol plus NSAIDs versus NSAIDs alone and the results of the MA of Cox-2 coxibs vs NSAIDs alone to estimate the effect of misoprostol plus NSAIDs versus Cox-2 coxibs. They provide lower quality evidence than studies which directly compare misoprostol plus NSAIDs versus Cox-2 coxibs.

Primary outcomes

No significant effect of misoprostol compared with Cox-2 coxibs on any primary outcomes were suggested by indirect comparisons.

Secondary outcomes

Significant increases in endoscopic ulcers ($RR_{indirect}$ 1.32, 95% CI 1.00 to 1.74), total drop-outs ($RR_{indirect}$ 1.35, 95% CI 1.16 to 1.58) and drop-outs due to GI symptoms ($RR_{indirect}$ 1.97, 95% CI 1.61 to 2.41) were seen in those on misoprostol over those on Cox-2 coxibs, in the adjusted indirect comparisons. No significant RRs were seen for GI symptoms, anaemia or occult bleeding.

Summary

One RCT directly compared misoprostol with a Cox-2 coxib, randomising 283 participants with OA. Mean age was 62 years. None had baseline endoscopies, but 7% had previous GI ulcers or bleeds. The study compared rofecoxib with misoprostol plus diclofenac over 6 weeks.

Summary risk of bias was 'moderate', allocation concealment was unclear and baseline comparability was adequate. A pharmaceutical company funded the study. Publication bias was not assessable.

Of the primary outcomes, only serious cardiovascular or renal events were directly assessed, with no significant difference in risk between misoprostol and Cox-2 coxibs. None of the primary outcomes assessed by indirect comparisons suggested significant differences in risk.

Cox-2 coxibs were significantly better at preventing GI symptoms (RR for misoprostol 1.68, 95% CI 1.32 to 2.13) and drop-outs due to GI symptoms (RR for misoprostol 9.04, 95% CI 1.15 to 70.78) than misoprostol, but no significant differences were seen for total drop-outs. Indirect comparisons suggested an increased risk of endoscopic ulcers ($RR_{indirect}$ 1.32, 95% CI 1.00 to 1.74), total drop-outs ($RR_{indirect}$ 1.35, 95% CI 1.16 to 1.58) and drop-outs due to GI symptoms ($RR_{indirect}$ 1.97, 95% CI 1.61 to 2.41) in those on misoprostol instead of Cox-2 coxibs. No other significant differences were observed.

Chapter 16

H_2RA plus NSAID versus Cox-2 preferentials: systematic review – included studies, results, analysis and robustness

Included studies

No studies were found that directly assessed this comparison. Only indirect comparisons can inform our understanding.

Publication bias

Publication bias could not be assessed in the absence of direct comparison studies.

Results

Direct comparisons, H_2RAs versus Cox-2 preferentials

No studies were included that directly compared H_2RAs with Cox-2 preferential NSAIDs.

Indirect comparisons

Results are summarised in *Table 24*.

TABLE 24 *Indirect comparisons, H_2RA vs Cox-2 preferentials displayed with relevant direct comparisons, and the data on which the indirect comparisons are based*

Outcome	RR, indirect (95% CI)	RR, H_2RA vs placebo (95% CI), events	RR, Cox-2 preferential vs placebo (95% CI), events
Serious GI complications	0.54 (0.02 to 16.24)	0.33 (0.01 to 8.14), 1	0.61 (0.34 to 1.10)
Symptomatic ulcers	3.56 (0.14 to 89.54)	1.46 (0.06 to 35.53), 1	0.41 (0.26 to 0.65)
Serious CV or renal events	0.56 (0.08 to 3.97)	0.53 (0.08 to 3.46), 5	0.95 (0.55 to 1.66)
Deaths	4.41 (0.17 to 114.25)	3.00 (0.13 to 68.26), 1	0.68 (0.28 to 1.64)
GI symptoms	0.99 (0.76 to 1.28)	0.72 (0.56 to 0.92), 201	0.73 (0.68 to 0.79)
Endoscopic ulcers	1.34 (0.51 to 3.53)	0.55 (0.44 to 0.70), 250	0.41 (0.16 to 1.05)
Anaemia	10.00 (0.29 to 339.32)	3.00 (0.12 to 73.29), 1	0.30 (0.07 to 1.30)
Occult bleeding			0.86 (0.33 to 2.24)
Drop-outs, total	1.04 (0.90 to 1.21)	0.97 (0.84 to 1.12), 362	0.93 (0.89 to 0.97)
Drop-outs, due to GI symptoms	1.13 (0.67 to 1.91)	0.71 (0.43 to 1.20), 57	0.63 (0.56 to 0.71)

Indirect comparisons use the results of the MA of H_2RAs plus NSAIDs versus NSAIDs alone and the results of the meta-analysis of Cox-2 preferentials versus NSAIDs alone to estimate the effect of H_2RAs plus NSAIDs versus Cox-2 preferentials. They provide lower quality evidence than studies which directly compare H_2RAs plus NSAIDs versus Cox-2 preferentials.

Primary and secondary outcomes

No significant differences were seen between H_2RAs with Cox-1 NSAIDs and Cox-2 preferential NSAIDs for any primary or secondary outcomes.

Summary

There were no included RCTs that directly compared the effects of H_2RA plus NSAID vs Cox-2 preferential NSAID. Indirect comparisons do not suggest any statistically significant differences between H_2RAs with a Cox-1 NSAID and Cox-2 preferential NSAIDs.

Chapter 17

PPI plus NSAID versus Cox-2 preferentials: systematic review – included studies, results, analysis and robustness

Included studies

No studies were found that directly assessed this comparison. Only indirect comparisons can inform our understanding.

Publication bias

Publication bias could not be assessed in the absence of direct comparison studies.

Results

Direct comparisons, PPIs versus Cox-2 preferentials

No studies were included that directly compared PPIs with Cox-2 preferential NSAIDs.

Indirect comparisons

Results are summarised in *Table 25*.

Indirect comparisons use the results of the MA of PPIs plus NSAIDs versus NSAIDs alone and the

TABLE 25 *Indirect comparisons, PPI versus Cox-2 preferentials displayed with relevant direct comparisons, and the data on which the indirect comparisons are based*

Outcome	RR, indirect (95% CI)	RR, PPI vs placebo (95% CI), events	RR, Cox-2 preferential vs placebo (95% CI), events
Serious GI complications	0.75 (0.11 to 5.33)	0.46 (0.07 to 2.92), 3	0.61 (0.34 to 1.10)
Symptomatic ulcers	0.22 (0.04 to 1.14)	0.09 (0.02 to 0.47), 18	0.41 (0.26 to 0.65)
Serious CV or renal events	0.82 (0.10 to 6.98)	0.78 (0.10 to 6.26), 3	0.95 (0.55 to 1.66)
Deaths	0.25 (0.01 to 5.71)	0.17 (0.01 to 4.05), 1	0.68 (0.28 to 1.64)
GI symptoms	0.59 (0.33 to 1.05)	0.43 (0.24 to 0.76), 45	0.73 (0.68 to 0.79)
Endoscopic ulcers	0.90 (0.34 to 2.37)	0.37 (0.30 to 0.46), 281	0.41 (0.16 to 1.05)
Anaemia			0.30 (0.07 to 1.30)
Occult bleeding			0.86 (0.33 to 2.24)
Drop-outs, total	1.05 (0.67 to 1.66)	0.98 (0.62 to 1.53), 116	0.93 (0.89 to 0.97)
Drop-outs, due to GI symptoms	0.71 (0.41 to 1.25)	0.45 (0.26 to 0.78), 48	0.63 (0.56 to 0.71)

results of the MA of Cox-2 preferentials versus NSAIDs alone to estimate the effect of PPIs plus NSAIDs versus Cox-2 preferentials. They provide lower quality evidence than studies which directly compare PPIs plus NSAIDs versus Cox-2 preferentials.

Primary and secondary outcomes

No significant differences were seen between PPIs with Cox-1 NSAIDs and Cox-2 preferential NSAIDs for any primary or secondary outcomes.

Summary

There were no included RCTs that directly compared the effects of PPI plus NSAID versus Cox-2 preferential NSAID. Indirect comparisons do not suggest any statistically significant differences between PPIs with a Cox-1 NSAID and Cox-2 preferential NSAIDs.

Chapter 18

Misoprostol plus NSAID versus Cox-2 preferentials: systematic review – included studies, results, analysis and robustness

Included studies

Table 26 summarises the included studies. For a complete table of characteristics of included studies, see Appendix 6k.

Characteristics of studies

Three RCTs directly compared misoprostol plus Cox-1 NSAIDs with Cox-2 preferentials, randomising 1088 participants (68% female). The studies varied in size from at least 53[78] to 395 participants per arm.[145] The studies were performed in North and South America and China. Publication dates were from 1993 to 2001.

Participants

All three studies recruited participants with OA only. Mean duration of arthritis was reported in one study only[145] as being 10–11 years. Mean ages ranged from 62 years to 75 years. The baseline GI status of participants varied from excluding those with more than three or 10 erosions on endoscopy at baseline, or including only those who had just completed a healing phase for ulcers.

Interventions

The studies compared misoprostol plus ibuprofen, diclofenac (as Arthrotec) or naproxen with nabumetone. All the drugs were within the recommended dosages. The maximum duration of intervention ranged from 6 to 24 weeks. Patient education was not mentioned in any study.

Study quality

The summary risk of bias was 'moderate' for two studies, and 'high' for the third.[78] The method of randomisation was described as 'randomised' in all studies. Allocation concealment was unclear in two studies and adequate in one.[146] Baseline comparability was unclear in one study, comparable in one and not comparable in the third. Participants were blinded in two studies, unclear in the third. Assessors were blinded in two studies and unclear in one.

ITT analyses were not undertaken in any study. *A priori* sample size calculations were performed in

TABLE 26 *Brief characteristics of included misoprostol versus Cox-2 preferential studies*

Study	*N*	Participants	Interventions
Roth, 1993[78] **Summary risk of bias:** high	**Allocated:** a 58, c 60	**Baseline GI status:** no more than 3 erosions at baseline endoscopy **Type of arthritis:** OA	**Comparison:** misoprostol plus ibuprofen (c) vs nabumetone (a) **Duration:** 12 weeks
Agrawal, 1999[145] **Summary risk of bias:** moderate	**Allocated:** a 426, b 395	**Baseline GI status:** baseline endoscopy performed and excluded patients with 10 or more gastric and/or duodenal erosions, participants had history of ulcers or erosions **Type of arthritis:** OA	**Comparison:** Arthrotec (b) vs nabumetone (a) **Duration:** 6 weeks
Chan, 2001[146] **Summary risk of bias:** moderate	**Allocated:** unclear, 96 in total	**Baseline GI status:** complete ulcer healing following 8 weeks of omeprazole 20 mg daily for bleeding peptic ulcers **Type of arthritis:** OA	Comparison: naproxen plus misoprostol (b) vs nabumetone plus placebo misoprostol (a) **Duration:** 24 weeks

TABLE 27 *Indirect comparisons, misoprostol versus Cox-2 preferentials displayed with relevant direct comparisons, and the data on which the indirect comparisons are based*

Outcome	RR, direct (95% CI), events	RR, indirect (95% CI)	RR, misoprostol vs placebo (95% CI), events	RR, Cox-2 preferential vs placebo (95% CI), events
Serious GI complications	3.05 (1.03 to 9.06), 16	0.93 (0.44 to 1.97)	0.57 (0.36 to 0.91), 75	0.61 (0.34 to 1.10)
Symptomatic ulcers	0.25 (0.03 to 2.15), 5	0.88 (0.41 to 1.87)	0.36 (0.20 to 0.67), 44	0.41 (0.26 to 0.65)
Serious CV or renal events	1.00 (0.06 to 15.50), 2	1.87 (0.25 to 13.80)	1.78 (0.26 to 12.07), 4	0.95 (0.55 to 1.66)
Deaths	1.00 (0.15 to 6.79), 4	1.31 (0.43 to 3.96)	0.89 (0.46 to 1.74), 35	0.68 (0.28 to 1.64)
GI symptoms	0.50 (0.16 to 1.54), 12	1.33 (0.95 to 1.86)	0.97 (0.70 to 1.35), 1218	0.73 (0.68 to 0.79)
Endoscopic ulcers	0.37 (0.21 to 0.65), 60	0.80 (0.31 to 2.11)	0.33 (0.27 to 0.41), 658	0.41 (0.16 to 1.05)
Anaemia	2.90 (0.12 to 69.81), 1	8.87 (0.27 to 293.96)	2.66 (0.11 to 63.84), 1	0.30 (0.07 to 1.30)
Occult bleeding		0.53 (0.13 to 2.22)	0.46 (0.16 to 1.32), 16	0.86 (0.33 to 2.24)
Drop-outs, total	1.00 (0.67 to 1.50), 63	1.19 (1.07 to 1.34)	1.11 (1.00 to 1.23), 4772	0.93 (0.89 to 0.97)
Drop-outs, due to GI symptoms		2.16 (1.88 to 2.48)	1.36 (1.26 to 1.46), 2332	0.63 (0.56 to 0.71)

two studies and unclear in the third. Compliance was assessed by tablet count in two studies and not mentioned in the other, and one study reported the results of this assessment.

One study declared funding by a pharmaceutical company[78] and one by the Health Services Research Council of Hong Kong.[146] The other study[145] did not state its funding, but five of nine authors appeared to be employed by Searle.

Publication bias

There were insufficient included studies to assess publication bias.

Results

Results are summarised in *Table 27* and forest plots are shown in *Figures 77–84*. For SAs see Appendix 11f.

Primary outcomes

Serious GI events were reported by two studies (16 people with events for 909 participants) and MA showed a significantly increased risk of events in those taking misoprostol compared with Cox-2 preferentials (RR 3.05, 95% CI 1.03 to 9.06). There was no suggestion of heterogeneity. Significance was maintained when studies with high risk of bias or with high-dose arms were removed.

One study[146] reported symptomatic ulcers (five ulcers among 90 participants, RR 0.25, 95% CI 0.03 to 2.15), serious cardiovascular or renal events (two events in 90 participants) and deaths (four deaths). Neither MA nor any of the SAs suggested a significant effect. No data on QoL were reported.

Secondary outcomes

Total GI symptoms were reported in 12 of 90 participants (13%) in one study. The RR of developing GI symptoms was 0.50 (95% CI 0.16 to

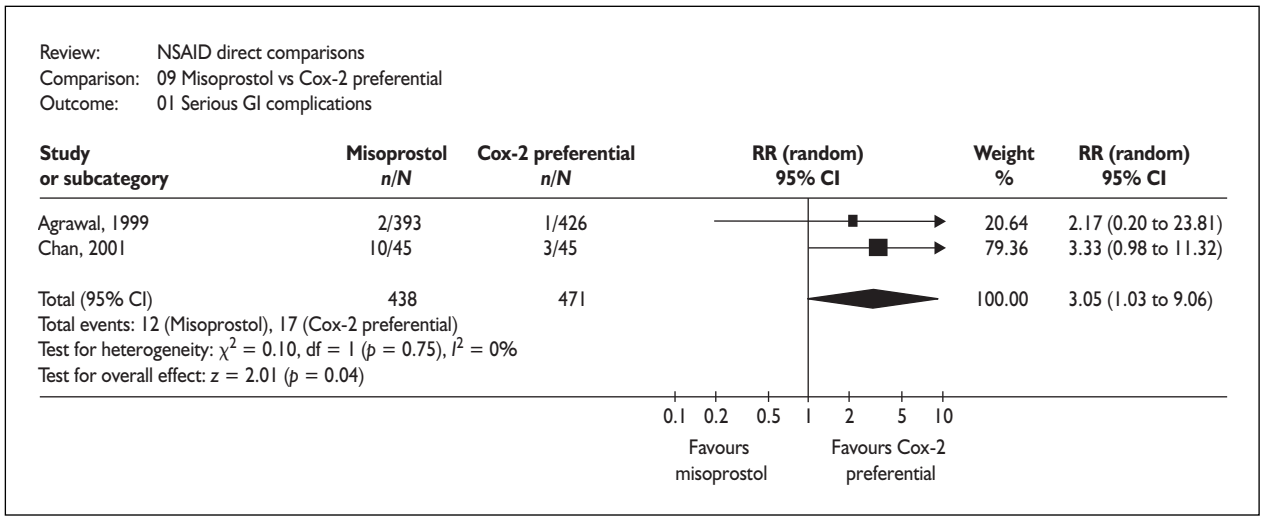

FIGURE 77 *Forest plot of misoprostol plus NSAID versus Cox-2 preferential NSAID, outcome serious GI complications*

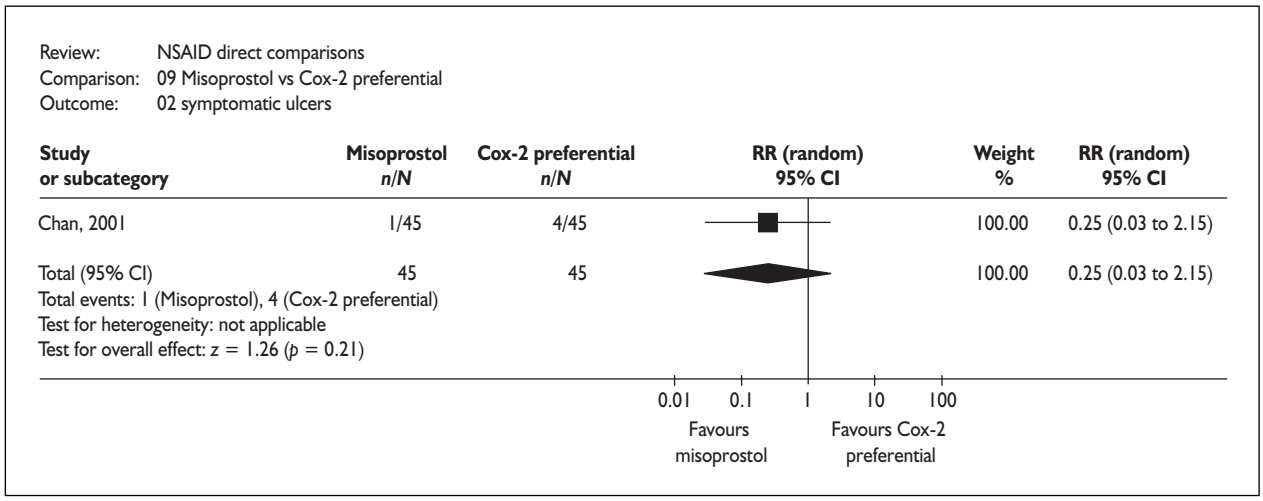

FIGURE 78 *Forest plot of misoprostol plus NSAID vs Cox-2 preferential NSAID, outcome symptomatic ulcers*

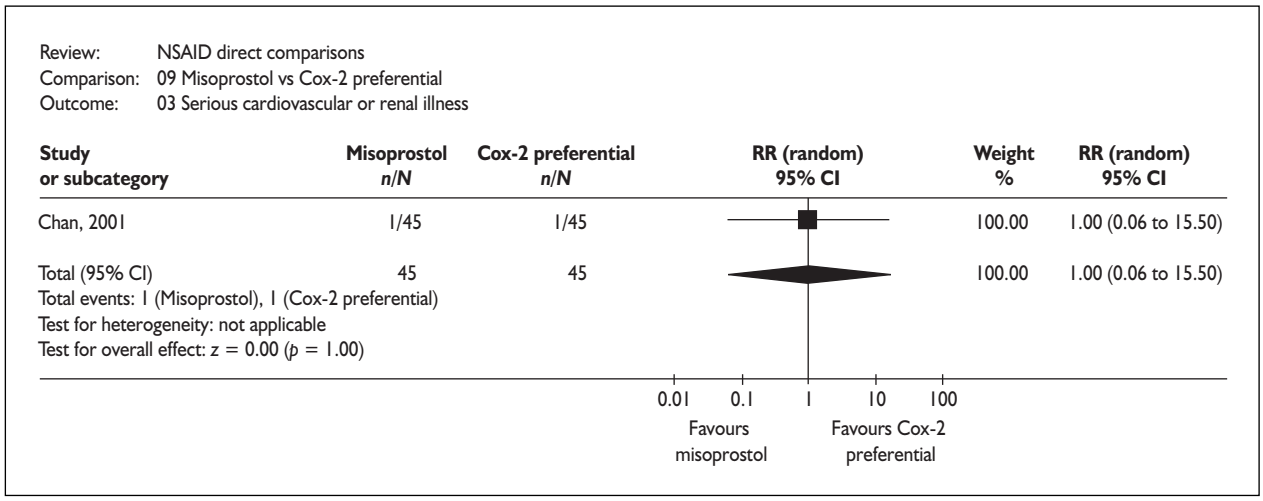

FIGURE 79 *Forest plot of misoprostol plus NSAID versus Cox-2 preferential NSAID, outcome serious cardiovascular or renal illness*

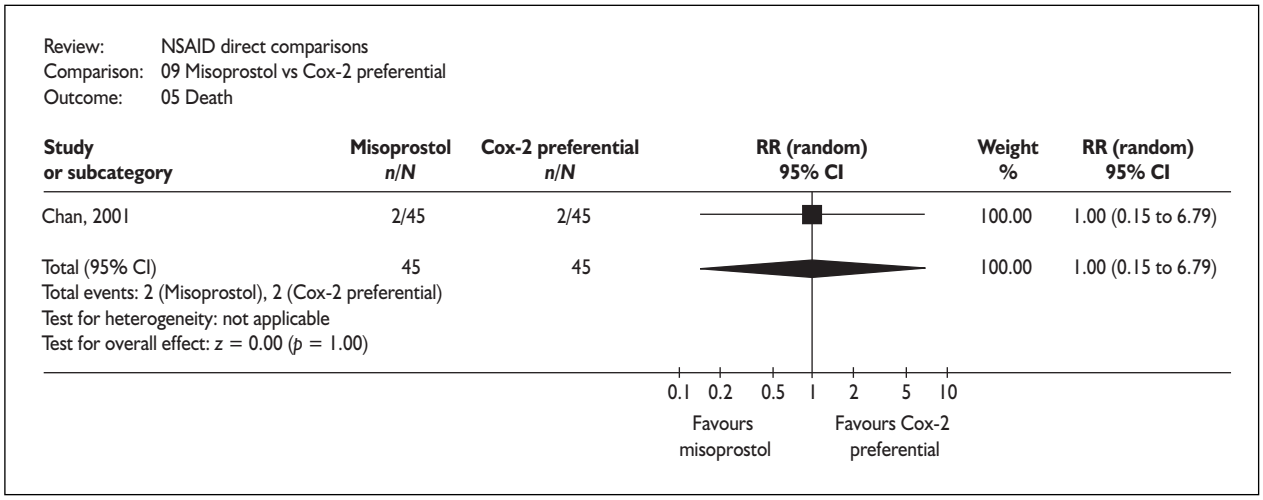

FIGURE 80 *Forest plot of misoprostol plus NSAID versus Cox-2 preferential NSAID, outcome deaths*

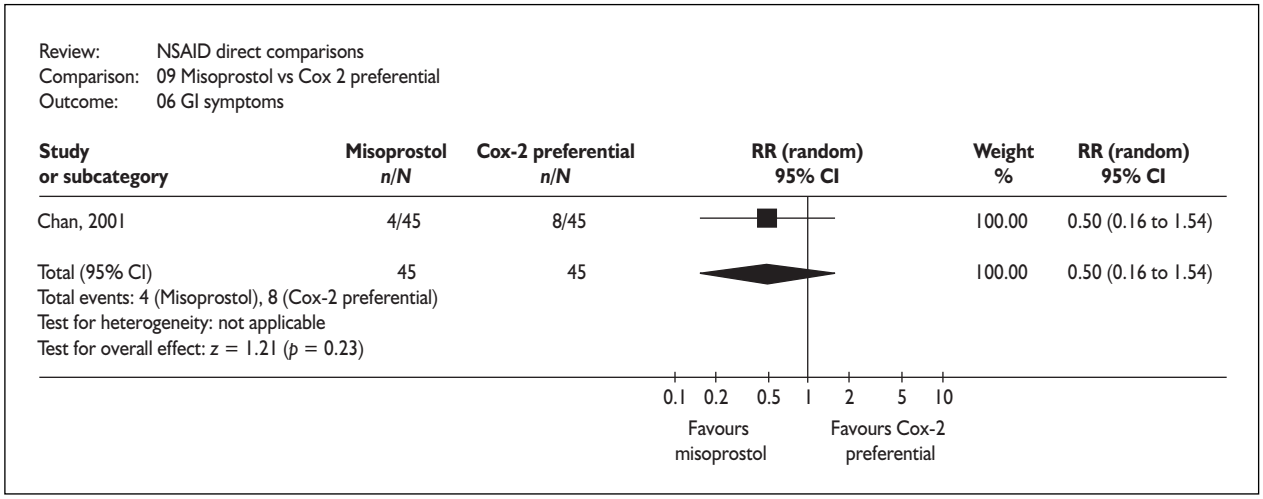

FIGURE 81 *Forest plot of misoprostol plus NSAID versus Cox-2 preferential NSAID, outcome GI symptoms*

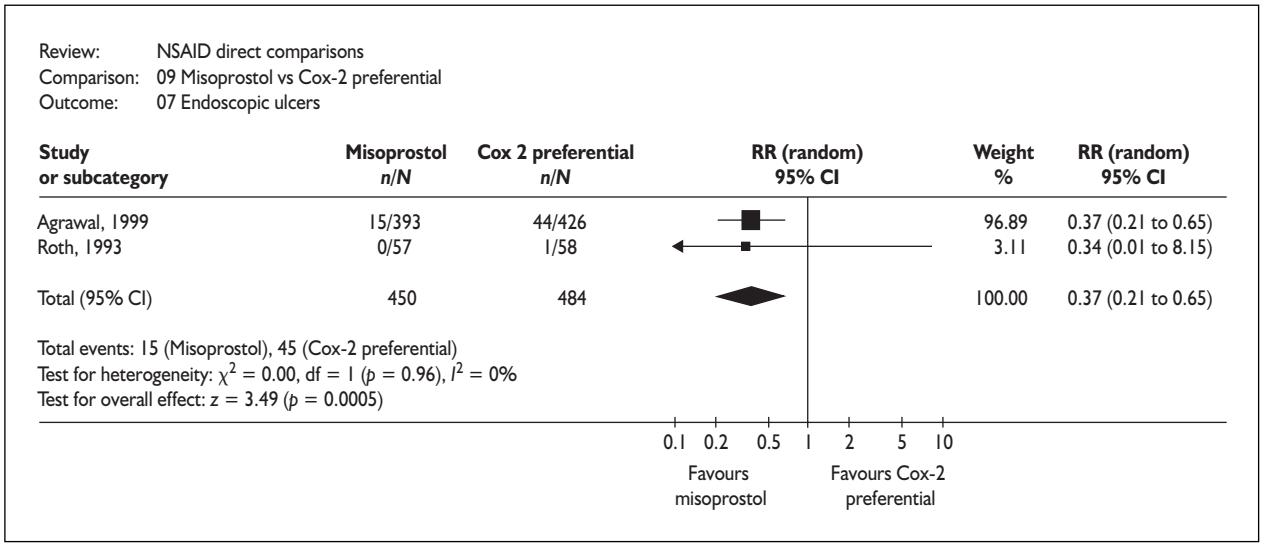

FIGURE 82 *Forest plot of misoprostol plus NSAID versus Cox-2 preferential NSAID, outcome anaemia*

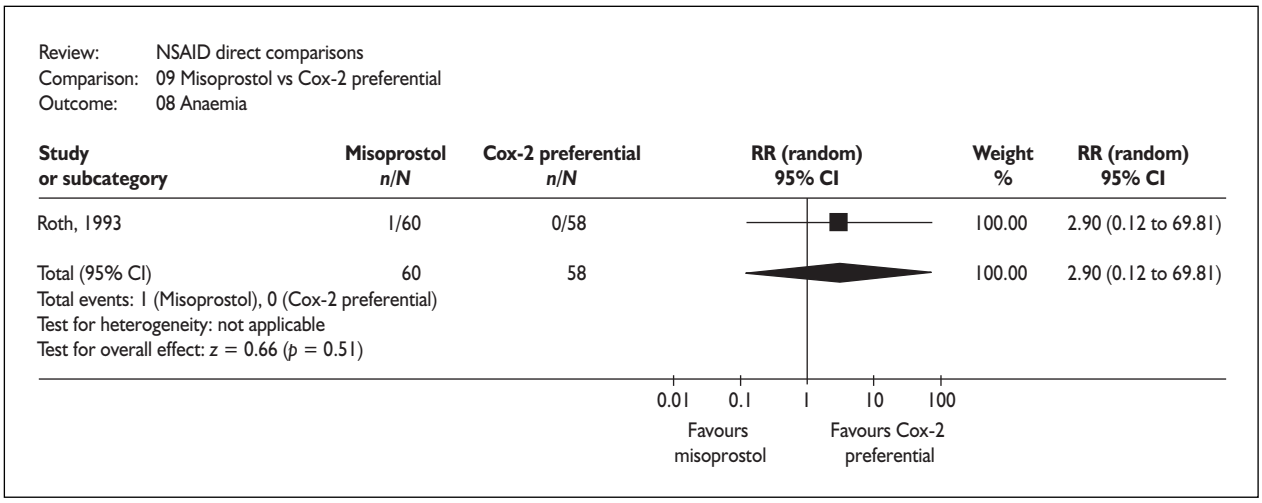

FIGURE 83 *Forest plot of misoprostol plus NSAID versus Cox-2 preferential NSAID, outcome anaemia*

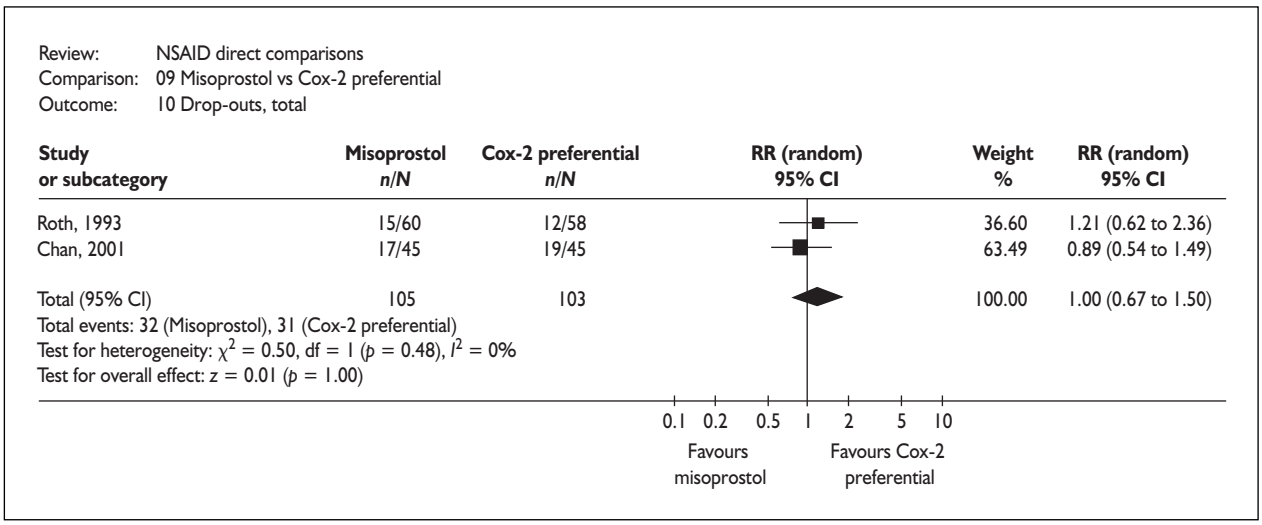

FIGURE 84 *Forest plot of misoprostol plus NSAID versus Cox-2 preferential NSAID, outcome total drop-outs*

1.54) in the misoprostol group compared with the Cox-2 preferential group. SAs did not remove this study.

Endoscopic ulcers were reported in two studies, overall 60 ulcers in 877 participants (7%). The RR of developing at least one gastroduodenal ulcer was 0.37 (95% CI 0.21 to 0.65) in the misoprostol group compared with the Cox-2 preferential group. There was no suggestion of heterogeneity ($p = 0.96$), and significance was not lost on SA.

One study reported anaemia (in one of 118 participants). No studies reported occult bleeding or drop-outs due to GI symptoms.

Total drop-outs were reported in two studies, with 63 drop-outs from 208 participants (30%). There was no significant difference between participants on misoprostol or Cox-2 preferentials (RR 1.00, 95% CI 0.67 to 1.50), with no suggestion of heterogeneity.

Indirect comparisons

Indirect comparisons use the results of the MA of misoprostol plus NSAIDs versus NSAIDs alone and the results of the MA of Cox-2 preferentials versus NSAIDs alone to estimate the effect of misoprostol plus NSAIDs versus Cox-2 preferentials. They provide lower quality evidence than studies which directly compare misoprostol plus NSAIDs versus Cox-2 preferentials.

Primary outcomes

No significant effects of misoprostol compared with Cox-2 preferentials on any primary outcomes were suggested by indirect comparisons.

Secondary outcomes

No differences in GI symptoms, endoscopic ulcers, anaemia or occult bleeding were seen. Total drop-outs ($RR_{indirect}$ 1.19, 95% CI 1.07 to 1.34) and drop-outs due to GI symptoms ($RR_{indirect}$ 2.16, 95% CI 1.88 to 2.48) were significantly more likely in the misoprostol arm compared with the Cox-2 preferential arm in the adjusted indirect comparisons.

Summary

Three RCTs directly compared misoprostol with Cox-2 preferentials, randomising 1088 participants with OA. Mean ages of participants were 62–75 years and people had varied GI status at baseline. Studies compared misoprostol plus Cox-1 with nabumetone for 6–24 weeks.

Summary risk of bias was 'moderate' in two studies and 'high' in one. Allocation concealment was unclear in two studies and adequate in one. Baseline comparability was adequate in one study, unclear in one and inadequate in one.

Pharmaceutical companies funded two studies and one was funded independently. Publication bias was not assessable.

A significantly increased risk of serious GI events (RR 3.05, 95% CI 1.03 to 9.06) was seen in those on misoprostol compared with Cox-2 preferentials. This relationship was stable to sensitivity analyses but not supported by indirect comparisons. There were no statistically significant differences for other primary outcomes in either direct or indirect comparisons.

Risk of endoscopic ulcers was significantly reduced in those on misoprostol compared with those on Cox-2 preferentials in direct comparisons (RR 0.37, 95% CI 0.21 to 0.65), but not supported by the indirect comparisons. No further differences between misoprostol and Cox-2 preferentials were seen in the direct comparisons, but indirect comparisons suggested that those on misoprostol were significantly more likely to drop out and to drop out due to GI symptoms than those on Cox-2 preferentials.

Chapter 19

Cox-2 coxib NSAID versus Cox-2 preferential NSAID: systematic review – included studies, results, analysis and robustness

Included studies

Table 28 summarises the included studies. For a complete table of characteristics of included studies, see Appendix 6l.

Characteristics of studies

One RCT directly compared a Cox-2 coxib NSAID with a Cox-2 preferential, randomising 289 participants (63% female).[147] The study was performed in 22 centres in Europe (not including the UK). No additional outcome data were provided by the authors of this study.

Participants

All participants had OA with a mean duration of 14–17 years (in different arms). Mean age was 83 years. Participants were excluded only if they had had active GI bleeding in the past 3 months (no endoscopy was performed).

Interventions

The study compared rofecoxib (in two doses) with nabumetone, all within the recommended dosages. The maximum duration was 6 weeks, with a 7–10-day post study assessment. Patient education was not mentioned.

Study quality

The summary risk of bias was 'high'. Randomisation was by centralised computer-generated allocation schedule, stratified by low-dose aspirin use and study site. Allocation concealment was unclear. Baseline comparability was not accomplished (as duration of OA and history of ulcers and bleeds were different in different arms). Participants and assessors were blinded.

ITT analyses was undertaken. *A priori* sample size calculations were performed. Compliance was not mentioned. Funding was declared provided by Merck Research Laboratories.

Publication bias

There were insufficient included studies to assess publication bias.

Results

Results are summarised in *Table 29* and forest plots are shown in *Figures 85–90*. For SAs see Appendix 11g.

Primary outcomes

One serious GI event and one serious cardiovascular or renal illness were reported, along with a lack of symptomatic ulcers. No data on QoL or deaths were reported.

Secondary outcomes

One case of occult bleeding, 40 drop-outs and 20 drop-outs due to GI symptoms were reported, with no significant differences suggested between Cox-2 coxibs and Cox-2 preferentials.

TABLE 28 *Brief characteristics of included Cox-2 coxib versus Cox-2 preferential studies*

Study	*N*	Participants	Interventions
Truitt, 2001[147] **Summary risk of bias:** high	Allocated: a 115, b 118, c 56	**Baseline GI status:** no baseline endoscopy performed but participants excluded if active GI bleeding in previous 3 months **Type of arthritis:** OA	**Comparison:** rofecoxib (b, c) vs nabumatone **Duration:** 6 weeks plus 7–10 days post-study assessment

TABLE 29 *Indirect comparisons, Cox-2 coxibs versus Cox-2 preferentials displayed with relevant direct comparisons, and the data on which the indirect comparisons are based*

Outcome	RR, direct (95% CI), events	RR, indirect (95% CI)	RR, Cox-2 coxib vs placebo (95% CI), events	RR, Cox-2 preferential vs placebo (95% CI), events
Serious GI complications	0.22 (0.01 to 5.38), 1	0.90 (0.45 to 1.81)	0.55 (0.38 to 0.80), 114	0.61 (0.34 to 1.10)
Symptomatic ulcers		1.20 (0.71 to 2.01)	0.49 (0.38 to 0.62), 281	0.41 (0.26 to 0.65)
Serious CV or renal events	0.22 (0.01 to 5.38), 1	1.25 (0.64 to 2.46)	1.19 (0.80 to 1.75), 241	0.95 (0.55 to 1.66)
Deaths		1.50 (0.51 to 4.43)	1.02 (0.55 to 1.92), 78	0.68 (0.28 to 1.64)
GI symptoms		1.11 (0.99 to 1.25)	0.81 (0.74 to 0.89), 5184	0.73 (0.68 to 0.79)
Endoscopic ulcers		0.61 (0.23 to 1.59)	0.25 (0.21 to 0.30), 522	0.41 (0.16 to 1.05)
Anaemia		2.07 (0.47 to 9.01)	0.62 (0.51 to 0.74), 464	0.30 (0.07 to 1.30)
Occult bleeding	1.99 (0.08 to 48.40), 1			0.86 (0.33 to 2.24)
Drop-outs, total	1.10 (0.61 to 2.00), 40	0.88 (0.78 to 1.00)	0.82 (0.73 to 0.92), 9510	0.93 (0.89 to 0.97)
Drop-outs, due to GI symptoms	0.99 (0.42 to 2.35), 20	1.10 (0.88 to 1.37)	0.69 (0.57 to 0.83), 2171	0.63 (0.56 to 0.71)

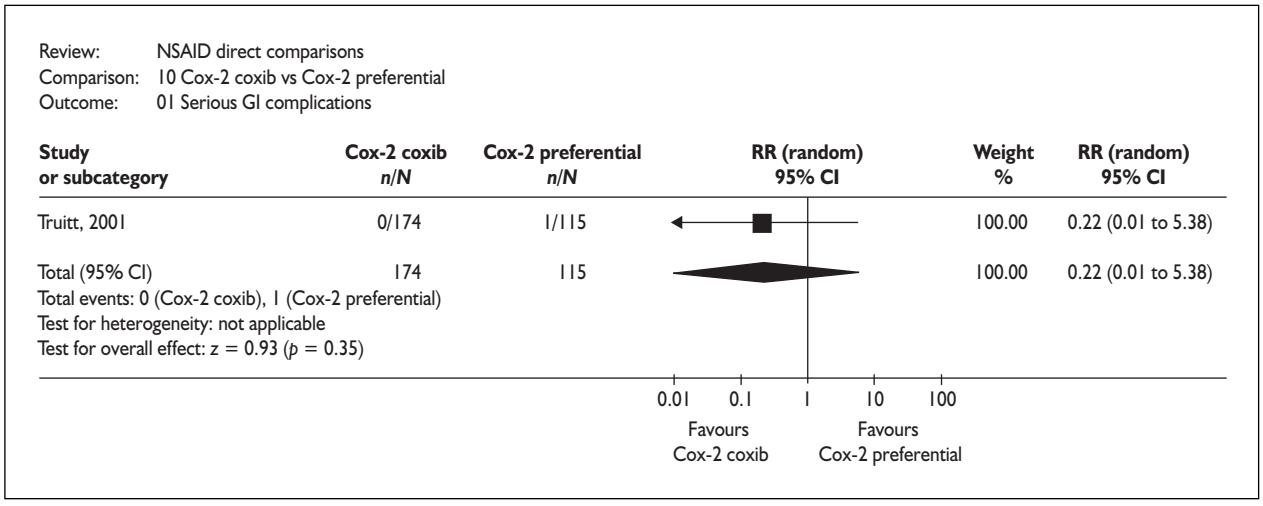

FIGURE 85 *Forest plot of Cox-2 coxib NSAID versus Cox-2 preferential NSAID, outcome serious GI complications*

Indirect comparisons

Indirect comparisons use the results of the MA of Cox-2 coxibs versus NSAIDs alone and the results of the MA of Cox-2 preferentials versus NSAIDs alone to estimate the effect of Cox-2 coxibs versus Cox-2 preferentials. They provide lower quality evidence than studies which directly compare Cox-2 coxibs versus Cox-2 preferentials.

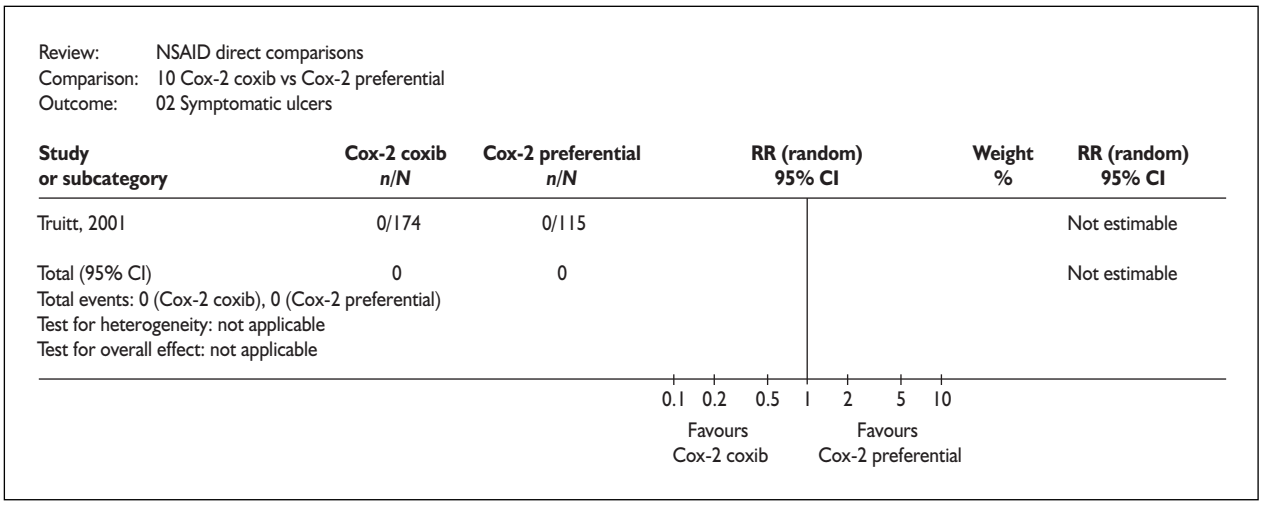

FIGURE 86 *Forest plot of Cox-2 coxib NSAID versus Cox-2 preferential NSAID, outcome symptomatic ulcers*

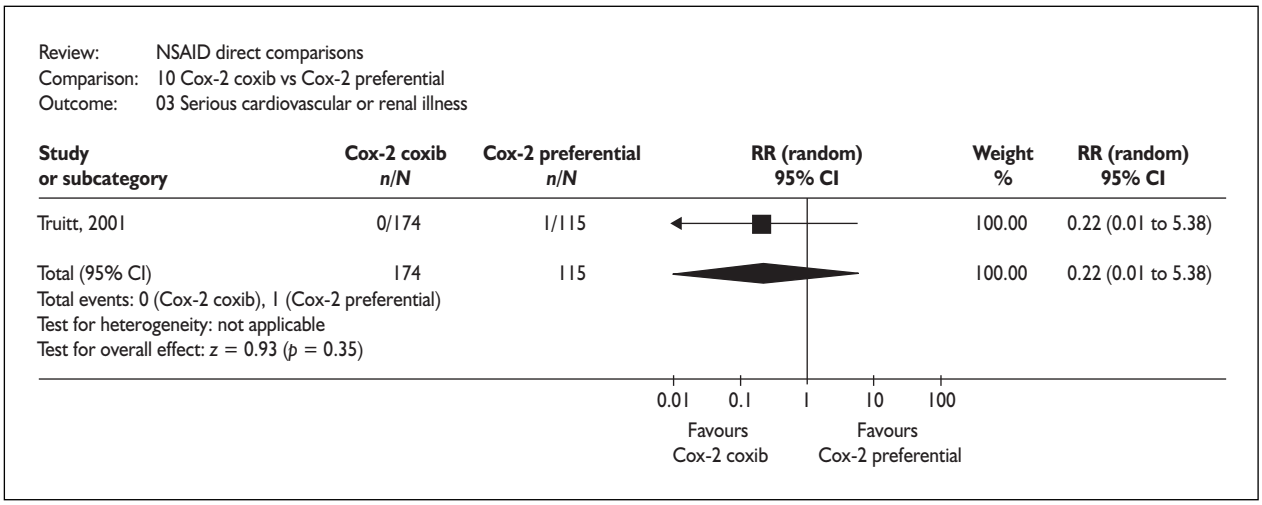

FIGURE 87 *Forest plot of Cox-2 coxib NSAID versus Cox-2 preferential NSAID, outcome serious cardiovascular or renal illness*

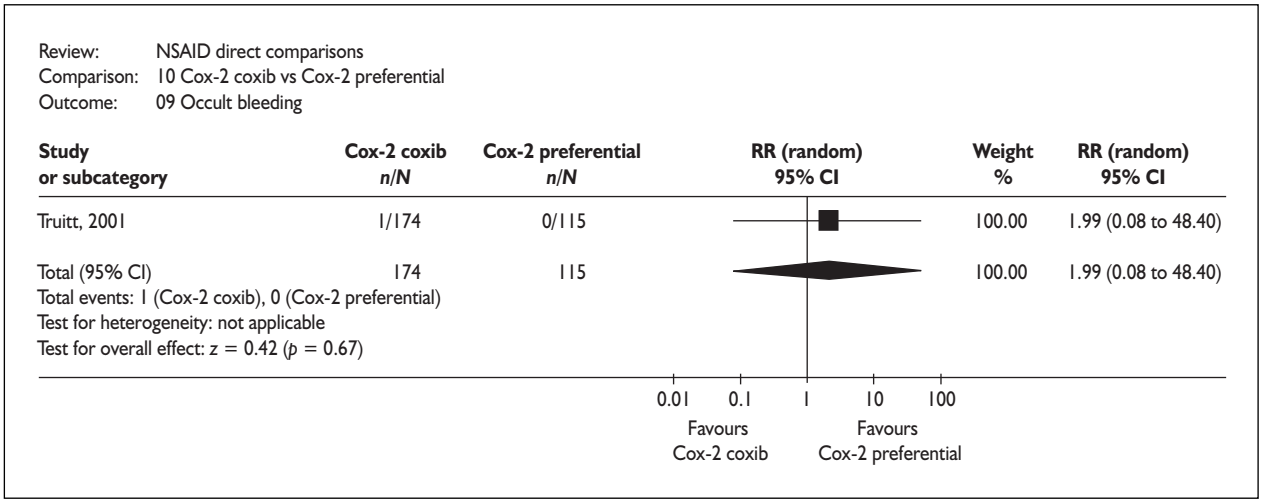

FIGURE 88 *Forest plot of Cox-2 coxib NSAID versus Cox-2 preferential NSAID, outcome occult bleeding*

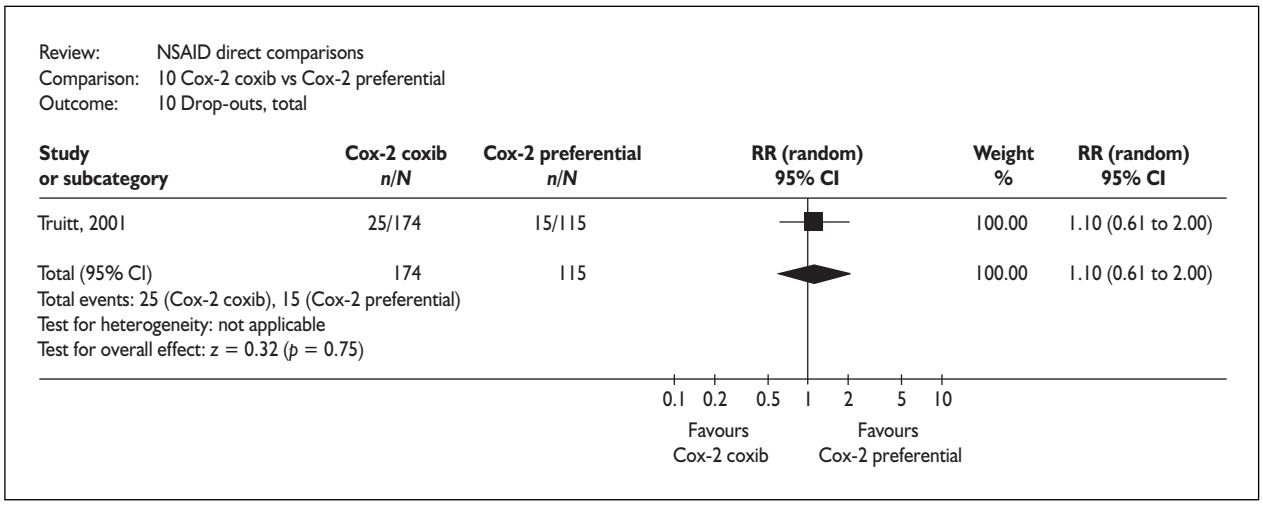

FIGURE 89 *Forest plot of Cox-2 coxib NSAID versus Cox-2 preferential NSAID, outcome total drop-outs*

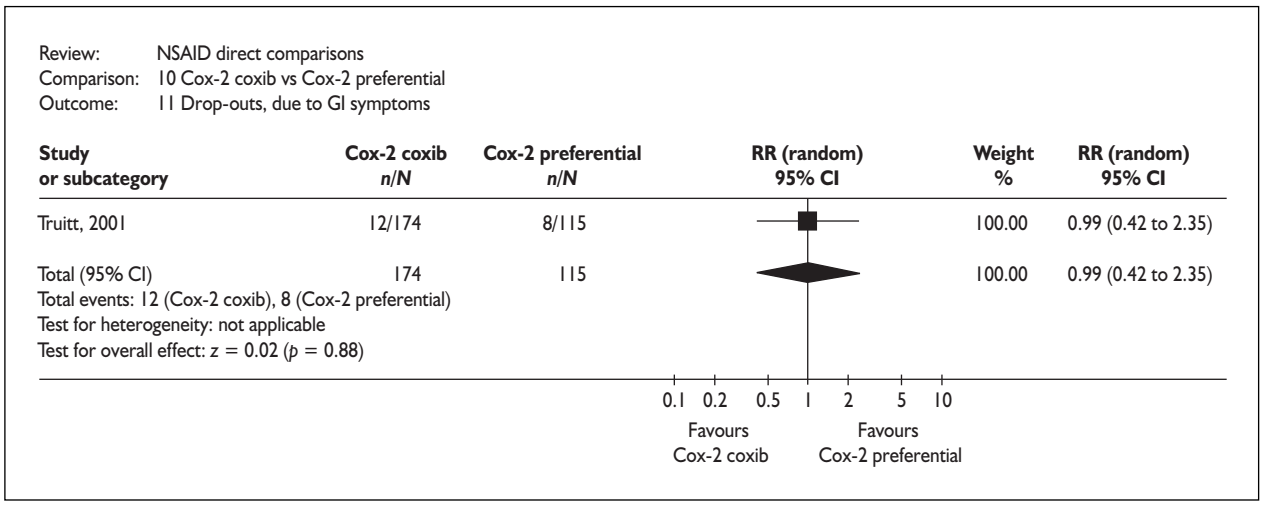

FIGURE 90 *Forest plot of Cox-2 coxib NSAID versus Cox-2 preferential NSAID, outcome drop-outs due to GI symptoms*

Primary outcomes

No significant effects of Cox-2 coxibs compared with Cox-2 preferentials on any primary outcomes were suggested by indirect comparisons.

Secondary outcomes

No differences in GI symptoms, endoscopic ulcers, anaemia or drop-outs due to GI symptoms were seen. Total drop-outs ($RR_{indirect}$ 0.88, 95% CI 0.78 to 1.00) were significantly less likely in the Cox-2 coxib arm compared with the Cox-2 preferential arm in the adjusted indirect comparisons.

Summary

One RCT directly compared a Cox-2 coxib NSAID with a Cox-2 preferential, randomising 289 participants with OA. Mean age was 83 years and participants were excluded only if they had had active GI bleeding in the past 3 months (no endoscopy was performed). Rofecoxib was compared with nabumetone over 6 weeks.

Summary risk of bias was 'high'. Allocation concealment was unclear and baseline comparability was inadequate. A pharmaceutical company funded the study.

There were no statistically significant differences between Cox-2 coxibs and Cox-2 preferentials for any primary outcomes in either direct or indirect comparisons.

No significant differences were seen in any secondary outcomes in direct or indirect comparisons, except that drop-outs were less likely in Cox-2 coxibs than Cox-2 preferentials in indirect comparisons (of borderline significance).

Chapter 20

Summary of findings of the systematic review and robustness of the results

Principal objectives of the review

Our study had six principal objectives, two of which related directly to the systematic review:

1. to assess the effectiveness of the five preventive strategies on mortality, health-related QoL, serious GI complications, symptomatic ulcers, serious cardiovascular or renal illness and side-effects
2. to indicate the rate of change in the evidence base.

Effectiveness of the five preventive strategies

H_2RA plus NSAID versus placebo plus NSAID

The 15 RCTs (including 2621 participants) comparing H_2RAs plus NSAIDs with placebo plus NSAIDs included a mixture of middle-aged participants with OA and RA and with a varied baseline GI status. Many studies gave H_2RA doses well over those now recommended. Study quality was far from ideal, with no study reporting adequate allocation concealment and half of the studies having unclear baseline comparability. At least 11 of the 15 RCTs were funded by pharmaceutical companies. There was no suggestion of publication bias.

Very few studies reported on our primary outcomes and there were insufficient data to allow conclusions to be drawn regarding the effect of H_2RA compounds compared with placebo on serious GI complications, symptomatic ulcers, serious CVD or renal illness, QoL or death.

More data were provided on GI symptoms and endoscopic ulcers, both of which appear to be significantly reduced in participants randomised to take H_2RAs compared with placebo (GI symptoms RR 0.72, 95% CI 0.56 to 0.92; endoscopic ulcers RR 0.55, 95% CI 0.44 to 0.70). However, the significance of the effects on GI symptoms was lost with SA removing studies with doses higher than recommended, and the quality of the studies was not high, so it is possible that these results may be biased. Total drop-outs and drop-outs due to GI symptoms were not significantly different between placebo and H_2RA groups.

PPI plus NSAID versus placebo plus NSAID

Six RCTs were included in this comparison, including 1358 mainly middle-aged participants with both OA and RA, and with varied baseline GI status. Only one study gave doses of PPI higher than currently recommended. Summary risk of bias was 'low' in one study, 'moderate' in three and 'high' in two. Pharmaceutical companies funded five of the studies. There was no suggestion of publication bias.

Overall, very few studies reported on our primary outcomes, and it was not possible to comment on the effect of PPIs compared with placebo on serious GI complications, serious CVD or renal illness, QoL or death. The suggestion that symptomatic ulcers were significantly reduced on PPIs compared with placebo (RR 0.09, 95% CI 0.02 to 0.47) was lost on SA.

Endoscopic ulcers appeared to be significantly reduced in participants randomised to take PPIs compared with placebo (RR 0.37, 95% CI 0.30 to 0.46) and the results did not alter on SA. However, the quality of the studies was not high and it is possible that this result may be biased. Suggestions that GI symptoms (RR 0.43, 95% CI 0.24 to 0.76) and drop-outs due to GI symptoms (RR 0.45, 95% CI 0.26 to 0.78) were reduced in those on PPIs were lost on SA. Total drop-outs were not significantly different between placebo and H_2RA groups.

Misoprostol plus NSAIDs versus placebo plus NSAIDs

This comparison included 23 studies (16,945 participants) comparing the long-term effects of misoprostol vs placebo in combination with NSAIDs. Participants were people with RA and OA, mean ages from 38 to 70 years, with normal GI status through to recently healed ulcers.

Misoprostol doses were all within the current recommended range. Studies ran from 4 to 52 weeks.

One study was assessed as at 'low' risk of bias, 18 at 'moderate' risk and four at 'high' risk. Allocation concealment was adequate in one study and baseline characteristics were judged 'comparable' in 13. Eighteen studies reported funding by pharmaceutical companies. There was no suggestion of publication bias.

Misoprostol significantly reduced serious GI complaints (RR 0.57, 95% CI 0.36 to 0.91), symptomatic ulcers (RR 0.36, 95% CI 0.20 to 0.67) and endoscopic ulcers (RR 0.33, 95% CI 0.27 to 0.41), all stable to SA and with no suggestion of heterogeneity. No significant effects of misoprostol on serious cardiovascular or renal illness (four events), deaths (35 deaths), anaemia (one event) or occult bleeding (16 events) were seen, but few events were recorded. GI symptoms were recorded in greater numbers, with no significant difference between misoprostol or placebo arms (RR 0.97, 95% CI 0.70 to 1.35). Both total drop-outs (RR 1.11, 95% CI 1.00 to 1.23) and drop-outs due to GI symptoms (RR 1.36, 95% CI 1.26 to 1.46) were significantly more frequent in misoprostol arms, suggesting that symptoms with misoprostol may have been of greater severity.

Cox-2 coxib NSAID versus Cox-1 NSAID

Seventeen RCTs were included in this comparison. Studies usually included participants either with OA or with RA, but not both, and mean ages ranged from 38 to 64 years. Baseline GI status was unclear in many studies as baseline endoscopies were usually not carried out. Five study arms provided Cox-2 coxibs at doses over the current recommended levels. Study duration ranged from 3 to over 52 weeks.

The summary risk of bias was calculated as being 'low' in three studies, 'moderate' in 13 studies and 'high' in one study. Only three studies had 'adequate' allocation concealment, and 14 studies were judged as having comparable baseline characteristics. Pharmaceutical funding was used in all 17 studies. Publication bias was not apparent.

The development of serious GI complications (RR 0.55, 95% CI 0.38 to 0.80) and symptomatic ulcers (RR 0.49, 95% CI 0.38 to 0.62) appears to be significantly reduced in participants randomised to take Cox-2 coxib drugs compared with Cox-1 drugs, and these results are generally robust to SA and without apparent heterogeneity. Serious cardiovascular or renal illness (RR 1.19, 95% CI 0.80 to 1.75) and total deaths (RR 1.02, 95% CI 0.55 to 1.92) were not significantly different between Cox-2 coxibs and Cox-1 groups. There were no usable data to allow conclusions to be drawn regarding QoL.

Total GI symptoms (RR 0.81, 95% CI 0.74 to 0.89), endoscopic ulcers (RR 0.25, 95% CI 0.21 to 0.30) and anaemia (RR 0.62, 95% CI 0.51 to 0.74) were significantly less common in participants' randomised to receive Cox-2 coxib drugs compared with Cox-1 drugs, and these results were stable to SA. Total drop-outs (RR 0.82, 95% CI 0.73 to 0.92) and drop-outs due to GI symptoms (RR 0.69, 95% CI 0.57 to 0.83) also appeared to be significantly reduced in the Cox-2 groups. However, there was evidence of heterogeneity in these analyses. No studies reported data on occult bleeding.

Cox-2 preferential NSAID versus Cox-1 NSAID

Fifty-one RCTs were included in this comparison. Studies usually included participants either with OA or with RA, but not both, and mean ages ranged from 38 to 72 years. Baseline GI status was unclear in many studies as baseline endoscopies were usually not carried out. Five study arms provided Cox-2 preferential doses over the current recommended levels and all four Cox-2 preferentials (etodolac, nimesulide, meloxicam and nabumetone) were studied. Study duration ranged from 3 weeks to 3 years.

The summary risk of bias was calculated as being 'moderate' in 34 and 'high' in 17. Only two studies had 'adequate' allocation concealment, and 10 studies were judged as having comparable baseline characteristics. Pharmaceutical funding was used in 40 studies. Publication bias was not apparent.

The development of symptomatic ulcers (RR 0.41, 95%CI 0.26 to 0.65), GI symptoms (RR 0.73, 95% CI 0.68 to 0.79), total drop-outs (RR 0.93, 95% CI 0.89 to 0.97) and drop-outs due to GI symptoms (RR 0.63, 95% CI 0.56 to 0.71) all appear to be significantly reduced in participants randomised to take Cox-2 preferential drugs compared with Cox-1 drugs, and these results are robust to SA and without apparent heterogeneity. Serious GI complications (RR 0.61, 95%CI 0.34 to 1.10), serious cardiovascular or renal illness (RR 0.95, 95% CI 0.55 to 1.66), QoL, total deaths (RR 0.68, 95% CI 0.28 to 1.64), anaemia (RR 0.30, 95% CI 0.07 to 1.30) and endoscopic ulcers (RR 0.41,

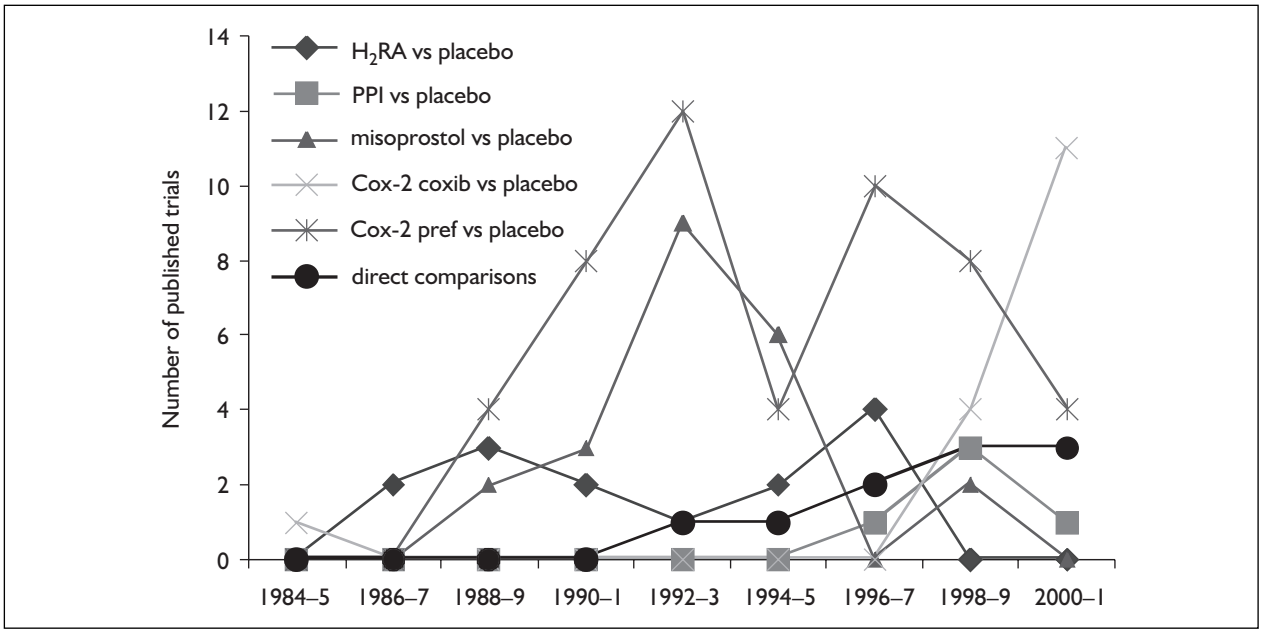

FIGURE 91 *Rate of change of the evidence by numbers of published trials*

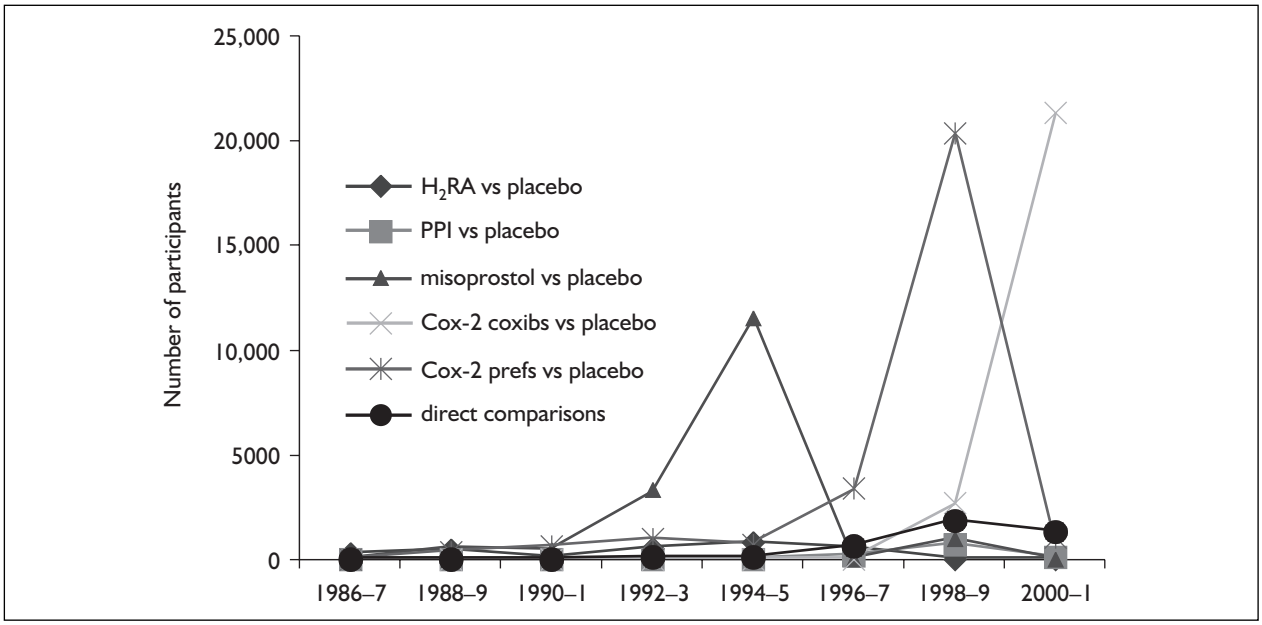

FIGURE 92 *Rate of change of the evidence by numbers of participants*

95% CI 0.16 to 1.05) were not significantly different between Cox-2 preferential and Cox-1 groups, but the numbers of people with these outcomes were low.

Rate of change of the evidence base

To assess the rate of change in the evidence base, the authors plotted the number of publications in each comparison in 2-year blocks (*Figure 91*).

However, since the effect on the level of evidence of a very large study is not the same as that from a very small study, the number of participants in studies in each 2-year block was also plotted (*Figure 92* and *Table 30*).

As the electronic search was performed in mid-2002 (and there is some delay in getting published studies on to electronic databases following publication), the authors assumed that the list of included studies to the end of 2001 was reasonably complete, but that collection of studies

TABLE 30 *Numbers of participants in trials published in 2-year blocks*

Period	H_2RA vs placebo	PPI vs placebo	Misoprostol vs placebo	Cox-2 coxibs vs placebo	Cox-2 preferentials vs placebo	Direct comparisons
1986–7	272	0	0	0	0	0
1988–9	465	0	488	0	319	0
1990–1	128	0	451	0	580	0
1992–3	496	0	3294	0	1002	118
1994–5	773	0	11512	0	733	61
1996–7	487	177	0	0	3403	570
1998–9	0	712	932	2734	20392	1816
2000–1	0	104	0	21329	1032	1271

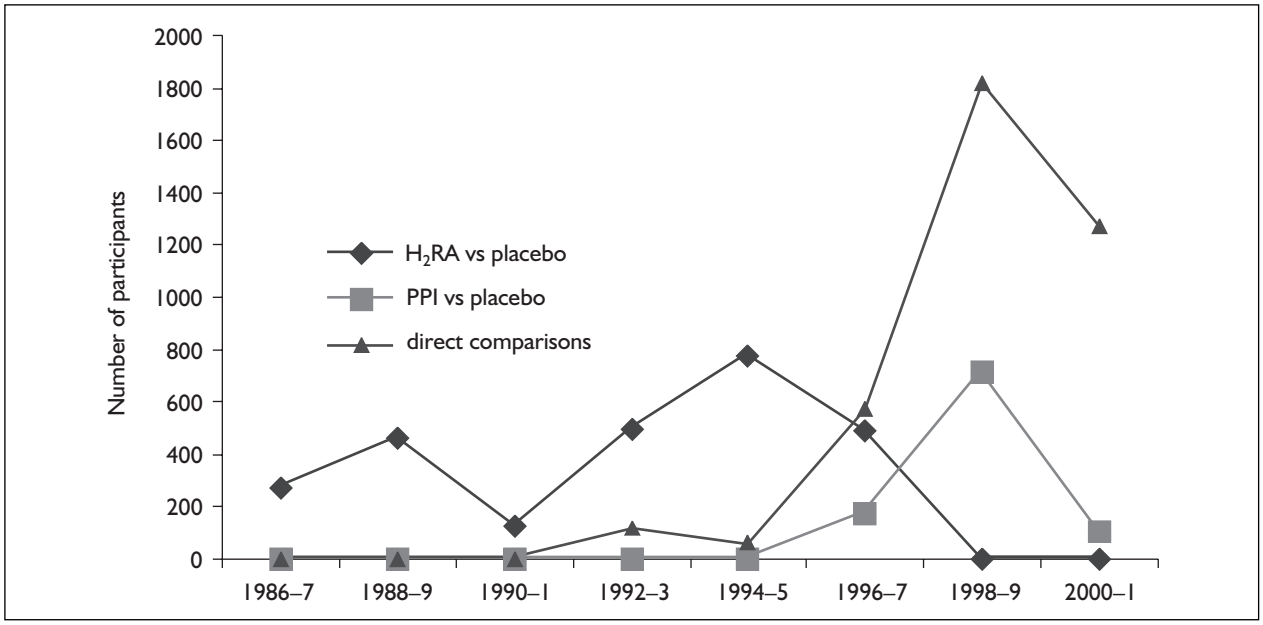

FIGURE 93 *Rate of change of the evidence by numbers of participants (without including data on Cox-2s or misoprostol)*

published in 2002 would be incomplete. For this reason, none of the 2002 studies was included in the assessment.

By either measure, it appears that little evidence is now emerging on the effect of H_2RAs, PPIs or misoprostol compared with placebo on outcomes relevant to this review, and work on Cox-2 preferentials is tailing off. However, the publication rate of studies comparing Cox-2 coxibs with Cox-1 NSAIDs is still high, with the numbers of trials still rising and the numbers of participants in studies remaining high over the last two 2-year time points. (For more detail on the trends for H_2RAs, PPIs and direct comparisons, see *Figure 93*).

There is a suggestion that trials assessing the effects of direct comparisons of different gastroprotectors are tailing off, and the numbers of participants involved to date is very small compared with the numbers involved in the Cox-2 coxib or preferential versus Cox-1 studies.

Principal research questions of the systematic review

Are there differences in the effectiveness of the five preventive strategies on mortality, health-related QoL, serious GI complications, symptomatic ulcers, serious cardiovascular or renal illness and side-effects?

H_2RA plus NSAID versus PPI plus NSAID

Only one study directly compared the efficacy of a H_2RA plus NSAIDs versus a PPI plus NSAIDs. It

included 425 participants with OA, RA and other types of arthritis, and a mean age of 56 years. All participants had undergone treatment of ulcers or erosions. Drugs were all prescribed at appropriate doses and follow-up was 26 weeks. The summary risk of bias was 'moderate', with unclear allocation concealment and apparent comparability at baseline. A pharmaceutical company funded the study.

There were insufficient data to assess any primary outcomes in the included study, and indirect comparisons did not suggest any significant relationships. Endoscopic ulcers were significantly more likely in participants on H_2RAs rather than PPIs (RR 3.11, 95% CI 1.62 to 5.95) in the included direct comparison study. This was supported by the adjusted indirect comparison data. There was no significant difference in total drop-outs in either direct or indirect comparisons. No other secondary outcomes were reported in the direct comparison RCT, and no significant results were seen for GI symptoms, drop-outs or drop-outs due to GI symptoms in the indirect comparisons.

H_2RA plus NSAID versus misoprostol plus NSAID

Three studies (including 631 participants) directly compared the efficacy of H_2RAs with Misoprostol, including participants with cancer pain, OA and RA and aged 37–61 years on average. Baseline GI status was variable within each of the studies. Two studies prescribed either the H_2RA or NSAIDs at higher than recommended doses. Duration was from 4 to 8 weeks. The summary risk of bias was 'moderate' for all three studies, with allocation concealment unclear in all studies and baseline comparability unclear in two. At least two of the studies were funded by a pharmaceutical company.

Comparability of primary outcomes could not be assessed by direct or indirect comparisons. Endoscopic ulcers were significantly more common in those on H_2RAs compared with those on misoprostol according to both direct (RR 4.35, 95% CI 1.51 to 12.55, robust to SA) and indirect methods of assessment, whereas GI symptoms were less likely in those on H_2RAs (RR 0.85, 95% CI 0.74 to 0.97, robust to SA but not supported by indirect comparison). The included direct comparisons suggested that drop-outs due to GI symptoms were less likely in those randomised to H_2RAs as compared with misoprostol (RR 0.40, 95% CI 0.22 to 0.74, robust to SA), and this was confirmed by indirect comparisons. No other secondary outcomes suggested significant differences in effect in either direct or indirect comparisons.

H_2RA plus NSAID versus Cox-2 coxib NSAID

There were no included RCTs that directly compared the effects of H_2RA plus NSAID versus Cox-2 NSAID. Indirect comparison only suggests that endoscopic ulcers are more common in those on H_2RAs and a Cox-1 NSAID than in those on Cox-2 coxib NSAIDs.

PPI plus NSAID versus misoprostol plus NSAID

Two RCTs directly compared PPI with misoprostol. Participants had OA and RA, were middle aged and all had previously had ulcers or erosions. Lansoprazole and omeprazole were compared with misoprostol, all within current recommended doses. Duration was 12–26 weeks. One study was assessed as being of moderate risk of bias and the other of low risk of bias. Allocation concealment was adequate in one study, unclear in the other and baseline comparability was adequate in both studies. It was not possible to assess publication bias.

There were no significant differences between those on PPIs and misoprostol as regards any primary outcomes, from direct or indirect comparisons. Total drop-outs were significantly less frequent in those on PPIs than those on misoprostol in direct comparisons (RR 0.71, 95% CI 0.52 to 0.98), but there were no significant differences in indirect comparisons. GI symptoms and drop-outs due to GI symptoms were not reported in the direct comparisons. Indirect comparisons suggest significantly fewer GI symptoms and drop-outs due to GI symptoms in those on PPIs compared with those on misoprostol. Endoscopic ulcers occurred to similar degrees in those on PPIs and misoprostol according to both the direct and indirect comparisons. Anaemia and occult bleeding were not reported in the direct comparisons and did not show significant differences in the indirect comparisons.

PPI plus NSAID versus Cox-2 coxib NSAID

One RCT directly compared PPIs with Cox-2 in 287 participants with OA and RA and a mean age of 68 years, following healing of bleeding ulcers. Omeprazole and celecoxib were compared at doses within the recommended ranges for 26 weeks. The summary risk of bias was 'low', with adequate allocation concealment and baseline

comparability. Funding was from non-pharmaceutical industry sources.

No significant differences were reported between those on PPIs and Cox-2 coxibs in respect of any primary outcomes in the study directly comparing the two treatments. However, indirect comparisons suggested significantly fewer symptomatic ulcers in those on PPIs compared with Cox-2 coxibs.

Similarly, there were no significant differences in secondary outcomes between the PPI and Cox-2 groups in the direct comparison. Indirect comparisons suggested a significant reduction in GI symptoms in those on PPIs as compared with those on Cox-2 coxib NSAIDs, alongside a significant increase in endoscopic ulcers.

Misoprostol plus NSAID versus Cox-2 coxib NSAID

One RCT directly compared misoprostol with a Cox-2 coxib, randomising 283 participants with OA. Mean age was 62 years. None had baseline endoscopies, but 7% had previous GI ulcers or bleeds. The study compared rofecoxib with misoprostol over 6 weeks. Summary risk of bias was 'moderate', allocation concealment was unclear and baseline comparability adequate. A pharmaceutical company funded the study. Publication bias was not assessable.

Of the primary outcomes, only serious cardiovascular or renal events were directly assessed, with no significant difference in risk between misoprostol and Cox-2 coxibs. None of the primary outcomes assessed by indirect comparisons suggested significant differences in risk.

Cox-2 coxibs were significantly better at preventing GI symptoms and drop-outs due to GI symptoms than misoprostol, but no significant differences were seen for total drop-outs. Indirect comparisons suggested an increased risk of endoscopic ulcers, total drop-outs and drop-outs due to GI symptoms in those on misoprostol instead of Cox-2 coxibs. No other significant differences were observed.

H_2RA plus NSAID versus Cox-2 preferential NSAID

There were no included RCTs that directly compared the effects of H_2RA plus NSAID versus Cox-2 preferential NSAID, and indirect comparisons do not suggest any statistically significant differences between H_2RAs with a Cox-1 NSAID and Cox-2 preferential NSAIDs.

PPI plus NSAID versus Cox-2 preferential NSAID

There were no included RCTs that directly compared the effects of PPI plus NSAID versus Cox-2 preferential NSAID, and indirect comparisons do not suggest any statistically significant differences between PPIs with a Cox-1 NSAID and Cox-2 preferential NSAIDs.

Misoprostol plus NSAID versus Cox-2 preferential NSAID

Three RCTs directly compared misoprostol with Cox-2 preferentials, randomising 1088 participants with OA. Mean ages of participants were 62–75 years and people had varied GI status at baseline. Studies compared misoprostol with nabumetone for 6–24 weeks. Summary risk of bias was 'moderate' in two studies and 'high' in one. Allocation concealment was unclear in two studies and adequate in one. Baseline comparability was adequate in one study, unclear in one and inadequate in one. Two studies were funded by pharmaceutical companies; one was funded independently. Publication bias was not assessable.

A significantly increased risk of serious GI events was seen in those on misoprostol compared with Cox-2 preferentials. This relationship was stable to SA but not supported by indirect comparisons. There were no statistically significant differences for other primary outcomes in either direct or indirect comparisons.

Risk of endoscopic ulcers was significantly reduced in those on misoprostol compared with those on Cox-2 preferentials in direct comparisons, but not supported by the indirect comparisons. No further differences between misoprostol and Cox-2 preferentials were seen in the direct comparisons. Indirect comparisons suggested that those on misoprostol were significantly more likely to drop out and to drop out due to GI symptoms than those on Cox-2 preferentials.

Cox-2 coxib NSAID versus Cox-2 preferential NSAID

One RCT directly compared a Cox-2 coxib NSAID with a Cox-2 preferential, randomising 289 participants with OA. Mean age was 83 years and participants were excluded only if they had had active GI bleeding in the past 3 months (no endoscopy was performed). Rofecoxib was compared with nabumetone over 6 weeks. Summary risk of bias was 'high'. Allocation concealment was unclear and baseline comparability was inadequate. A pharmaceutical company funded the study.

TABLE 31 *Summary of comparisons between gastroprotective strategies*

Outcome	Direct comparisons	Indirect comparisons
Primary outcomes		
Serious GI complications	Cox-2 preferentials >> misoprostol	NSR
Symptomatic ulcers	NSR	PPIs >> Cox-2 coxibs
Serious cardiovascular or renal events	NSR	NSR
Deaths	NSR	NSR
Secondary outcomes		
GI symptoms	H_2RAs and Cox-2 coxibs >> misoprostol	PPIs >> misoprostol and Cox-2 coxibs
Endoscopic ulcers	PPIs and misoprostol >> H_2RAs, misoprostol >> Cox-2 preferentials	Cox-2 coxibs >> PPIs and misoprostol, PPIs and misoprostol and Cox-2 coxibs >> H_2RAs
Anaemia	NSR	NSR
Occult bleeding	NSR	NSR
Total drop-outs	PPIs >> misoprostol	Cox-2 coxibs >> Cox-2 preferentials, Cox-2 coxibs and preferentials >> misoprostol
Drop-outs due to GI symptoms	H_2RAs and Cox-2 coxibs >> misoprostol	H_2Rs, PPIs, Cox-2 coxibs and Cox-2 preferentials >> misoprostol

NSR, no significant relationships; >> means 'is better than' (at preventing this outcome).

There were no statistically significant differences between Cox-2 coxibs and Cox-2 preferentials for any primary outcomes in either direct or indirect comparisons. No significant differences were seen in any secondary outcomes in direct or indirect comparisons, except that drop-outs were less likely in Cox-2 coxibs than Cox-2 preferentials in indirect comparisons (of borderline significance).

Which strategies were better than which?

The combined direct and indirect evidence offers suggestions as to which gastroprotective strategies are most effective (see *Table 31*). Cox-2 preferentials appear better than misoprostol at preventing serious GI complications, and it may be that PPIs are better than Cox-2 coxibs at prevention of symptomatic ulcers (although the latter is from indirect comparison only).

Given the positive relationship of Cox-2 preferentials over misoprostol in prevention of serious GI complications, it is interesting that misoprostol is better than Cox-2 preferentials at preventing endoscopic ulcers. PPIs and misoprostol are better than H_2RAs at preventing endoscopic ulcers.

Does the effectiveness of the five strategies vary according to whether participants have a history of peptic ulceration or GI bleeding?

Meta-regression of ln (RR) against percentage of participants with a history of ulcers or bleeds (where this could be ascertained) suggests no change in RR (of endoscopic or symptomatic ulcers) with changing baseline risk for any of the four strategies (see Appendix 8 for meta-regression results). However, it does appear that poorer baseline GI status increases the ARR of H_2RAs and PPIs on endoscopic ulcers, while decreasing the ARR of misoprostol on endoscopic ulcers (see Appendix 10a for details of subgrouping ARRs).

Does the effectiveness of the five strategies vary according to whether participants have a history of H_2RA use?

There were virtually no RCTs that specified a history of H_2RA use in their participants, so this assessment was not possible.

Does the effectiveness of the five strategies vary according to whether participants concurrently use anticoagulants or corticosteroids?

There were virtually no RCTs that specified whether participants were currently using

TABLE 32 *Relationship between development of endoscopic and symptomatic ulcers*

Study	Intervention arm				Control arm				Duration (weeks)	Intervention type	Proportion of endoscopic ulcers becoming symptomatic	
	Endoscopic ulcers		Symptomatic ulcers		Endoscopic ulcers		Symptomatic ulcers					
	n	*N*	*n*	*N*	*n*	*N*	*n*	*N*			Intervention	Control
Cullen, 1998[61]	3	83	0	83	14	85	6	85	6	PPI	0.00	0.43
Ekstrom, 1996[59]	4	85	1	85	15	90	11	90	12	PPI	0.25	0.73
Elliott, 1994[80]	5	32	2	32	11	38	4	38	52	Misoprostol	0.40	0.36
Goldstein, 2001[39]	24	269	5	296	109	267	5	270	12	Cox-2	0.19	0.05
Kivitz, 2002[96]	15	359	5	359	18	183	7	183	12	Cox-2	0.33	0.39
Perpignano, 1994[118]	2	24	0	24	2	29	1	29	8	Cox-2	0.00	0.50

n, Number of people with events; *N*, number of people exposed.

anticoagulants or corticosteroids, so this assessment was not possible.

Does the effectiveness of the five strategies vary according to whether participants are using more than one type of NSAID?

There were virtually no RCTs that specified whether participants were currently using more than one NSAID (although occasionally it was stated that only one NSAID was allowed), so this assessment was not possible.

Does the effectiveness of the five strategies vary according to initial age of the participants?

Meta-regression of ln (RR) against baseline mean age (where this could be ascertained) suggests no change in RR (of endoscopic or symptomatic ulcers) with changing age for any of the four strategies (see Appendix 8 for meta-regression results). When subgrouping according to baseline age (see Appendix 9a for details of subgrouping ARRs), it does appear that greater baseline age increases the ARR of H_2RAs and misoprostol on endoscopic ulcers. However, age does not appear to alter the ARR of Cox-2s compared with Cox-1s on symptomatic ulcers.

Does the effectiveness of the five strategies vary according to the number of initial risk factors (elderly, history of peptic ulceration or GI bleeding, history of H_2RA use, concurrent use of anticoagulants or corticosteroids, use of more than one type of NSAID)?

Data were very rarely provided on numbers of risk factors in trial participants, so there were not enough data to assess this relationship.

Does the effectiveness of the five strategies vary according to length of exposure?

Meta-regression of ln (RR) against intervention time (where this could be ascertained) suggests no change in RR (of endoscopic or symptomatic ulcers) with changing intervention period for H_2RAs, PPIs or Cox-2s. However, a significant relationship was seen in the effect of intervention time on endoscopic ulcers in misoprostol, suggesting that the protective effect of misoprostol lessens over time. See Appendix 8 for meta-regression results.

Does the effectiveness of the five strategies vary according to initial dose of NSAID used?

This question aimed to discover whether the policy of starting with a low dose of NSAID and working up gently was an effective way to reduce side-effects. Unfortunately, very few studies allowed this process to occur and so its effect could not be assessed.

Does the effectiveness of the five strategies vary according to whether usual or slow-release NSAIDs are used?

There were not enough data to answer this question.

Relationship between development of endoscopic and symptomatic ulcers

We expected that studies that measured both endoscopic and symptomatic ulcers would provide some information on the relationship between numbers of endoscopic and subsequent symptomatic ulcers developing. However,

relatively few studies assessed both types of ulcers in a systematic way.

In the six studies in which both endoscopic ulcers and symptomatic ulcers appeared to be fully reported, we estimated the apparent conversion rate between endoscopic and symptomatic ulcers (*Table 32*).

There were no obvious relationships. It may be that participants were removed from the study when endoscopic ulcers appeared, so that only very acute ulcers can become symptomatic. If this is the case, then the time interval between endoscopies may be what determines how many symptomatic ulcers develop.

Chapter 21

Economic evaluation and published data

Data sources and search strategy

The search strategy used to collect studies for the systematic review of effectiveness was also used to collect studies for the systematic review of cost-effectiveness.

RCTs and observational studies were taken from this search for use in the economic evaluation and modelling (see above and Appendix 1 for more details).

Study selection

Keywording for economic studies is not standardised, so an inclusive, exhaustive search strategy was required. This generated over 600 references. In addition, RCTs from the systematic review were screened to assess whether they also contained economic evaluations. The papers retrieved for the economics literature review were screened for inclusion using the following criteria:

1. **Types of studies.** All prospective studies including any parallel controlled trial, crossover studies and prospective cohorts. Case–control studies and cross-sectional studies were excluded.
2. **Types of participants.** Studies of adults (18 years or older) who had taken NSAIDs for at least 3 weeks were included.
3. **Types of interventions.** The evaluation included cost and outcome data for comparison of the following specific gastric protection techniques or agents alongside chronic NSAID therapy in adults:
   (a) Cox-1 NSAIDs plus H_2RAs compared with Cox-1 NSAIDs (alone or with placebo gastroprotection).
   (b) Cox-1 NSAIDs plus PPIs compared with Cox-1 NSAIDs (alone or with placebo gastroprotection).
   (c) Cox-1 NSAIDs plus misoprostol compared with Cox-1 NSAIDs (alone or with placebo gastroprotection).
   (d) Cox-2 inhibitors compared with Cox-2 NSAIDs alone (later expanded to Cox-2 coxib NSAIDs and Cox-2 preferential NSAIDs).
   (e) Any of the active interventions above compared with any other active intervention.

Doses of drugs used were compared with the standard suggested prescribed doses in the March 2003 version of the BNF (or as described in Martindale for those drugs not prescribed in the UK). Generic and trade names of the various NSAIDs and gastroprotective agents included in the review are given in Appendix 2. Aspirin was not included as an NSAID. At least one comparator was an NSAID with gastroprotective strategy, Cox-2 preferential or Cox-2 coxib.

4. **Types of data.** Sufficient data were reported to extract costs and outcome data relevant to comparisons of gastroprotection techniques and agents for the literature review or the economic model. The evaluations were based on primary data collection or systematic review.
5. **Types of economic evaluation.** The study was a cost-effectiveness (generated an incremental cost effectiveness ratio), cost–utility (cost per QALY) or cost–consequences analysis (expected cost, incorporating probabilistic cost associated with adverse events).
6. **Outcomes.**
   (a) Primary clinical outcomes: symptomatic ulcers, perforations, ulcers and bleeds, (PUBs), death rates.
   (b) Secondary clinical outcomes: endoscopic ulcers.

Methods for assessment of inclusion

An 'inclusion/exclusion' form (developed specifically for the review) was used to assess inclusion (see Appendix 3). Studies that are 'included' on any of the three sheets were then included in the economic evaluation and modelling.

Titles and abstracts resulting from the search strategy were assessed independently by two assessors (against the inclusion/exclusion form criteria). Articles were only rejected on initial screen if the reviewer could determine from the title and abstract that the article did not fulfil the inclusion criteria. When a title/abstract could not be rejected with certainty, by either of the assessors, the full text of the article was obtained

for further evaluation. If the reviewer was uncertain about the appropriateness of rejecting the article, the full text article was retrieved. This occurred frequently owing to the difficulty in identifying resource use from titles or abstracts of studies.

Full text articles were formally assessed for inclusion, again using the inclusion/exclusion form. Inclusion of studies was assessed independently by two assessors and differences between reviewers' results were resolved by discussion and, when necessary, in consultation with a third reviewer. Most of the studies retrieved discussed resource use, but did not report primary data. There were a large number of reviews and discussion documents. Thirty-five studies were found that met the broad criteria above. All 35 studies are described and summarised in this report. Only nine studies were found that compared directly NSAID plus GPAs or Cox-2 preferential or Cox-2 coxib. These are presented separately.

Quality assessment

Economic studies quality assessment was applied to primary economic evaluations of head-to-head comparisons, using *BMJ* guidelines.[148]

Data extraction

A data extraction form was specifically designed for this review. Data concerning participants, interventions and outcomes (as described in the section 'Methods for assessment of inclusion', p. 127) were extracted and tabulated.

Two reviewers independently extracted original reports of study results. Differences between reviewers' extraction results were resolved by discussion and, when necessary, in consultation with a third reviewer.

Characteristics of included studies

Tables 33–35 summarise the main characteristics of each study and a detailed summary of each study is provided in Appendix 12.

Country of origin

The studies (from 1989 to 2003) originate from the USA (12), UK (seven), Canada (five), France (two), Italy (two), Norway (two), Spain (two), Australia (one), Belgium (one), Greece (one), Hong Kong (one), The Netherlands (one), Sweden (one) and Switzerland (one).

Type of economic analysis method

There were 16 cost-effectiveness analyses, using the following ICERs: cost per GI event averted, PUB avoided, life saved, life-year gained, ulcer-free days. Three studies reported cost–utility analyses.[12,156,170] Sixteen studies carried out cost-effectiveness analysis where they incorporated probabilities into a decision-analytic model, but did not report ICERs, just expected costs.

Perspective

Five studies reported a societal perspective, although the quality of data used was variable. The remaining studies either stated a healthcare provider perspective, or this was assumed by the reviewers.

Patient group

A range of patient groups were investigated: only OA, only RA, OA and RA, 'arthritis', 'rheumatic disease', 'NSAID users' or not stated. Some studies examined older or 'at-risk' patient groups separately. Many studies had combined clinical data from a range of sources to populate their models. It was not always clear whether the clinical data from disparate sources used in the analysis came from patient groups with similar characteristics, such as age and previous GI risk.

Comparators

Twenty-six studies compared a Cox-1 NSAID plus gastroprotective strategy, Cox-2 preferential or Cox-2 coxib with a Cox-1-NSAID only. Fourteen compared a Cox-1 NSAID with a Cox-1 NSAID plus misoprostol (see *Table 33*) and 12 compared a Cox-1 NSAID with a Cox-2 preferential or Cox-2 coxib inhibitor (see *Table 34*). Nine studies carried out head-to-head comparisons of gastroprotective strategies (see *Table 35*) and these are discussed more fully below.

Time horizon

The length of follow-up ranged from 15 days to the patient's lifetime, although 3 months (11 studies), 6 months (eight studies) and 1 year (nine studies) were the most commonly used time horizons.

Data synthesis method

No studies other than that of Maetzel and colleagues[11] reported a primary economic evaluation. All other studies synthesised data from a range of sources and nearly all studies used a

TABLE 33 *Summary of economic evaluations of Cox-1 versus Cox-1 plus misoprostol*

Study	Study details								
	Country	**Perspective**	**Patients**	**Comparators**	**Time horizon**	**Methods**	**ICER**	**Funded by**	**Conclusions**
Hillman, 1989[149]	USA	Healthcare provider	OA	Cox-1 versus Cox-1 plus misoprostol	3 months	Decision-analytic model	Expected cost	Searle	Cox-1/misoprostol is cost saving below a certain misoprostol price
Carrin, 1990[150]	Belgium	Societal	OA	Cox-1 versus Cox-1 plus misoprostol	Not clear	Decision-analytic model	Expected cost	Searle	Cox-1 plus misoprostol cost saving
Edelson, 1990[151]	USA	Healthcare provider	General population, over 60, RA	Cox-1 versus Cox-1 plus misoprostol	1 year	Decision-analytic model	Cost per life saved	NIH	Cost-effective only in patients with a history of GI bleeds
Knill-Jones, 1990[15]	UK	Healthcare provider	Not stated	Cox-1 versus Cox-1 plus misoprostol	6 months	Shadow price calculation	Shadow price (expected cost)	Not stated	Shadow price lowest for Cox-1 plus misoprostol
Jonsson, 1992[152]	Sweden	Societal	OA	Cox-1 versus Cox-1 plus misoprostol	3 months	Decision-analytic model	Cost per ulcer avoided	University	Cox-1/misoprostol cost-effective
Knill-Jones, 1992[153]	UK	Healthcare provider	Not stated	Cox-1 versus Cox-1 plus misoprostol	3 months	Decision-analytic model	Expected cost	Searle	Cox-1 plus misoprostol cost saving
Gabriel, 1993[154]	Canada	Healthcare provider	OA, OA over 60	Cox-1 versus Cox-1 plus misoprostol	3 months	Decision-analytic model	Cost per UGI event	University	Cox-1/misoprostol cost saving in high-risk patients, cost-effective in general population
Peacock, 1993[155]	UK	Healthcare provider	Rheumatic conditions	Oral Cox-1 versus topical felbinac versus diclofenac plus misoprostol	1 year	Decision-analytic model	Expected cost	Lederle	Topical felbinac was cost saving compared with oral Cox-1s and diclofenac plus misoprostol
Gabriel, 1994[156]	USA	Healthcare provider	RA, RA over 60	Cox-1 versus Cox-1 plus misoprostol	3 months	Decision-analytic model with Monte Carlo simulation	Cost per QALY	University	Cox-1/misoprostol cost saving but can cause reduction in QoL
Al,1996[157]	The Netherlands	Societal	RA	Diclofenac versus diclofenac/misoprostol	3 months	Decision-analytic model	Cost per symptomatic ulcer, life saved	Searle	Diclofenac/misoprostol cost saving in high-risk patients, cost-effective in general population

continued

TABLE 33 *Summary of economic evaluations of Cox-1 versus Cox-1 plus misoprostol (cont'd)*

Study	Study details								
	Country	**Perspective**	**Patients**	**Comparators**	**Time horizon**	**Methods**	**ICER**	**Funded by**	**Conclusions**
Maetzel, 1998[11]	Canada	Healthcare provider	RA	Cox-1 versus Cox-1 plus misoprostol	6 months	Decision-analytic model with Monte Carlo simulation	Cost per serious adverse event	Searle	Diclofenac/misoprostol cost-effective in high-risk patients, cost-effective in general population
Kristiansen, 1999[12]	Norway	Societal	RA	Diclofenac versus diclofenac/misoprostol	6 months	Decision-analytic model	Cost per QALY	Searle	Diclofenac/misoprostol cost saving in high-risk patients, cost-effective in general population
Davey, 2000[158]	Australia	Healthcare provider	MUCOSA, GI risk, over 65	Cox-1 versus Cox-1 plus misoprostol	1 year	Decision-analytic model	Cost per life-year gained	Searle	Misoprostol more effective and more costly
Rahme, 2001[159]	Canada	Healthcare provider	Patients prescribed Cox-1s	Cox-1 versus diclofenac plus misoprostol	2 years	Regression model to estimate costs	Expected cost	Merck	No differences in expected costs

MUCOSA, Misoprostol Ulcer Complications Outcome Safety Assessment; NIH, National Institutes of Health.

TABLE 34 *Summary of economic evaluations of Cox-1 NSAID versus Cox-2 coxib or Cox-2 preferential*

Study	Study details								
	Country	Perspective	Patients	Comparators	Time horizon	Methods	ICER	Funded by	Conclusions
Jansen, 1996[160]	UK	Healthcare provider	OA	Meloxicam versus diclofenac	1 month	Decision-analytic model	Expected cost	Boehringer Ingelheim	Meloxicam is cost saving compared with diclofenac
Jansen, 1997[161]	UK, France, Italy	Healthcare provider	OA	Meloxicam versus diclofenac	1 month	Decision-analytic model	Expected cost	Boehringer Ingelheim	Meloxicam is cost saving compared with diclofenac
McCabe, 1998[13]	UK	Healthcare provider	OA and RA	Nabumetone versus ibuprofen	3 months	Decision-analytic model	Cost per life-year gained	SmithKline Beecham and Novartis	Nabumetone is more effective and more costly than ibuprofen
Liaropoulos, 1999[13,162]	Greece	Healthcare provider	OA	Nimesulide versus diclofenac	15 days	Not stated	Expected cost	University	Nimesulide is cost saving
Svarvar, 2000[13,163]	Norway	Societal	OA and RA	Celecoxib versus Cox-1	1 year	ACCES decision-analytic model	Cost per GI event averted, cost per life-year gained	Pfizer	Celecoxib dominates Cox-1s alone
Marshall, 2001[164]	Canada	Healthcare provider	OA over 65	Cox-1 versus rofecoxib	1 year	Decision-analytic model	Cost per PUB	Merck Frosst	Rofecoxib is cost-effective in over-65s
Tarricone, 2001[165]	France, Italy, Spain	Healthcare provider	OA	Nimesulide versus diclofenac	15 days	Decision-analytic model	Expected cost	Helsinn	Nimesulide is cost saving
Peris, 2001[166]	Spain	Healthcare provider	OA and RA	Aceclofenac versus Cox-1s	3 months	Decision-analytic model	Iatrogenic cost (expected cost)	Almirall Prodesfarma	Aceclofenac has a similar expected cost to other Cox-1s despite higher acquisition costs
Moore, 20001[167]	UK	Healthcare provider	OA	Cox-1 versus rofecoxib	1 year	Decision-analytic model	Expected cost	Merck	Rofecoxib is cost-effective
Pellissier, 2002[167,168]	USA	Healthcare provider	OA	Cox-1 versus rofecoxib	1 year	Decision-analytic model	Cost per PUB, cost per life-year gained	Merck	Rofecoxib is cost-effective
Fendrick, 2002[169]	USA	Healthcare provider	OA and RA	Restricted use of 'safer Cox-1' versus unrestricted use of 'safer Cox-1' (data on celecoxib, rofecoxib, nabumetone)	1 year	Markov model	Cost per ulcer avoided	SmithKline Beecham	Restricting use of safer Cox-1s reduces costs and increases adverse outcomes

continued

TABLE 34 *Summary of economic evaluations of Cox-1 NSAID versus Cox-2 coxib or Cox-2 preferential (cont'd)*

Study	Study details								
	Country	**Perspective**	**Patients**	**Comparators**	**Time horizon**	**Methods**	**ICER**	**Funded by**	**Conclusions**
Spiegel, 2003[170]	USA	Healthcare provider	OA and RA	Celecoxib or rofecoxib versus naproxen	Lifetime	Decision-analytic model	Cost per QALY	NIH (grants from Pharmacia)	Rofecoxib and celecoxib are cost-effective in high-risk patients

ACCES, arthritis cost and consequences evaluation system; NIH, National Institutes of Health.

TABLE 35 *Summary of economic evaluations of head-to-head comparisons of Cox-1 NSAID plus GPA versus Cox-2 coxib or Cox-2 preferential*

Study	Study details								
	Country	**Perspective**	**Patients**	**Comparators**	**Time horizon**	**Methods**	**ICER**	**Funded by**	**Conclusions**
Bentkover, 1994[171]	USA	Healthcare provider	OA over 60	Nabumetone versus ibuprofen versus ibuprofen plus misoprostol	3 months	Decision-analytic model	Cost per GI lesion	Pfizer	Nabumetone cost saving
Brixner, 1994[172]	USA	Healthcare provider	OA and RA over 60	Nabumetone versus ibuprofen versus ibuprofen plus misoprostol	3 months	Decision-analytic model	Expected cost model	SmithKline Beecham	Nabumetone cost saving
Goldstein, 1993[173]	USA	Healthcare provider	RA	Cox-1 plus H_2RA versus Cox-1 plus misoprostol versus Cox-1	6 months	Decision-analytic model with Monte Carlo simulation	Expected cost	Searle	Cox-1 plus misoprostol cost saving
Ko, 2000[174]	USA	Healthcare provider	Inflammatory disease, over 65	Cox-1 plus *H. pylori* eradication versus Cox-1 plus low-dose H_2RA versus Cox-1 plus low-dose H_2RA versus Cox-1 plus misoprostol, versus Cox-1	3 months	Decision-analytic model	Cost per life-year gained	University	Cox-1 plus bismuth, tetracycline and metronidazole cost saving, Cox-1 plus metronidazole, omeprazole and clarithromycin, misoprostol, PPI or H_2RA more costly and more effective
Zabinski, 2001[175]	Canada	Healthcare provider	OA and RA	Celecoxib versus Cox-1 plus PPI versus Cox-1 plus H_2RA versus Cox-1 plus misoprostol versus Cox-1	6 months	Decision-analytic model	Expected cost	Pfizer and Pharmacia	Celecoxib has a lower expected cost than H_2RA, misoprostol or PPI
Chancellor, 2001[176]	Switzerland	Healthcare provider	Arthritis	Celecoxib versus Cox-1 plus PPI versus Cox-1 plus H_2RA versus Cox-1 plus misoprostol versus Cox-1	6 months	Decision-analytic model with Monte Carlo simulation	Cost per adverse event	Pharmacia	Celecoxib dominates Cox-1s alone

continued

TABLE 35 *Summary of economic evaluations of head-to-head comparisons of Cox-1 NSAID plus GPA versus Cox-2 coxib or Cox-2 preferential (cont'd)*

Study	Study details								
	Country	**Perspective**	**Patients**	**Comparators**	**Time horizon**	**Methods**	**ICER**	**Funded by**	**Conclusions**
You, 2002[177]	Hong Kong	Healthcare provider	OA and RA	Celecoxib versus Cox-1 plus PPI versus Cox-1 plus H_2RA versus Cox-1 plus misoprostol	6 months	Decision-analytic model	Expected cost	Pfizer and Pharmacia	Celecoxib has lowest expected cost
El-Serag, 2002[178]	USA	Healthcare provider	Cox-1 users	Ibuprofen versus Cox-1 plus misoprostol versus Cox-1 plus PPI versus celecoxib	1 year	Decision-analytic model	Cost per UGI event	University	In high-risk patients, Cox-2 inhibitors are dominant, followed by Cox-1 plus PPI
Kamath, 2003[179]	USA	Healthcare provider	OA	Celecoxib versus rofecoxib versus ibuprofen versus ibuprofen plus misoprostol	6 months	Decision-analytic model	Cost per adverse event	McNeil	Rofecoxib has lowest ICER

decision-analytic model to do this. Some reported using non-parametric bootstrapping or Monte Carlo simulation, and one study developed a Markov model.[169]

Sources of clinical data

Data were taken from one clinical trial in four studies[159–161,171] and MA was used in eight studies.[13,102,104–166,168,175,176] The remaining 23 studies sourced clinical data from multiple studies without MA.

Owing to the lack of data available in most RCTs, most of the economic analyses utilised epidemiological studies or cohort studies to determine rates of serious GI events and the probability of subsequent interventions.

Sources of resource use and cost data

Resource use associated with treatment pathways was obtained using expert opinion in 17 studies,[15,149,150,155,157,158,160–163,165–168,173,175,176] patient records in five studies,[11,154,156,160,177] insurance or hospital billing in five studies,[13,157,172,174,179] national or diagnosis related group (DRG)-linked reimbursement in four studies[159,164,171,180] and was not reported in five studies.[12,153,169,170,178]

Funding

The studies were funded by Almirall (one), Boehringer Ingelheim (two), Helsinn (one), Lederle (one), McNeill (one), Merck (four) and Novartis (one), Pfizer (four), Pharmacia (four) and Searle (eight), SmithKline Beecham (three), public funders (seven). In two studies, the funding source was not reported.

Quality assessment results

All of the studies, except four which used a cohort design, were based on data collected on patients enrolled in RCTs. The most common problems with the design of economic comparisons included:

- lack of specification of the viewpoint or perspective of the study against which the range of included costs and outcomes could be assessed
- inadequate or no justification of the alternatives included, or the form of evaluation used
- inadequate descriptions of the methods used to measure and value resource use
- inadequate information about the currency and price data used, the year to which the data pertain, methods used to adjust price data for inflation or currency conversions
- lack of justification for the limited time horizon and range of resource use and cost measures used
- inadequate information about the time horizon for measurement and valuation of resource use and outcomes and the need for discounting
- lack of SA to evaluate uncertainty in the results which could not be assessed by statistical analysis (for example, sources of price data, range of costs included, use of charges rather than opportunity costs)
- inadequate consideration of sample size and power calculations for economic variables.

Head-to-head economic evaluation results

There were no primary economic evaluations of head-to-head comparisons. All nine head-to-head economic analyses were modelling, or secondary economic evaluations, synthesising clinical and cost data from a range of sources. The results of these studies therefore are dependent on the quality of the models developed and the data used to populate them. Some of these studies used robust and considered methods and provide useful answers within their own context. Good practice in modelling methods from these studies was applied to the models generated in this report. However, there were no UK head-to-head economic analyses, so these studies have limited applicability to the UK context. The results are reported briefly below.

Cox-2 preferential versus Cox-1 NSAID plus misoprostol

Two US studies from 1994[171,172] reported nabumetone to be dominant, from the healthcare provider's perspective, compared with a Cox-1 NSAID (ibuprofen), plus misoprostol, in elderly or at-risk patients.

Cox-2 coxib versus Cox-1 NSAID plus misoprostol

One Swiss study[176] and one US study[178] reported celecoxib to be cost saving with fewer adverse outcomes (dominant) than Cox-1NSAIDs with misoprostol. One US study[179] reported rofecoxib to be cost saving with fewer adverse outcomes (dominant) than celecoxib or ibuprofen plus misoprostol. A Hong Kong study[177] and a Canadian study[175] reported that celecoxib had a lower expected cost than NSAIDs with misoprostol.

Cox-2 coxib versus Cox-1 NSAID plus PPIs

One Swiss study[176] and one US study[178] reported celecoxib to be cost saving with fewer adverse outcomes than Cox-1 NSAIDs with PPIs. A Hong Kong study[177] and a Canadian study[175] reported that celecoxib had a lower expected cost than NSAIDs with PPIs.

Cox-2 coxib versus Cox-1 NSAID plus H_2RAs

One Swiss study[176] reported celecoxib to be cost saving with fewer adverse outcomes (dominant) than Cox-1 NSAIDs with H_2RAs. One Hong Kong study[177] reported that celecoxib had a higher expected cost than NSAIDs with H_2RAs. One Canadian study[175] reported that celecoxib had a lower expected cost than NSAIDs with H_2RAs.

Cox-1 NSAID plus misoprostol versus Cox-1 NSAID plus H_2RAs

One US study[173] reported Cox-1 NSAID plus misoprostol to be cost saving with fewer adverse outcomes than Cox-1 NSAIDs with H_2RAs. One US study[174] reported Cox-1 NSAID plus misoprostol to be more costly with fewer adverse outcomes than Cox-1 NSAIDs with H_2RAs. One Hong Kong study[177] reported that Cox-1 NSAIDs with H_2RAs had a lower expected cost than Cox-1 NSAIDs with misoprostol. However, a Canadian study[175] reported that Cox-1 NSAIDs with H_2RAs had a higher expected cost than Cox-1 NSAIDs with misoprostol.

Cox-1 NSAID plus misoprostol versus Cox-1 NSAID plus PPIs

One US study[174] reported Cox-1 NSAID plus H_2RAs misoprostol to be less costly with more adverse outcomes than Cox-1 NSAIDs with PPIs. One Hong Kong study[177] and a Canadian study[175] reported that Cox-1 NSAIDs with PPIs had a higher expected cost than Cox-1 NSAIDs with misoprostol.

Cox-1 NSAID plus H_2RAs versus Cox-1 NSAID plus PPIs

One US study[174] reported Cox-1 NSAID plus H_2RAs to be less costly with more adverse outcomes than Cox-1 NSAIDs with PPIs. One Hong Kong study[177] and a Canadian study[175] reported that Cox-1 NSAIDs with PPIs had a higher expected cost than Cox-1 NSAIDs with H_2RAs.

Summary of results

1. Cox-1 NSAIDs plus PPIs appear to be effective, but more costly than other gastroprotective regimens.
2. Cox-2 preferential and Cox-2 coxib agents have the potential to dominate Cox-1 NSAIDs plus misoprostol, H_2RAs or PPIs.
3. Cox-1 NSAIDs plus H_2RAs appear to be a low-cost option, but may be less effective than other strategies.
4. Cox-1 NSAIDs plus misoprostol appear to be dominated by Cox-2s, but their ranking compared with PPIs and H_2RAs is not clear. The impact of intolerance to misoprostol leading to a high drop-out rate requires more detailed analysis.
5. Twenty-six studies were funded by pharmaceutical manufacturers and 23 found in favour of their product, the remaining three reporting neutral results.

Owing to the lack of relevant primary economic evaluations, comparing Cox-1 NSAIDs plus gastroprotective strategies or Cox-2 agents, in a UK context, it is not possible to draw conclusions about the cost-effectiveness of individual strategies.

Chapter 22

Economic analysis of Cox-1 NSAIDs plus gastroprotective agents, Cox-2 preferentials and Cox-2 coxib: methods

Introduction

Modelling within economic analysis allows research questions to be answered without recourse to primary research. It provides a simplified version of reality to allow analysis, links diverse sources of information into a coherent whole rather than using one trial and allows more questions to be asked (and answered) than just within one setting. There are limitations associated with the use of modelling, particularly as the researcher defines the model structure and the data used to populate that model. Misspecification of the model will produce erroneous and misleading results. Furthermore, data used to populate models come from diverse sources and there is an assumption that it is appropriate to combine these data and use them as though they come from a homogeneous source.

The model required for this study should allow us to piece together the process of care such that the model is realistic in terms of alternatives under investigation and the sequence of events. The data requirements are probabilistic events for which we can obtain data and resource use and unit costs. This section describes and justifies the specification of the model and data sources used. All assumptions and limitations are made explicit.

Model specification

The model developed for this study is a stochastic probabilistic model in which events occur with specified probabilities. The stochastic nature of the data used to populate the model provides a measure of uncertainty around the data and thus provides more useful cost-effectiveness information to decision-makers.

Previous modelling approaches

There are many published decision-analytic models relating to the use of NSAIDs, reviewed in Chapter 21. These models primarily concentrate on two areas: switching between NSAIDs and the point at which GPAs or Cox-2 inhibitors need to be added to therapy. The arthritis cost consequence evaluation system (ACCES) model is a recent model that examines the use of different GPAs and Cox-2 inhibitors.[181] The specification of the model for this study is described in the context of these previous approaches.

Patient population

The patients who are eligible for chronic NSAID therapy suffer from a wide range of disease states. This study concerns patients with chronic musculoskeletal conditions (primarily RA and OA) who require regular NSAID therapy for more than 3 weeks. Patients at risk of NSAID-induced GI side-effects who are eligible for GPAs or a switch to a Cox-2 inhibitor are the principal patient population of interest. Definitions of 'at-risk' groups are given and the impact of age is also investigated.

Alternatives under investigation

The principal GPA strategies, PPIs, H_2RAs and misoprostol, are compared with each other. These are compared with constitutional Cox-2 coxibs and preferential Cox-2 inhibitors. A further comparison examines the incremental costs and effects of each of these five strategies over the use of a Cox-1 alone. This provides information on the difference in impact of these strategies compared with one another and also the impact of the strategies over the use of a Cox-1 alone.

Comparators in decision-analytic model

The most commonly prescribed Cox-1 NSAIDs in the UK are ibuprofen, diclofenac and naproxen (*Figure 94*). The most commonly prescribed Cox-2 coxibs agents are meloxicam and nabumetone and the most commonly prescribed Cox-2 inhibitors are rofecoxib and celecoxib. A wide range of comparator NSAIDs were used in the RCTs included in the MA, and it was not always clear which NSAID was being used. This meant that reported probabilities of GI events are combinations of probabilities for individual agents.

The base-case Cox-1 comparator selected for this economic analysis was diclofenac. The alternative method was to use a 'basket' of Cox-1s to reflect the UK prescribing patterns of non-naproxen NSAIDs (see section 'Naproxen', p. 140. for discussion on naproxen), but it was considered that it would be more meaningful to decision-makers to use real comparators.

The selection of the Cox-1 is important because different agents have different RRs for GI side-effects. It is often suggested that ibuprofen is safer than diclofenac. However, this may be due to the fact that it tends to be prescribed in the community at lower doses. Also, ibuprofen is prescribed more often in 'NSAID-naïve' patients than diclofenac, which is likely to lead to a higher reported incidence of GI side-effects in the diclofenac patients. A UK observational case–control study of baseline GI risk associated with patients compared meloxicam, ibuprofen and diclofenac.[182] They used the General Practice Research Database (GPRD) to select a random sample of 5000 users of each of meloxicam, diclofenac, ibuprofen and naproxen and 2500 of indomethacin. Groups were matched according to age and sex. Recent use of NSAIDs was reported in 7.9% of ibuprofen, 22.2% of diclofenac and 49.8% of meloxicam users. History of dyspepsia was reported in 20.3% ibuprofen, 21.9% diclofenac and 38.4% meloxicam users. This shows that GPs are selecting NSAIDs on the basis of perceived NSAID safety and patients' baseline risk for adverse GI outcomes. This means that epidemiological studies of adverse GI outcomes in individual NSAIDs are only of use when data are controlled for dose and baseline risk.

Henry and colleagues carried out a random-effects MA of 12 observational studies looking at risk of GI complications and looking at variability between different NSAIDs (review period: 1985–94).[182] The outcome of interest was serious peptic ulcer complications necessitating admission to hospital. Ibuprofen had the lowest risk in 10/11 studies and diclofenac was second or third lowest risk (*Table 36*) In the meta-analysis, the authors merged different doses. However, they reported that odds ratios increased with dose. They suggest

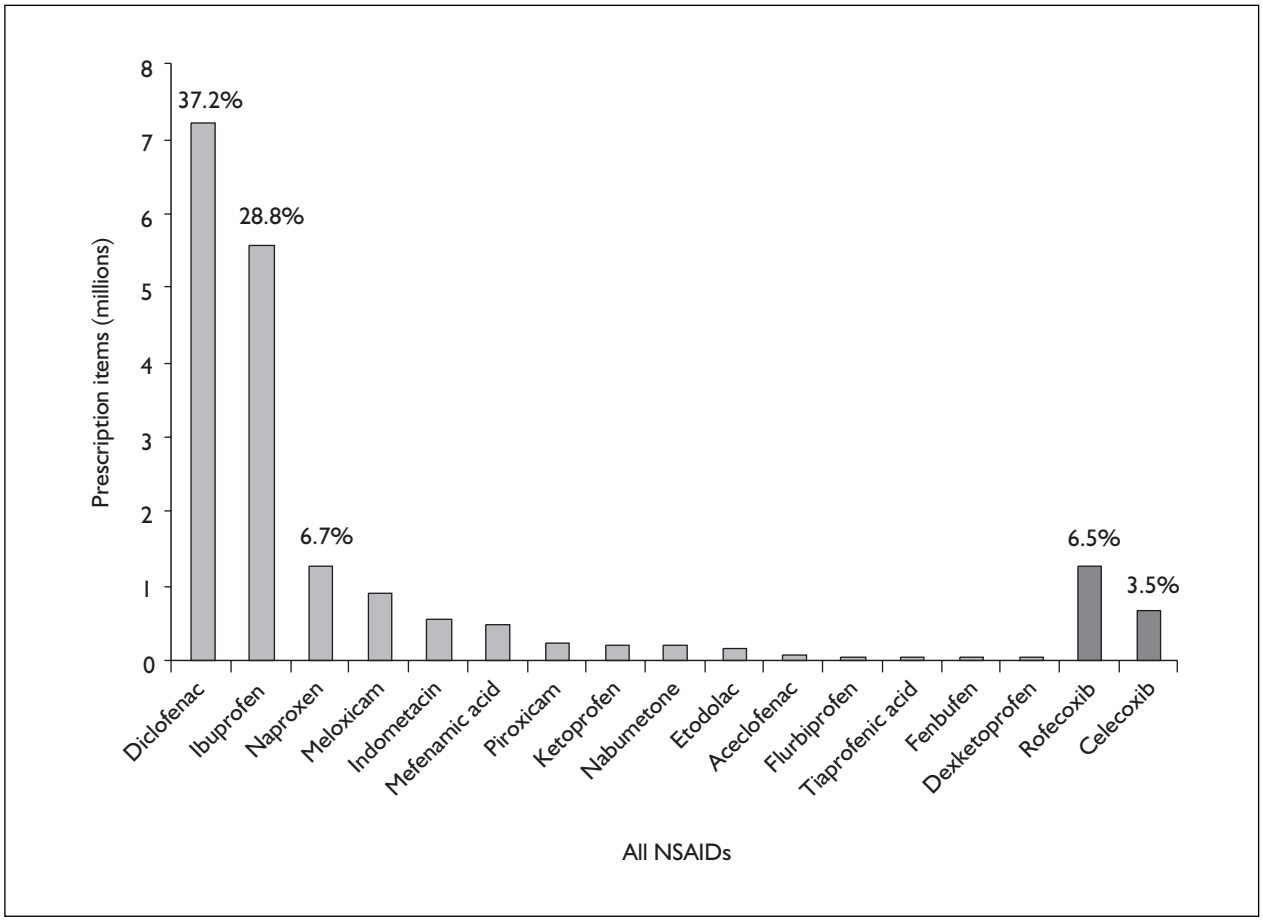

FIGURE 94 *NSAID prescription items dispensed in England for 2000 (Department of Health, national statistics)*

TABLE 36 *Results of meta-analysis*[183]

Comparator	No. of studies	Pooled RR (95% CI)
Ibuprofen	–	1.0
Fenoprofen	2	1.6 (1.0 to 2.5)
Aspirin	6	1.6 (1.3 to 2.0)
Diclofenac	8	1.8 (1.4 to 2.3)
Sulindac	5	2.1 (1.6 to 2.7)
Diflunisal	2	2.2 (1.2 to 4.1)
Naproxen	10	2.2 (1.7 to 2.9)
Indomethacin	11	2.4 (1.9 to 3.1)
Tolmetin	2	3.0 (1.8 to 4.9)
Piroxicam	10	3.8 (2.7 to 5.2)
Ketoprofen	7	4.2 (2.7 to 6.4)
Azapropazone	2	9.2 (4.0 to 21.0)

that ibuprofen only appears safer because it is used in lower doses in the community.

A UK cohort study reported that the odds ratio for a complicated event for diclofenac was 1.35 (95% CI 0.59 to 3.10), compared with 1.00 for ibuprofen.[184] This was not corrected for dose or baseline GI risk. When odds ratios are corrected for previous NSAID use, age and sex, the odds ratios compared with non-use for diclofenac and ibuprofen are 2.7 (95% CI 1.5 to 4.8) and 2.1 (95% CI 0.6 to 7.1), suggesting that there is no difference in the safety of these two NSAIDs.[185]

Epidemiological research suggests that risk of adverse GI outcomes in individual NSAIDs is increased as the dose increases.[183,186] In this economic analysis, it was assumed that a medium dose of each agent was used, in line with the defined daily dose (DDD) for that drug.[187] These are provided in detail in Appendix 2.

The base-case Cox-2 preferential comparator selected for this economic analysis was meloxicam and the base case Cox-2 coxib was rofecoxib, as these two agents are most commonly prescribed in the UK. The PPI used was omeprazole and the H_2RA was ranitidine. Misoprostol was assumed to be prescribed as a separate preparation to the NSAID. DDDs were used for all agents apart from rofecoxib, where the DDD is currently 12.5 mg, which is a lower dose than would be used in moderate RA.

Outcome measures

In concordance with current evidence, equivalent doses of Cox-1 NSAIDs, Cox-2 coxibs and Cox-2 preferentials are assumed to have equal analgesic and anti-inflammatory efficacy in a group of patients, although it is recognised that there is interpatient variability in efficacy. It has been suggested that there may be differences in GI, cardiac and renal outcomes between Cox-1 NSAIDs and Cox-2 coxibs inhibitors. Previous models have used a range of GI outcomes only, variably defined.

The systematic review found no data relating to renal outcomes. Differences in cardiac outcomes were found between Cox-1 NSAIDs and Cox-2 Coxibs in the VIGOR study,[87] but subsequent analyses have suggested that this may have been due to a cardioprotective effect specific to naproxen.[188,189] No other data relating to cardiac outcomes were available from the MA. The main economic analysis therefore concentrated on GI outcomes owing to the lack of other data to populate a decision-analytic model.

Individual clinical trials have used a range of definitions for minor and major GI side-effects, rendering MA somewhat complex. Previous modelling analyses and MAs have handled this issue by combining side-effects into larger categories, For example, the clinical outcomes used in the ACCES model were serious GI complications, symptomatic ulcers, anaemia with occult bleeding, intolerable diarrhoea and GI discomfort. Also, clinically useful outcomes such as symptomatic ulcers and death rates from serious GI events were reported rarely and unreliably. This required the model to use the following strategies to derive values for these outcomes:

- **symptomatic ulcers**: use the outcome 'endoscopic ulcers' and assume that a proportion of those ulcers become symptomatic;

- **death rates from serious GI events**: extract data on death rates from other longitudinal epidemiological sources.

Sequence of events

There are two principal approaches to handling the sequence of events. GI events can be assumed to occur as independent events as in the ACCES model[181] or they can be assumed to occur in succession.[160,181] These two approaches require the probabilities and costs to be handled in the following way:

1. **Events occur as independent events (ACCES)[181]**

Minor GI event	→	*p*[minor], cost[minor]
Major GI event	→	*p*[major], cost[major]
Death	→	*p*[death], cost[death]

2. **Events occur as conditional events[160,181]**

Minor GI event →	Major GI event →	death
p(minor)	*p*[major, given *p*(minor)]	*p*{death, given *p*[major, given *p*(minor)]}
cost(minor)	cost[major, given cost (minor)]	cost{death, given cost[major, given cost (minor)]}

The first approach assumes that minor and major adverse events occur independently from one another. The second approach assumes that major events tend to occur after a minor event, which can feel more close to reality. The first approach uses data in the same way that they are reported in RCTs. There are few data available to populate a model using the second approach, so it will have more assumptions and more extensive synthesis of data for multiple sources and will result in a weaker model.

Evidence suggests that there is little correlation between abdominal symptoms and the presence of NSAIDs-induced gastric lesions.[190,191] Ming and colleagues demonstrated that the clinical course of major events such as duodenal ulcer haemorrhage is not significantly different in patients with and without minor events such as dyspepsia.[192]

Switching between NSAIDs

Patients on NSAIDs may switch from one agent to another until they find one that works for them. To incorporate this into this model would have increased the complexity unnecessarily and require the synthesis of data from disparate sources. In this study, it is assumed that switching rates would be the same in all arms where diclofenac was used. It is also assumed that patients on Cox-2 coxibs and Cox-2 preferentials would have the same switching rate. Therefore, switching was assumed to occur at the same rate in all arms and so was excluded from the model.

Naproxen

Evidence suggests that naproxen is the Cox-1 NSAID most similar to the traditional NSAID aspirin in terms of action on platelets. The lower rate of MIs in the naproxen group in the VIGOR study was consistent with an aspirin-like effect.[87] Not all Cox-1 NSAIDs appear to inhibit platelet aggregation. Naproxen and flurbiprofen do, but diclofenac and ibuprofen do not.[193,194] Ibuprofen may interfere with the action of aspirin by displacing it from platelets. Cox-2 coxibs appear to have no effect on platelet function.[87] Rofecoxib had no effect on platelet function (measured by bleeding time and platelet aggregation) and the drug was not expected to interfere with the cardiovascular benefits of low-dose aspirin. More primary research is required to determine the impact of Cox-1 NSAIDs and Cox-2 inhibitors on aspirin function and cardiac outcomes such as MI.

Use of branded versus generic combinations

In the UK, generic preparations are prescribed preferentially whenever possible. This economic analysis used generic preparations wherever possible.

Arthrotec versus individual components given separately

Arthrotec is a diclofenac–misoprostol combination product. This economic analysis used generic preparations of the individual products, assuming equal efficacy and compliance. The acquisition costs per month are £13.50 for Arthrotec 50 and £12.97 for diclofenac 50 mg twice daily and misoprostol 200 μg twice daily.[195]

Compliance

Compliance was assumed to be the same between all the arms as there is no evidence to suggest that this is not the case. The intolerance experienced to misoprostol leads to a significant number of patients withdrawing from this treatment. This was dealt with explicitly in the decision-analytic model structure.

Length of follow-up

Our study examined the clinical and economic impact of treatment for 6 months. Assessment over a period of 1 year would have provided decision-

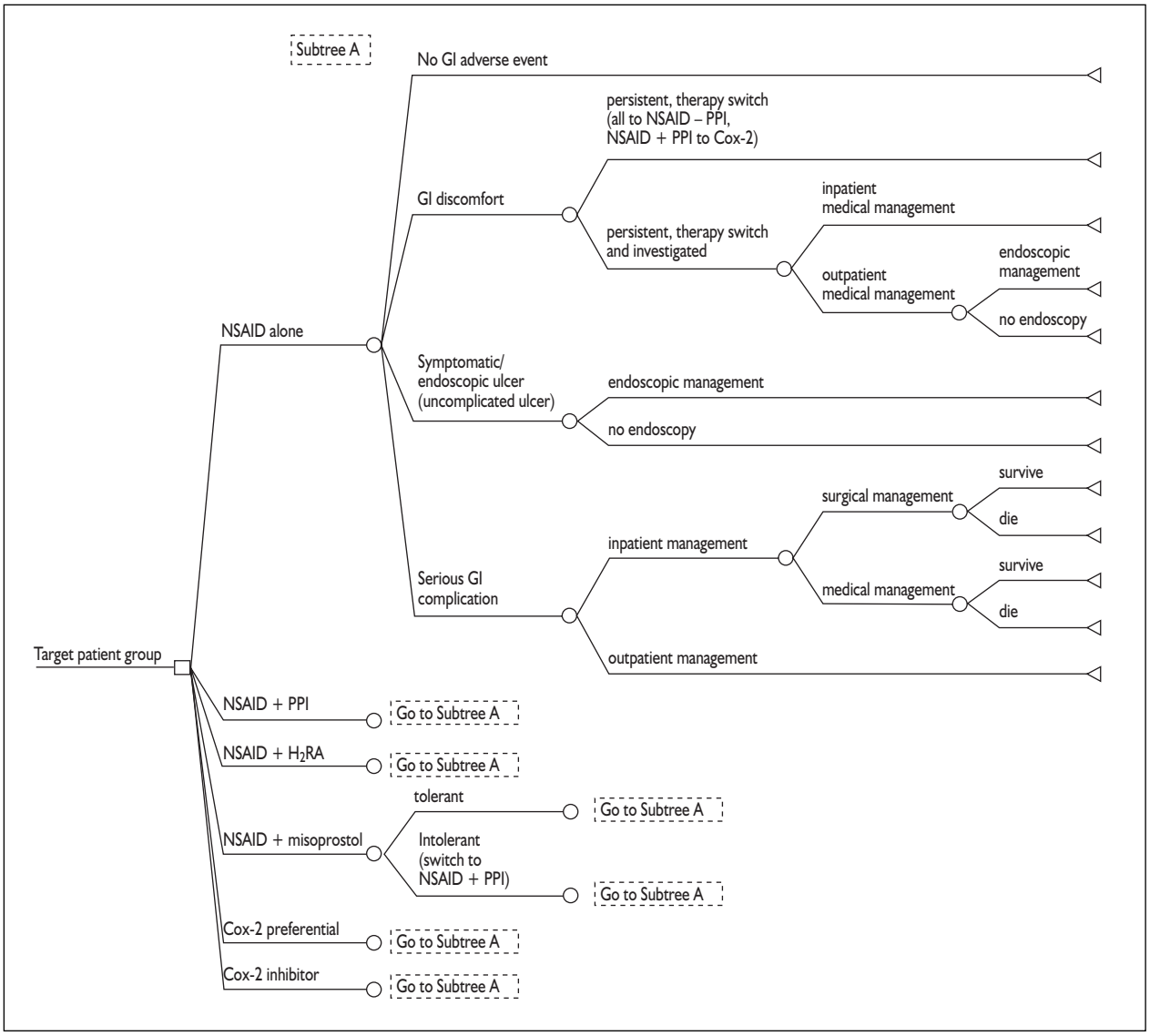

FIGURE 95 *Decision-analytic model for economic analysis of Cox-1 NSAIDs versus Cox-1 NSAIDs plus GPAs versus Cox-2 coxib or Cox-2 preferential drugs*

makers with information regarding the annual clinical and economic impact of treatment, which is more relevant in policy decision-making. However, the clinical data available from the systematic review meant that probability data for 1 year were not available, as most studies were much shorter than this. Therefore, the assumption was made that adverse event rates, associated costs and compliance remain constant over the 6-month period. No distributions were assigned to these probabilities in the simulation.

Decision-analytic model for economic analysis

Figure 95 represents the decision-analytic model used in this economic analysis. The data requirements for population of this model can be divided into probabilistic (see the next section) and resource use (see section 'Resource use data requirements for economic analysis', p. 144) data.

Probabilistic data requirements for economic analysis

Probabilistic data for Arm 1 (Cox-1 NSAID only) were required from the systematic review as RRs, with 95% CI. Data for Arms 2–6 (NSAID plus PPI; NSAID plus H_2RA; NSAID plus misoprostol; Cox-2 inhibitor; Cox-2 preferential) were required as RR ratios, with 95% CI, compared with Arm 1. Where this was not possible, observational cohort data were obtained. The four principal GI outcomes were no GI adverse event, GI

TABLE 37 *Probabilities taken from meta-analysis*

Data parameter	Mean	Source
NSAID arm		
p(No GI adverse event)[a]	0.678	From control group in MA
p(GI discomfort)[b]	0.284	From control group in MA
p(Symptomatic/endoscopic ulcer)[b,c]	0.032	From control group in MA
p(Serious GI complication)[b]	0.006	From control group in MA
NSAID plus H_2RA		
p(No GI adverse event)[a]	0.775	
p(GI discomfort)[d]	0.205	From MA
p(Symptomatic/endoscopic ulcer)[c,d]	0.018	From MA
p(serious GI complication)[d]	0.002	From MA
NSAID plus PPI		
p(No GI adverse event)[a]	0.863	
p(GI discomfort)[d]	0.122	From MA
p(Symptomatic/endoscopic ulcer)[c,d]	0.012	From MA
p(Serious GI complication)[d]	0.003	From MA
NSAID plus misoprostol		
p(No GI adverse event)[a]	0.710	
p(GI discomfort)[d]	0.276	From MA
p(symptomatic/endoscopic ulcer)[c,d]	0.011	From MA
p(Serious GI complication)[d]	0.003	From MA
Cox-2 inhibitor		
p(No GI adverse event)[a]	0.759	
p(GI discomfort)[d]	0.230	From MA
p(Symptomatic/endoscopic ulcer)[c,d]	0.008	From MA
p(Serious GI complication)[d]	0.003	From MA
Cox-2 preferential		
p(No GI adverse event)[a]	0.777	
p(GI discomfort)[d]	0.207	From MA
p(Symptomatic/endoscopic ulcer)[c,d]	0.013	From MA
p(Serious GI complication)[d]	0.003	From MA

[a] The probability of no GI adverse event = 1 – (*p*[GI discomfort] + *p*[symptomatic/endoscopic ulcer] + p[serious GI complication]).

[b] The estimates for the baseline risk of each event were calculated from the MA assuming that the control arm represented using an NSAID alone. Probability = [(number of events in control group$_{\text{NSAID plus H}_2\text{RA studies}}$) + (number of events in control group$_{\text{NSAID plus PPI studies}}$) + (number of events in control group$_{\text{NSAID plus misoprostol studies}}$) + (number of events in control group$_{\text{Cox-2 studies}}$) + (sample size in control group$_{\text{Cox-2preferential studies}}$)]/[(sample size in control group$_{\text{NSAID plus H}_2\text{RA studies}}$) + (sample size in control group$_{\text{NSAID plus PPI studies}}$) + (sample size in control group$_{\text{NSAID plus misoprostol studies}}$) + (sample size in control group$_{\text{Cox-2 studies}}$) + (sample size in control group$_{\text{Cox-2 preferential studies}}$)]

[c] The probability of symptomatic/endoscopic ulcer = *p*[endoscopic ulcer] × 0.15.

[d] The probability of each event = baseline risk of each event from NSAID arm × RR ratio from MA.

discomfort, uncomplicated ulcer (symptomatic or endoscopic) and serious GI complication. The data for these outcomes for each arm were obtained from the MA. *Table 37* summarises the probability data taken from the MA.

Probabilities of events occurring as a result of these principal GI outcomes were required, but were not available from the MA. These data had to be obtained from different sources. The data for this model were taken from the MUCOSA study as this provides the largest sample size of patients, the most naturalistic design and the most comprehensive follow-up of treatment pathways.[11] Observational data on death rates were obtained from Blower and colleagues, which provided the most relevant, detailed and up-to-date information on death rates associated with hospitalisation for a gastric bleed in the UK.[2] *Table 38* summarises the probability data taken from other sources.

TABLE 38 *Probabilities taken from alternative sources*

Data parameter	Mean	Source
NSAID arm		
p(Investigation after GI discomfort)	0.0223	Maetzel, 1998[11]
p(Inpatient management of GI discomfort)	0.24	Maetzel, 1998[11]
p(Outpatient management of GI discomfort)	0.76	Maetzel, 1998[11]
p(Outpatient endoscopy of GI discomfort)	0.35	Maetzel, 1998[11]
p(Outpatient no endoscopy of GI discomfort)	0.65	Maetzel, 1998[11]
p(Endoscopy, given ulcer)	0.27	Maetzel, 1998[11]
p(Inpatient management of complication)	0.67	Maetzel, 1998[11]
p(Outpatient management of complication)	0.33	Maetzel, 1998[11]
p(Inpatient surgical intervention)	0.39	Maetzel, 1998[11]
p(Inpatient medical intervention)	0.61	Maetzel, 1998[11]
p(Death after surgical intervention)	0.173	Blower, 1997[2]
p(Death after medical intervention)	0.173	Blower, 1997[2]
NSAID plus GPA, Cox-2 or Cox-2 preferential		
p(Investigation after GI discomfort)	0.0176	Maetzel 1998,[11]
p(Inpatient management of GI discomfort)	0.39	Maetzel, 1998[11]
p(Outpatient management of GI discomfort)	0.61	Maetzel, 1998[11]
p(Outpatient endoscopy of GI discomfort)	0.15	Maetzel, 1998[11]
p(Outpatient no endoscopy of GI discomfort)	0.85	Maetzel ,1998[11]
p(Endoscopy, given ulcer)	0.27	Maetzel, 1998[11]
p[(Inpatient management of complication)	0.56	Maetzel, 1998[11]
p(Outpatient management of complication)	0.44	Maetzel, 1998[11]
p(Surgical intervention)	0.29	Maetzel, 1998[11]
p(Medical intervention)	0.71	Maetzel, 1998[11]
p(Death after surgical intervention)	0.173	Blower, 1997[2]
p(Death after medical intervention)	0.173	Blower, 1997[2]

From the four principal outcomes, the decision-analytic model developed has 12 possible pathways for each arm. It was necessary to attach probabilities to each of the treatment pathways, as detailed below.

Probability of no GI adverse event

No further probabilities were required for this outcome.

Probability and management of GI discomfort

It was assumed that GI discomfort rates reported in the RCTs in the MA related to persistent, rather than transient, GI discomfort and required the patient to return to their GP. Evidence suggests that most patients who experience GI discomfort do so within the first 2 weeks of initiating therapy.[166] It is assumed that patients who experience GI discomfort after 1 month will not remain on the same therapy, but will be converted to the most effective alternative, an NSAID plus a PPI. It is assumed that the following will occur:

1. Cox-1 NSAID alone: add in PPI
2. NSAID plus PPI: change to Cox-2
3. NSAID plus H_2RA: change to PPI
4. NSAID plus misoprostol: change to PPI
5. Cox-2 coxib: change to NSAID plus PPI
6. Cox-2 preferential: change to NSAID plus PPI.

A small proportion of these patients will also be investigated for PUB. In the MUCOSA study, 2.23% patients on an NSAID alone were investigated for a PUB in the absence of clinical evidence, 24% of whom were managed as inpatients and 76% as outpatients (35% received an endoscopy);[11] 1.76% patients on an NSAID with misoprostol were investigated for a PUB in the absence of clinical evidence, 39% of whom were managed as inpatients and 61% as outpatients (15% received an endoscopy). In the absence of other data, it was assumed for this model, that the investigation rates were the same for other NSAID–GPA combinations, the Cox-2 coxib and the Cox-2 preferential pathway.

Probability and management of an uncomplicated, confirmed ulcer

Owing to poor reporting of symptomatic ulcers in the trials, this parameter could not be used in the economic analysis. Endoscopic ulcers are reported more accurately and more frequently, but do not

TABLE 39 *Life-years lost by premature death from gastric bleed leading to hospitalisation*

GI bleed death rates[2]			Midpoint age taken from band (years)	Life expectancy from GAD tables (UK), 1999–2001		
Age band (years)	No. of patients	Death rate (%)		Life expectancy (years)		
				Women	Men	Average
<45	14	0	30	50.95	46.61	48.78
46–64	47	8.5	55	27.31	23.57	25.44
65–74	42	19.9	70	14.97	12.25	13.61
75+	82	24.4	80	8.57	6.96	7.765
Total	185	17.3	67.59	17.24	14.24	15.74

reflect the number of ulcers that become clinically significant. The relationship between endoscopic and symptomatic ulcers is not completely characterised. The MUCOSA study estimated that 85% of endoscopic ulcers remained silent.[11] Therefore, *p*[symptomatic ulcer, given endoscopic ulcer] in this analysis is assumed to be 15% of *p*[endoscopic ulcer]. The probability of endoscopic management of these ulcers is taken from Maetzel and colleagues ($p = 0.27$).[11]

Probability and management of a serious complication

Once a patient has been diagnosed as suffering a serious complication associated with NSAID use (perforated ulcer, bleed, etc.), they may be managed in a range of ways, depending on the severity of the complication. The division of patient management pathways is

- outpatient with endoscopy
- inpatient surgical
- inpatient medical management.

The probability of patients following any of these treatment pathways was not available in most of the trials and so was obtained from the MUCOSA study.[11]

Probability of death from PUB

These data could not be obtained from RCTs. Observational studies of deaths after surgical and non-surgical intervention for serious GI complications were used. There are many of these studies available in the literature. The most relevant, detailed and up-to-date information on death rates associated with hospitalisation for a gastric bleed is from Blower and colleagues, providing a UK estimate of emergency UGI admissions per annum due to NSAID use.[2] This was a retrospective case note survey in two English district general hospitals with a catchment population of 550,000 (Stockport and Rotherham), with age and socio-economic profiles very similar to the general UK population. A total of 620 admissions and 460 matched controls were used and the death rates reported in *Table 39* were derived. Surgical and non-surgical death rates were not differentiated, so it is assumed that the death rates are the same, although it is likely that surgical death rates are higher.

A midpoint was taken from each age band from the Blower study and the life expectancy for that age band was derived from figures from the Government Actuary's Department (GAD), Office for National Statistics, UK 1999–2001. This allowed calculation of mean life expectancy for the total patient cohort in the Blower study. Life-years lost would equate to the life expectancy average of 15.74 years. The assumption was made that the patients in the RCTs had a similar age distribution to those in the Blower study, with a mean age of 67.59 years (see *Table 39*).

Resource use data requirements for economic analysis

The perspective of the analysis was from the NHS, both primary and secondary care. The resource use data were obtained preferentially from up-to-date UK sources of observation of normal clinical practice, where units of resource use have been reported in a disaggregated manner, to allow attachment of current unit prices for drugs, patient stays, endoscopies and so on. Deterministic ranges had to be used for most parameters. These have been explicitly justified and their importance is tested in SA.

As no detailed resource use data were collected in clinical trials in the MA, published estimates of resource use were used. The most up-to-date, UK-

TABLE 40 *Sources of unit costs*

Cost parameter	Data source
Oral drug costs	Drug Tariff, July 2003[195]
Intravenous omeprazole	BNF, March 2003[23]
Helicobacter pylori test	BNF, March 2003[23]
GP consultation costs	Netten and Dennett, 2002[196]
Gastroenterological inpatient or outpatient visit, endoscopy, surgery, ICU	Department of Health reference costs 2002 (ranges for 50% NHS trusts)[197]
Labs and tests	Moore, 2001[167]
Blood products	National Blood Service (personal communication, 2002)

ICU, intensive care unit.

relevant, patient-based and disaggregated resource use data available were obtained from Dr RA Moore (University of Oxford; personal communication, 2002). In a previous UK study, Moore and colleagues used published US estimates of resource use associated with gastropathy[154] and reviewed these resource use data with UK clinicians and health economists to increase their likeness to UK practice. These resource data are used in this economic evaluation, with updated unit costs and are detailed in *Table 40*.

There are 12 possible pathways for each treatment arm. The resource use and unit costs are described below.

Cost (no adverse event)

The baseline cost of treating a patient for 6 months included only the acquisition cost of drugs for 6 months. All other resource use was assumed to be equal between arms. Mid-range doses were used for all drug regimens[23] and it was assumed that, where possible, generic preparations were used. The following drugs were used:

1. Cox-1 NSAID: diclofenac 50 mg twice daily
2. NSAID plus PPI: diclofenac 50 mg twice daily plus omeprazole 20 mg once daily
3. NSAID plus H_2RA: Diclofenac 50 mg twice daily plus ranitidine 150 mg twice daily
4. NSAID plus misoprostol: diclofenac 50 mg twice daily plus misoprostol 200 µg twice daily
5. Cox-2 coxib: rofecoxib 25 mg once daily
6. Cox-2 preferential: meloxicam 7.5 mg twice daily.

Table 41 summarises the cost per patient for this pathway.

Cost (GI discomfort, no investigation)

These patients are assumed to receive 1 month of original drug therapy, return to the GP for one extra visit and then be switched to an alternative therapy, with no further investigation. Therapy switch is assumed to occur as follows:

1. Cox-1 NSAID alone: add in PPI
2. NSAID plus PPI: change to Cox-2
3. NSAID plus H_2RA: change to PPI

TABLE 41 *Cost per patient for pathway: no GI adverse event*

	NSAID	NSAID + misoprostol	NSAID + PPI	NSAID + H_2RA	Cox-2	Cox-2 preferential
Dose used	Diclofenac 50 mg b.d.	Diclofenac 50 mg b.d. + misoprostol 200 µg b.d.	Diclofenac 50 mg b.d. + omeprazole 20 mg o.n.	Diclofenac 50 mg b.d. + ranitidine 150 mg b.d.	Rofecoxib 25 mg o.d.	Meloxicam 7.5 mg b.d.
Cost (no GI adverse event) (£)	16.82	77.83	168.03	66.46	140.66	121.67

b.d., twice daily; o.d., once daily; o.n., once a night.

TABLE 42 *Cost per patient for pathway: GI discomfort, no investigation*

	NSAID	NSAID + PPI	NSAID + H_2 RA	NSAID + misoprostol	Cox-2 coxib	Cox-2 preferential
Cost of original drugs (£)	2.80	28.01	11.08	12.97	23.44	21.85
One GP visit (£)	20	20	20	20	20	20
Remaining treatment period	Join NSAID + PPI arm for 5 months	Join Cox-2 arm for 5 months	Join NSAID + PPI arm for 5 months	Join NSAID + PPI arm for 5 months	Join NSAID + PPI arm for 5 months	Join NSAID + PPI arm for 5 months
Mean total cost (GI discomfort, no investigation) (£)	22.80 + expected cost for NSAID+ PPI arm	48.01 + expected cost for Cox-2 arm	31.08 + expected cost for NSAID + PPI arm	32.97 + expected cost for NSAID + PPI arm	43.44 + expected cost or NSAID + PPI arm	41.85 + expected cost for NSAID + PPI arm

4. NSAID plus misoprostol: change to PPI
5. Cox-2 coxib: change to NSAID plus PPI
6. Cox-2 preferential: change to NSAID plus PPI.

Table 42 summarises the cost per patient for this pathway.

Cost (inpatient management of GI discomfort)

These patients are assumed to receive 1 month of original drug therapy, return to the GP for one extra visit and then be switched to an alternative therapy, after inpatient investigation (*Table 43*) that does not reveal an ulcer. Therapy switch is assumed to occur as above. *Table 44* summarises the cost per patient for this pathway.

Cost (outpatient endoscopy of GI discomfort)

These patients are assumed to receive 1 month of original drug therapy, return to the GP for one extra visit and then be switched to an alternative therapy, after outpatient investigation with endoscopy (*Table 45*) that does not reveal an ulcer. Therapy switch is assumed to occur as above.

Table 46 summarises the cost per patient for this pathway.

Cost [outpatient management (no endoscopy) of GI discomfort]

These patients are assumed to receive 1 month of original drug therapy, return to the GP for one extra visit and then be switched to an alternative therapy, after outpatient investigation without endoscopy (*Table 47*) that does not reveal an ulcer. Therapy switch is assumed to occur as above.

Table 48 summarises the cost per patient for this pathway.

Cost (symptomatic ulcer with endoscopy)

These patients are assumed to be diagnosed with a symptomatic uncomplicated ulcer, using endoscopy. This is assumed to occur at 3 months after beginning original drug therapy. These patients are switched to paracetamol and treated with omeprazole 40 mg once daily for 4 weeks after outpatient investigation with endoscopy (*Table 49*) that reveals an ulcer.

Table 50 summarises the cost per patient for this pathway.

Treatment of symptomatic ulcers

The most recent survey of treatment of symptomatic ulcers in the UK was carried out by Kubba and colleagues in 1996 in Scotland.[191] They surveyed 130 (81 respondents) GI physicians and surgeons to assess their treatment practice for NSAID-induced ulcers. However, the practice patterns do not appear to be particularly evidence-based. Also, they are out of date in terms of drugs used and the use of agents to treat bleeding ulcers. In a non-bleeding ulcer caused by NSAID, 45% would use H_2-antagonists, 37% omeprazole, 14% misoprostol and 4% *H. pylori* eradication and 91% would use life-long maintenance therapy. In a bleeding ulcer, 38% would use intravenous acid-reducing drugs, 88% endoscopy, 5% endoscopy to confirm healing, 67% H_2-antagonists, 15% omeprazole and 11% *H. pylori* eradication; 64% would use this therapy for 6–8 weeks, 24% up to 1 year and 12% would use life-long maintenance therapy. Recent recommendations suggest that patients will require an endoscope, 4 weeks of omeprazole treatment and a further endoscopy to confirm healing.[198,199]

TABLE 43 *Resource use associated with inpatient investigation for a suspected PUB*

Resource use	Units	Mean cost (£)	Minimum (£)	Maximum (£)
PPI treatment (days)	28	23	23	23
GP visit	2	40	40	40
Gastroenterology outpatient	1	72	50	84
Laboratory and tests	2	54	54	54
Diagnostic endoscopy	1	435	283	651
Helicobacter pylori test	1	21	21	21
Inpatient day	2	498	498	498
Total		1143	969	1371

TABLE 44 *Cost per patient for pathway: GI discomfort, inpatient management*

	NSAID	NSAID + PPI	NSAID + H_2RA	NSAID + misoprostol	Cox-2 coxib	Cox-2 preferential
Cost of original drugs (£)	2.80	28.01	11.08	12.97	23.44	21.85
One GP visit (£)	20	20	20	20	20	20
Inpatient investigation for a suspected PUB (£)	1143	1143	1143	1143	1143	1143
Remaining treatment period	Join NSAID + PPI arm for 5 months	Join Cox-2 arm for 5 months	Join NSAID + PPI arm for 5 months	Join NSAID + PPI arm for 5 months	Join NSAID + PPI arm for 5 months	Join NSAID + PPI arm for 5 months
Mean total cost (GI discomfort, inpatient management) (£)	1165.80 + expected cost for NSAID + PPI arm	1191.01 + expected cost for Cox-2 arm	1141.93 + expected cost for NSAID + PPI arm	1175.08 + expected cost for NSAID + PPI arm	1186.44 + expected cost for NSAID + PPI arm	1184.85 + expected cost for NSAID + PPI arm
Minimum total cost (GI discomfort, inpatient management) (£)	991.80 + minimum expected cost for NSAID + PPI arm	1017.01 + minimum expected cost for Cox-2 arm	1000.08 + minimum expected cost for NSAID + PPI arm	1001.97 + minimum expected cost for NSAID + PPI arm	1012.44 + minimum expected cost for NSAID + PPI arm	1010.85 + minimum expected cost for NSAID + PPI arm
Maximum total cost (GI discomfort, inpatient management) (£)	1393.80 + maximum expected cost for NSAID + PPI arm	1419.01 + maximum expected cost for Cox-2 arm	1402.08 + maximum expected cost for NSAID + PPI arm	£1403.97 + maximum expected cost for NSAID + PPI arm	£1414.44 + maximum expected cost for NSAID + PPI arm	£1412.85 + maximum expected cost for NSAID+ PPI arm

Cost (symptomatic ulcer without endoscopy)

These patients are assumed to be diagnosed with a symptomatic uncomplicated ulcer, without using endoscopy. This is assumed to occur at 3 months after beginning the original drug therapy. These patients are switched to paracetamol and treated with omeprazole for 4 weeks after outpatient investigation without endoscopy (*Table 51*) that reveals an ulcer.

Table 52 summarises the cost per patient for this pathway.

TABLE 45 *Resource use associated with outpatient investigation (with endoscopy) for a suspected PUB*

Resource use	Units	Mean cost (£)	Minimum (£)	Maximum (£)
GP visit	2	40	40	40
Gastroenterology outpatient	1	72	50	84
Laboratory and tests	1	27	27	27
Diagnostic endoscopy	1	435	282	651
Helicobacter pylori test	1	21	21	21
Omeprazole 20 mg o.d.	28	23	23	23
Total		618	443	846

Adapted from Moore and colleagues.[167]

TABLE 46 *Cost per patient for pathway: GI discomfort, outpatient management with endoscopy*

	NSAID	NSAID + PPI	NSAID + H_2RA	NSAID + misoprostol	Cox-2	Cox-2 preferential
Cost of original drugs (£)	2.80	28.01	11.08	12.97	23.44	21.85
One GP visit (£)	20	20	20	20	20	20
Outpatient investigation (with endoscopy) for suspected PUB (£)	618	618	618	618	618	618
Remaining treatment period	Join NSAID + PPI arm for 5 months	Join Cox-2 arm for 5 months	Join NSAID + PPI arm for 5 months	Join NSAID + PPI arm for 5 months	Join NSAID + PPI arm for 5 months	Join NSAID + PPI arm for 5 months
Mean total cost (GI discomfort, outpatient endoscopy) (£)	640.46 + expected cost for NSAID + PPI arm	665.66 + expected cost for Cox-2 arm	648.73 + expected cost for NSAID + PPI arm	650.63 + expected cost for NSAID + PPI arm	661.44 + expected cost for NSAID + PPI arm	659.85 + expected cost for NSAID + PPI arm
Minimum total cost (GI discomfort, outpatient endoscopy) (£)	465.25 + minimum expected cost for NSAID + PPI arm	490.45 + minimum expected cost for Cox-2 arm	473.52 + minimum expected cost for NSAID + PPI arm	484.29 + minimum expected cost for NSAID + PPI arm	485.44 + minimum expected cost for NSAID + PPI arm	483.85 + minimum expected cost for NSAID + PPI arm
Maximum total cost (GI discomfort, outpatient endoscopy) (£)	869.18 + maximum expected cost for NSAID + PPI arm	894.38 + maximum expected cost for Cox-2 arm	877.43 + maximum expected cost for NSAID + PPI arm	879.45 + maximum expected cost for NSAID + PPI arm	889.44 + maximum expected cost for NSAID + PPI arm	887.85 + maximum expected cost for NSAID + PPI arm

Cost (inpatient surgical intervention for serious GI complication)

These patients are assumed to be diagnosed with a symptomatic serious GI complication, necessitating admission to hospital for surgical management. This is assumed to occur at 3 months after beginning original drug therapy. These patients are switched to paracetamol and treated with omeprazole daily for 6 weeks after inpatient surgical management.

How are patients who have a bleed treated?

Bleeding stops spontaneously in most patients, but aggressive management is required when bleeding

TABLE 47 *Resource use associated with outpatient investigation (without endoscopy) for a suspected PUB*

Resource use	Units	Mean cost (£)	Minimum (£)	Maximum (£)
Omeprazole treatment (days)	28	23	23	23
GP visit	2	40	40	40
Gastroenterology outpatient	2	144	100	168
Laboratory and tests	1	27	27	27
Helicobacter pylori test	1	21	21	21
Total		255	211	279

Adapted from Moore and colleagues.[167]

TABLE 48 *Cost per patient for pathway: GI discomfort, outpatient management without endoscopy*

	NSAID	NSAID + PPI	NSAID + H_2RA	NSAID + misoprostol	Cox-2	Cox-2 preferential
Cost of original drugs (£)	2.80	28.01	11.08	12.97	23.44	21.85
One GP visit (£)	20	20	20	20	20	20
Outpatient investigation (without endoscopy) for suspected PUB (£)	255	255	255	255	255	255
Remaining treatment period	Join NSAID + PPI arm for 5 months	Join Cox-2 arm for 5 months	Join NSAID + PPI arm for 5 months	Join NSAID + PPI arm for 5 months	Join NSAID + PPI arm for 5 months	Join NSAID + PPI arm for 5 months
Mean total cost (GI discomfort, outpatient no endoscopy) (£)	278.06 + expected cost for NSAID + PPI arm	303.26 + expected cost for Cox-2 arm	286.33 + expected cost for NSAID + PPI arm	288.22 + expected cost for NSAID + PPI arm	298.44 + expected cost for NSAID + PPI arm	296.85 + expected cost for NSAID + PPI arm
Minimum total cost (GI discomfort, outpatient, no endoscopy) (£)	233.75 + minimum expected cost for NSAID + PPI arm	258.96 + minimum expected cost for Cox-2 arm	242.03 + minimum expected cost for NSAID + PPI arm	243.92 + minimum expected cost for NSAID + PPI arm	254.44 + minimum expected cost for NSAID + PPI arm	251.85 + minimum expected cost for NSAID+ PPI arm
Maximum total cost (GI discomfort, outpatient no endoscopy) (£)	301.75 + maximum expected cost for NSAID + PPI arm	326.96 + maximum expected cost for Cox-2 arm	310.03 + maximum expected cost for NSAID + PPI arm	311.92 + maximum expected cost for NSAID + PPI arm	322.44 + maximum expected cost for NSAID + PPI arm	321.85 + maximum expected cost for NSAID + PPI arm

does not resolve quickly or when patients are at high risk of rebleeding. Management priorities include the maintenance of haemodynamic function by restoration of circulating blood volume and the prevention of complications such as pulmonary aspiration by protection of the airway. The development of endoscopic techniques has reduced markedly the need for surgery in patients with bleeding peptic ulcers. Once the initial bleeding episode has been controlled with haemostasis, the primary focus becomes the prevention of rebleeding, experienced by 20–33% of patients.[200,201] The failure of endoscopic therapy coupled with continued rebleeding

TABLE 49 *Resource use associated with symptomatic ulcer with endoscopy*

Resource use	Units	Mean cost (£)	Minimum (£)	Maximum (£)
Omeprazole treatment (days)	42	35	35	35
GP visit	2	40	40	40
Gastroenterology outpatient	2	144	100	168
Laboratory and tests	1	27	27	27
Therapeutic endoscopy	1	1159	682	1533
Diagnostic endoscopy	1	435	283	651
Helicobacter pylori test	1	21	21	21
Total		1861	1188	2474

Adapted from Moore and colleagues.[167]

TABLE 50 *Cost per patient for pathway: symptomatic ulcer with endoscopy*

	NSAID	NSAID + PPI	NSAID + H_2RA	NSAID + misoprostol	Cox-2	Cox-2 preferential
Cost of original drugs (£)	8.41	84.02	33.23	38.92	70.32	65.55
Symptomatic ulcer with endoscopy (£)	1861	1861	1861	1861	1861	1861
Paracetamol (£)	8	8	8	8	8	8
Mean total cost (symptomatic ulcer with endoscopy) (£)	1877.41	1953.02	1902.23	1907.92	1939.32	1934.55
Minimum total cost (£)	1204.41	1280.02	1229.23	1234.92	1266.32	1261.55
Maximum total cost (£)	2490.41	2566.02	2515.23	2520.92	2552.32	2547.55

indicates the need for surgery or interventional radiology.

Endoscopy is indicated if the ulcer is actively bleeding, a non-bleeding visible vessel or an adherent clot at the base of the ulcer. The main endoscopic techniques for managing bleeding are injection therapy (epinephrine), usually followed by thermocoagulation. Endoscopic therapy is effective in achieving haemostasis in more than 90% of cases.[202]

Evidence is equivocal regarding the efficacy of H_2RAs in the prevention of rebleeding. An MA seemed to suggest that, in a bleeding gastric ulcer, H_2RAs produce a decrease in the rate of continued bleeding, need for surgery and mortality rate.[202,203] However, a large multicentre RCT using famotidine reported no benefits when compared with placebo in terms of rates of rebleeding, need for surgery and mortality.[204] Evidence also appears to be equivocal regarding the efficacy of PPIs. Lau and colleagues reported that the use of omeprazole 80 mg intravenous bolus, followed by 8 mg/h for 72 hours and then 20 mg/day orally for 8 weeks reduced recurrent bleeding but did not affect the need for surgical intervention or decrease mortality.[205] Current British Society of Gastroenterology guidelines recommend that patients are administered intravenous omeprazole, in line with this study, and are given oral PPIs for 6 weeks, followed by a repeat endoscopy.[198]

Rebleeding rates vary in the literature. Rebleeding rates in this study are taken from Gralnek and colleagues at 33%.[201] Management of rebleeding

TABLE 51 *Resource use associated with symptomatic ulcer without endoscopy*

Resource use	Units	Mean cost (£)	Minimum (£)	Maximum (£)
Omeprazole treatment (days)	28	23	23	23
GP visit	2	40	40	40
Gastroenterology outpatient	2	144	100	168
Laboratory and tests	1	27	27	27
Helicobacter pylori test	1	21	21	21
Total		255	211	279

Adapted from Moore and colleagues.[167]

TABLE 52 *Cost per patient for pathway: symptomatic ulcer without endoscopy*

	NSAID	NSAID + PPI	NSAID + H_2RA	NSAID + misoprostol	Cox-2 coxib	Cox-2 preferential
Cost of original drugs (£)	8.41	84.02	33.23	38.92	70.32	65.55
Symptomatic ulcer without endoscopy (£)	255	255	255	255	255	255
Paracetamol (£)	8	8	8	8	8	8
Mean total cost (symptomatic ulcer without endoscopy) (£)	271.76	347.37	296.58	302.27	333.32	328.55
Minimum total cost (£)	227.46	303.07	252.28	257.97	289.32	284.55
Maximum total cost (£)	295.46	371.07	320.28	325.97	357.32	352.55

was reported by Heyland and colleagues[206] and is assumed to consist of:

- haematology tests: 6.6
- blood products: 10.8 units
- anti-ulcer medication: 23.6 days
- days on ICU: 11.4 days
- increased endoscopy and surgery.[206]

It is assumed, conservatively, that patients who rebleed have a further therapeutic and further diagnostic endoscopy. Resource use associated with rebleeds is summarised in *Table 53*.

TABLE 53 *Resource use associated with rebleeding*

Resource use	Units	Mean cost (£)	Minimum (£)	Maximum (£)
Laboratory and tests	6.6	178	178	178
Intensive care unit	11.4	14,045	12,278	16,405
Therapeutic endoscopy	1	1,158.61	682.31	1,532.73
Diagnostic endoscopy	1	435.38	282.68	650.67
Blood products	10.8	1,198	1,198	1,198
Total		17,015	14,619	19,964

Adapted from Heyland and colleagues.[206]

TABLE 54 *Resource use associated with inpatient surgical intervention for serious GI complication*

Resource use	Units	Mean cost (£)	Minimum (£)	Maximum (£)
Intravenous omeprazole	1 course	78.15	78.15	78.15
Omeprazole 20 mg treatment (days)	42	35	35	35
Blood products	2	222	222	222
Gastroenterology outpatient	1	72	50	84
GP visit	2	40	40	40
Laboratory and tests	2	54	54	54
Therapeutic endoscopy	1	1,158.61	682.31	1,532.73
Surgical procedure	1	3,181.80	1,731.00	3,804.13
Diagnostic endoscopy	1	435.38	282.68	650.67
Helicobacter pylori test	1	21	21	21
Inpatient day	10	2,490	2,490	2,490
Intensive care unit	1	1,232	1,077	1,439
Rebleed costs (33% patients)	1	5,615	4,824	6,588
Total		14,634	11,587	17,038

Adapted from Moore and colleagues.[167]

TABLE 55 *Cost per patient for pathway: inpatient surgical intervention for serious GI complication*

	NSAID	NSAID + PPI	NSAID + H_2RA	NSAID + misoprostol	Cox-2 coxib	Cox-2 preferential
Cost of original drugs (£)	8.41	84.02	33.23	38.92	70.32	65.55
Inpatient surgical intervention (£)	14,634	14,634	14,634	14,634	14,634	14,634
Paracetamol (£)	8	8	8	8	8	8
Mean total cost [inpatient surgical intervention]	14,650.41	14,726.02	14,675.23	14,680.92	14,712.32	14,707.55
Minimum total cost (£)	11,603.41	11,679.02	11,628.23	11,633.92	11,665.32	11,660.55
Maximum total cost (£)	17,054.41	17,130.02	17,079.23	17,084.92	17,116.32	17,111.55

Table 54 summarises resource use associated with inpatient surgical interventions for serious GI complications.

Table 55 summarises the cost per patient for this pathway.

Cost (inpatient medical intervention for serious GI complication)

These patients are assumed to be diagnosed with a symptomatic serious GI complication, necessitating admission to hospital for medical management. This is assumed to occur at 3 months after beginning original drug therapy. These patients are switched to paracetamol and treated with omeprazole 20 mg once daily for 6 weeks after inpatient medical management (*Table 56*).

Table 57 summarises the cost per patient for this pathway.

Cost (outpatient management of complication)

These patients are assumed to be diagnosed with a symptomatic serious GI complication, that is, managed medically without admission to hospital. This is assumed to occur at 3 months after beginning original drug therapy. These patients are switched to paracetamol, and treated with omeprazole 20 mg once daily for 6 weeks after inpatient medical management (*Table 58*). It is assumed that no patients rebleed or die.

Table 59 summarises the cost per patient for this pathway.

TABLE 56 *Resource use associated with inpatient medical intervention for serious GI complication*

Resource use	Units	Mean cost (£)	Minimum (£)	Maximum (£)
Intravenous omeprazole	1 course	78.15	78.15	78.15
Omeprazole 20 mg treatment (days)	42	35	35	35
Blood products	2	222	222	222
GP visit	2	40	40	40
Gastroenterology outpatient	1	72	50	84
Laboratory and tests	2	54	54	54
Therapeutic endoscopy	1	1,158.61	682.31	1,532.73
Diagnostic endoscopy	1	435.38	282.68	650.67
Helicobacter pylori test	1	21	21	21
Inpatient day	5	1,245	1,245	1,245
Rebleed costs (33% patients)	1	5,537	4,746	6,150
Total		8,897	7,456	10,472

Adapted from Moore and colleagues.[167]

TABLE 57 *Cost per patient for pathway: inpatient medical intervention for serious GI complication*

	NSAID	NSAID + PPI	NSAID + H_2RA	NSAID + misoprostol	Cox-2 coxib	Cox-2 preferential
Cost of original drugs (£)	8.41	84.02	33.23	38.92	70.32	65.55
Inpatient medical intervention (£)	8,897	8,897	8,897	8,897	8,897	8,897
Paracetamol	8	8	8	8	8	8
Mean total cost (inpatient medical intervention) (£)	8,914	8,990	8,939	8,944	8,971	8,966
Minimum total cost (£)	7,472	7,548	7,497	7,503	7,523	7,525
Maximum total cost (£)	10,488	10,564	10,513	10,519	10,546	10,541

TABLE 58 *Resource use associated with outpatient medical intervention for serious GI complication*

Resource use	Units	Mean cost (£)	Minimum (£)	Maximum (£)
Omeprazole 20 mg treatment (days)	42	34.80	34.80	34.80
GP visit	2	40.00	40.00	40.00
Gastroenterology outpatient	2	144.30	100.00	168.00
Laboratory and tests	1	27.00	27.00	27.00
Therapeutic endoscopy	1	1,158.61	682.31	1,532.73
Diagnostic endoscopy	1	435.38	282.68	650.67
Helicobacter pylori test	1	20.75	20.75	20.75
Total		1,860.85	1,187.53	2,473.95

Adapted from Moore and colleagues.[167]

TABLE 59 *Cost per patient for pathway: outpatient medical intervention for serious GI complication*

	NSAID	NSAID + PPI	NSAID + H_2RA	NSAID + misoprostol	Cox-2 coxib	Cox-2 preferential
Cost of original drugs (£)	8.41	84.02	33.23	38.92	70.32	65.55
Outpatient medical intervention (£)	1861	1861	1861	1861	1861	1861
Paracetamol (£)	8	8	8	8	8	8
Mean total cost (outpatient medical intervention) (£)	1877	1953	1902	1908	1934	1930
Minimum total cost (£)	1204	1280	1229	1235	1261	1256
Maximum total cost (£)	2490	2566	2515	2521	2548	2543

Analytic methods used in economic analysis

Probabilistic sensitivity analysis was used to generate measures of variance around the expected cost. For this analysis, each variable was assigned a base case or average value and a distribution of possible values. The type of distribution was informed by the nature of each variable (probability, cost, RR). The probabilistic analysis summed the results of multiple analyses (iterations). Each iteration sampled the values for the variables at random from the specified distributions (*Table 60*).

The probability values for the baseline risk in the NSAID alone arm were specified with the beta (alpha, beta) distribution, where alpha is the number of events and beta is the sample size minus the number of events. The point estimates for the probability of adverse events in the five remaining arms (NSAID plus H_2RA, NSAID plus PPI, NSAID plus misoprostol, Cox-2, Cox-2 preferential) were obtained from the MA and were specified with a log-normal specified distribution using the 95% CIs around the mean absolute RR. In some instances, the 95% CI around the mean RR ratio were too wide to allow a log-normal distribution to be specified and the gamma distribution was used.

Costs were assigned the gamma distribution (alpha, beta), where alpha = (mean^2)/(standard error of the mean^2) and beta = (standard error of the mean^2)/(mean). The standard error of the mean was estimated from the minimum (5th percentile) and maximum (95th percentile) values around the mean cost assigned to each arm. The standard error of the mean = (95th percentile – 5th percentile)/(1.96 × 2).

The sampling method used was Latin hypercube, expected value. Latin hypercube is designed to recreate accurately the input distribution through fewer iterations compared wth the Monte Carlo method. It is a more efficient sampling method. It aids analysis of situations where low probability outcomes are represented in input probability distributions.

The simulation software used was @RISK, as an add-on to Microsoft Office Excel v. 7.0. Every simulation requires sufficient iterations to ensure that each variable is sampled over the full distribution of values specified and the statistics generated are reliable. As the number of iterations increases, the distribution for the output is described in more detail and becomes more stable. The number of iterations for each simulation was determined by the software, which halted the simulation when convergence at less than 1.5% in percentile values, mean and standard deviation was achieved.

Base case analysis

Table 60 summarises the distributions around the means assigned to probabilities and costs in the probabilistic SA for base case analysis. The

TABLE 60 *Distributions around mean assigned to probabilities and costs in the probabilistic simulation for base case analysis*

Variable	Mean value (*Assigned distribution*)					
	NSAID	**NSAID + PPI**	**NSAID + H_2RA**	**NSAID + misoprostol**	**Cox-2**	**Cox-2 preferential**
p(GI discomfort)[a]	0.284 *(beta: 5304, 13,362)*	0.430 *(log-normal: 0.240–0.760)*	0.720 *(log-normal: 0.560–0.920)*	0.970 *(log-normal: 0.700–1.35)*	0.810 *(log-normal: 0.700–0.900)*	0.730 *(log-normal: 0.700 – 0.800)*
p(endoscopic ulcer)[a]	0.213 *(beta: 1134, 4184)*	0.370 *(log-normal: 0.300–0.460)*	0.550 *(log-normal: 0.440–0.700)*	0.330 *(log-normal: 0.280–0.410)*	0.250 *(log-normal: 0.210–0.300)*	0.410 *(log-normal: 0.200–1.100)*
p(Serious GI complication][a]	0.006 *(beta: 152, 27,413)*	0.4602 *(gamma: 0.400, 1.149)*	0.332 *(gamma: 0.025, 13.034)*	0.570 *(log-normal: 0.400–0.900)*	0.550 *(log-normal: 0.410–0.770)*	0.610 *(log-normal: 0.300–1.100)*
Cost (no GI adverse event)	16.82 *No distribution*	168.03 *No distribution*	66.46 *No distribution*	77.83 *No distribution*	140.66 *No distribution*	121.67 *No distribution*
Cost (GI discomfort) inpatient	1166 *(gamma: 129.2, 9.0)*	1191 *(gamma: 134.9, 8.8)*	1174 *(gamma: 124.2, 9.2)*	1175 *(gamma: 131.3, 8.9)*	1185 *(gamma: 133.8, 8.9)*	1184 *(gamma: 133.5, 8.9)*
Cost (GI discomfort) outpatient endoscopy	612 *(gamma: 38.7, 15.8)*	638 *(gamma: 42.0, 15.2)*	621 *(gamma: 39.8, 15.6)*	623 *(gamma: 41.9, 15.6)*	632 *(gamma: 41.4, 15.3)*	630 *(gamma: 41.2, 15.3)*
Cost (GI discomfort) outpatient no endoscopy	278 *(gamma: 256.9, 1.1)*	303 *(gamma: 305.6, 1.0)*	286 *(gamma: 272, 1.1)*	289 *(gamma: 277.1, 1.0)*	297 *(gamma: 296.3, 1.0)*	296 *(gamma: 276.3, 1.1)*
Cost (outpatient ulcer with endoscopy)	1877 *(gamma: 32.7, 57.4)*	1953 *(gamma: 35.4, 55.1)*	1902 *(gamma: 33.6, 56.6)*	1909 *(gamma: 33.8, 56.4)*	1934 *(gamma: 34.9, 55.7)*	1930 *(gamma: 34.8, 55.6)*
Cost (outpatient ulcer no endoscopy)	283 *(gamma: 245.4, 1.1)*	359 *(gamma: 401.2, 0.9)*	308 *(gamma: 292.3, 1.6)*	315 *(gamma: 303.6, 1.0)*	341 *(gamma: 369.3, 0.9)*	336 *(gamma: 358.7, 0.9)*
Cost (inpatient surgical intervention)	14,650 *(gamma: 111.0, 132.0)*	14,726 *(gamma: 105.1, 151.8)*	14,675 *(gamma: 112.4, 131.0)*	14,681 *(gamma: 111.1, 132.0)*	14,712 *(gamma: 112.0, 131.4)*	14,708 *(gamma: 112.0, 131.5)*
Cost (inpatient medical intervention)	8914 *(gamma: 134.2, 66.4)*	8990 *(gamma: 136.5, 65.9)*	8939 *(gamma: 134.9, 66.2)*	8946 *(gamma: 135.1, 66.2)*	8971 *(gamma: 135.3, 66.0)*	8966 *(gamma: 135.3, 66.3)*
Cost (outpatient medical intervention)	1877 *(gamma: 32.7,57.4)*	1953 *(gamma: 35.4, 55.1)*	1902 *(gamma: 33.6, 56.6)*	1909 *(gamma: 33.8, 56.4)*	1934 *(gamma: 34.7, 55.7)*	1930 *(gamma: 34.7, 55.7)*

[a] Distribution assigned to the absolute risk for NSAID and RR ratio for NSAID + PPI, NSAID + H_2RA, NSAID + misoprostol, Cox-2 specific and Cox-2 preferential.
[b] Defined using gamma distribution because the broad 95% CI around the RR ratio did not allow a log-normal distribution to be specified.

probability of symptomatic/endoscopic ulcer was specified with a triangular distribution (mean 0.15, minimum 0, maximum 0.30). *Table 61* provides a summary of the expected costs and outcomes used in the base case simulation.

Subgroup analysis

Table 62 summarises the distributions around the means assigned to probabilities and costs in the probabilistic SA for subgroup analysis.

TABLE 61 *Expected costs and outcomes used in base case simulation*

Variable	Mean (95% CI)					
	NSAID	**NSAID + PPI**	**NSAID + H_2RA**	**NSAID + misoprostol**	**Cox-2 coxib**	**Cox-2 preferential**
Expected costs (£)	139 (120 to 161)	200 (179 to 260)	120 (97 to 149)	147 (129 to 171)	187 (176 to 203)	175 (157 to 200)
p(Endoscopic ulcers]	0.213 (0.204 to 0.223)	0.080 (0.063 to 0.098)	0.119 (0.093 to 0.149)	0.073 (0.060 to 0.087)	0.054 (0.044 to 0.064)	0.087 (0.021 to 0.210)
p(PUBs)	0.006 (0.005 to 0.006)	0.002 (0 to 0.010)	0.002 (0 to 0.06)	0.003 (0.002 to 0.005)	0.003 (0.002 to 0.004)	0.003 (0.002 to 0.006)

TABLE 62 *Distributions around mean assigned to probabilities and costs in the probabilistic sensitivity analysis for subgroup analysis*

Variable	Mean value (***Assigned distribution***)					
	NSAID	**NSAID + PPI**	**NSAID + H_2RA**	**NSAID + misoprostal**	**Cox-2 coxib**	**Cox-2 preferential**
Age under 65 years						
p(Endoscopic ulcer)	0.216 *(beta: 1078, 3924)*	No data	0.57 *(log-normal: 0.45, 0.74)*	0.33 *(log-normal: 0.27, 0.41)*	0.25 *(log-normal: 0.21, 0.30)*	0.47 *(gamma: 0.785, 0.599)*
Age over 65 years						
p(Endoscopic ulcer)	0.306 *(beta: 568, 1288)*	No data	0.39 *(log-normal: 0.20, 0.77)*	0.54 *(log-normal: 0.21, 1.39)*	No data	1.21 *(gamma: 0.373, 3.247)*[a]
GI status group 1						
p(Endoscopic ulcer)	0.259 *(beta: 418, 1197)*	0.13 *(gamma: 0.26, 0.50)*	0.52 *(log-normal: 0.29, 0.94)*	0.09 *(gamma: 0.049, 1.83)*	No data	No data
GI status group 2						
p(Endoscopic ulcer)	0.177 *(beta: 611, 2842)*	0.42 *(log-normal: 0.14, 1.31)*	0.61 *(log-normal: 0.46, 0.82)*	0.31 *(log-normal: 0.23, 0.44)*	0.25 *(log-normal: 0.21, 0.30)*	0.29 *(log-normal: 0.10, 0.86)*
GI status group 3						
p(Endoscopic ulcer)	0.283 *(beta: 660, 2336)*	No data	0.19 *(gamma: 0.209, 0.910)*	0.39 *(log-normal: 0.30, 0.50)*	No data	No data
GI status group 4						
p(Endoscopic ulcer)	0.336 *(beta: 661, 1305)*	0.36 *(log-normal: 0.29, 0.46)*	0.45 *(log-normal: 0.27, 0.76)*	0.34 *(log-normal: 0.17, 0.67)*	No data	No data

[a] Truncated at maximum probability of 1.0.

Chapter 23

Economic analysis of NSAIDs plus GPA, Cox-2 preferential inhibitors and Cox-2 coxib inhibitors: results

Base case analysis

ICERs were generated for the primary outcome measure (endoscopic ulcer or serious GI event averted) against total cost and non-parametric bootstrapping was used to simulate the variance of these ICERs. Cost per life-year gained (LYG) was also estimated. The mean ICERs (with 2.5th percentile and 97.5th percentile) are reported in *Table 63*.

Cost per endoscopic ulcer

Figure 96 shows the distribution of the bootstrapped ICERs on the cost-effectiveness plane for cost per endoscopic ulcer avoided. NSAID plus H_2RA ICER point estimates are mostly in the south-east quadrant, suggesting that this strategy dominates NSAIDs alone. It can be seen that most of the other ICER point estimates are in the north-east quadrant, suggesting that these interventions are more costly and more effective than NSAIDs alone. NSAID plus H_2RA has the lowest ICER, followed by NSAID plus misoprostol, NSAID plus PPI, Cox-2 coxib inhibitors and Cox-2 preferential inhibitors with the highest ICER. *Figure 96* suggests that there is a degree of overlap between the ICER distributions of NSAID plus PPI and Cox-2 coxib inhibitors and between NSAID plus H_2RA and NSAID plus misoprostol. The wide spread of the ICERS, particularly for NSAID plus PPI and Cox-2 preferential inhibitors reflects the high level of uncertainty around the effectiveness measures.

Figure 97 shows the point estimates of ICERs for NSAID plus GPA, Cox-2 coxib or Cox-2 preferential inhibitor versus NSAID alone for cost per endoscopic ulcer avoided. This plot shows that extended dominance exists between the five strategies, with NSAID plus H_2RA or misoprostol dominating NSAID plus PPI, Cox-2 coxib inhibitor or Cox-2 preferential inhibitor. This suggests that NSAID plus H_2RA or misoprostol should be selected over the other three strategies. However, owing to the poor quality of the data leading to high levels of uncertainty, and thus wide ranges for ICERs, this conclusion is only tentatively drawn.

Owing to the ratio nature of ICERs, estimation of CIs is problematic, particularly if effects of cost differences approximate to zero. There is currently no optimal cost per outcome above which an intervention is not considered 'cost-effective'. However, using ICER data, it is possible to determine the probability that an intervention is cost-effective at a particular cost per outcome.[207] Generation of a cost-effectiveness acceptability curve (CEAC) is particularly useful in this situation as it provides a measure of the probability that an ICER will be less than the decision-maker's ceiling willingness to pay (WTP). The CEAC for NSAID plus GPA, Cox-2 coxib or Cox-2 preferential inhibitor versus NSAID alone for cost per endoscopic ulcer avoided is shown in *Figure 98*. From this analysis, we can say that there is a 95% probability that NSAID plus H_2RA is dominant

TABLE 63 *Summary of incremental base case analysis for cost per endoscopic ulcer or serious GI event averted and life-year gained*

Treatment arm versus NSAID	Cost per endoscopic ulcer avoided (£) (2.5th percentile, 97.5th percentile)	Cost per serious GI event averted (£) (2.5th percentile, 97.5th percentile)	Cost per LYG (£) (2.5th percentile, 97.5th percentile)
NSAID plus PPI	454 (251, 877)	5744 (–99537, 101364)	3204 (–55521, 56540)
NSAID plus H_2RA	–186 (–555,804)	–4477 (–9718, 22490)	–2534 (–9718, 22490)
NSAID plus misoprostol	54 (–112,238)	–2550 (–21103, 9510)	–1423 (–5305, 11771)
Cox-2 coxib inhibitor	301 (189, 418)	22843 (10742, 44896)	12742 (5992, 25093)
Cox-2 preferential inhibitor	263 (–570, 1280)	16153 (–58029, 104973)	9010 (–32368, 58553)

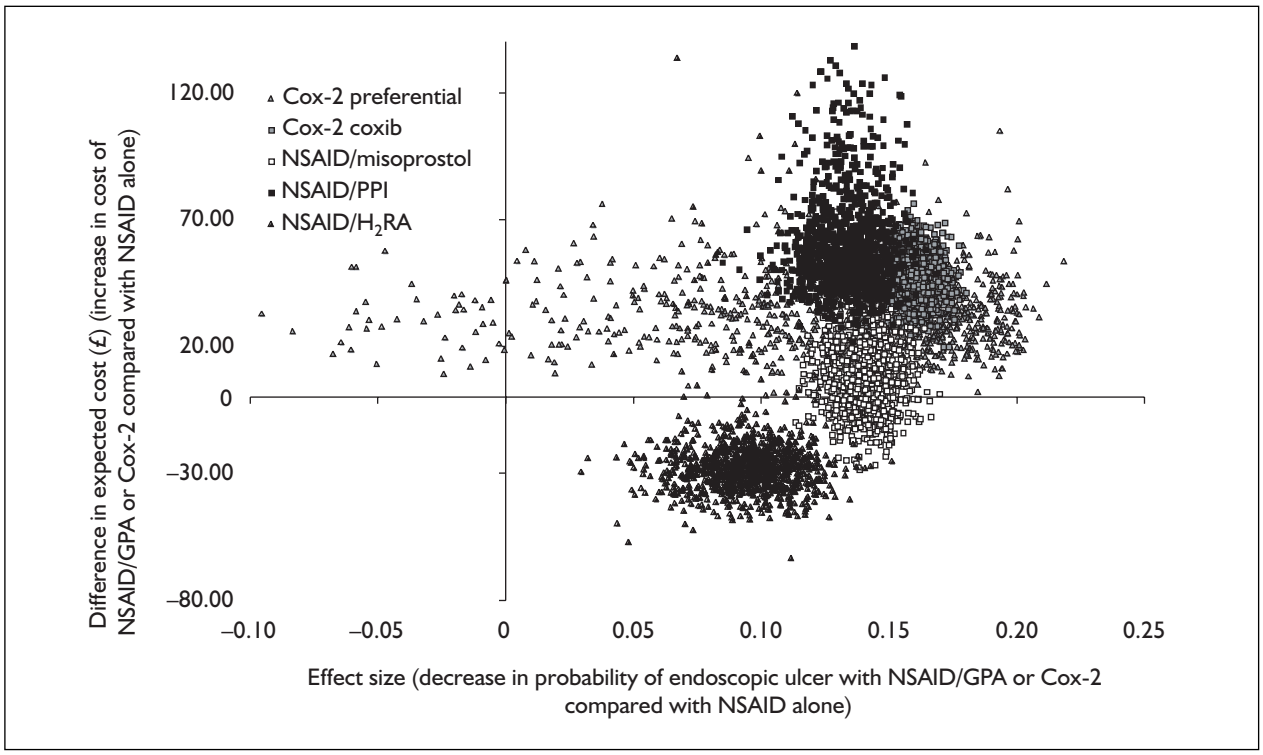

FIGURE 96 *Bootstrapped cost-effectiveness plane for NSAID plus GPA, Cox-2 coxib or Cox-2 preferential inhibitor versus NSAID alone for cost per endoscopic ulcer avoided*

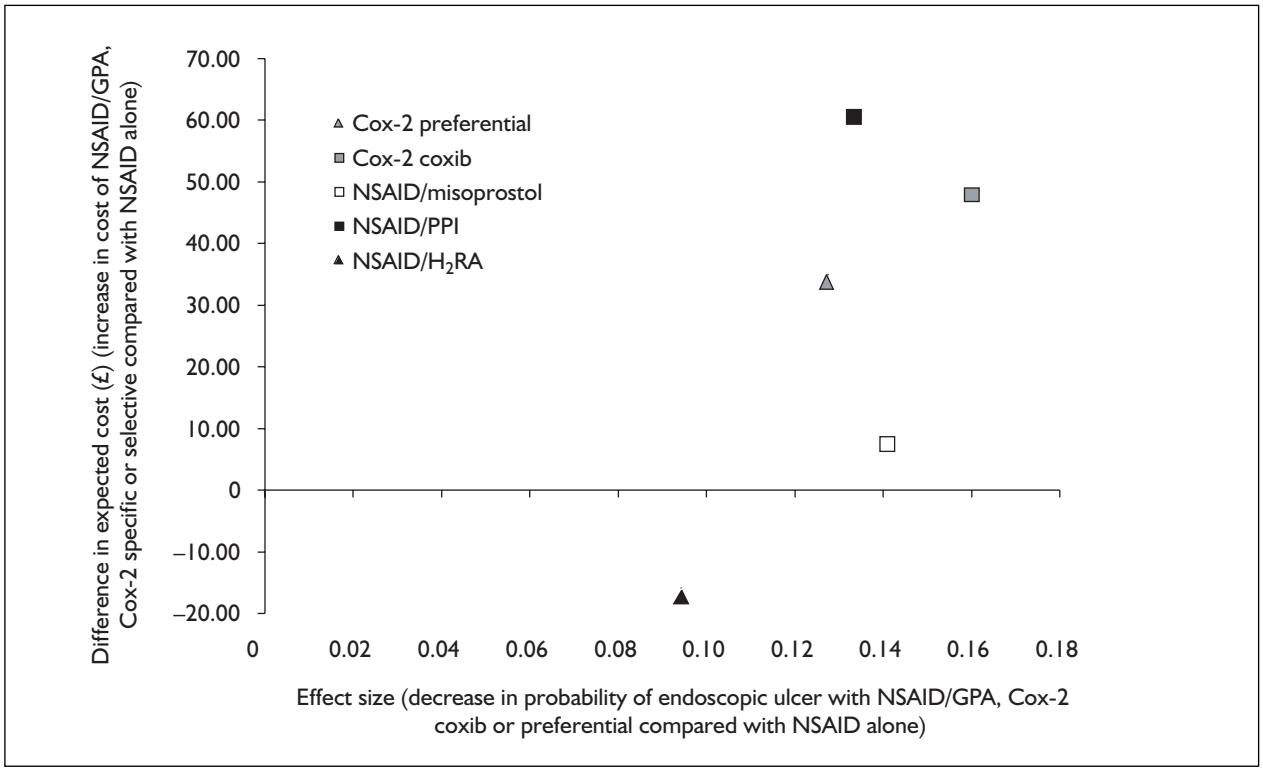

FIGURE 97 *Cost-effectiveness plane for NSAID plus GPA, Cox-2 coxib or Cox-2 preferential inhibitor versus NSAID alone for cost per endoscopic ulcer avoided, showing extended dominance*

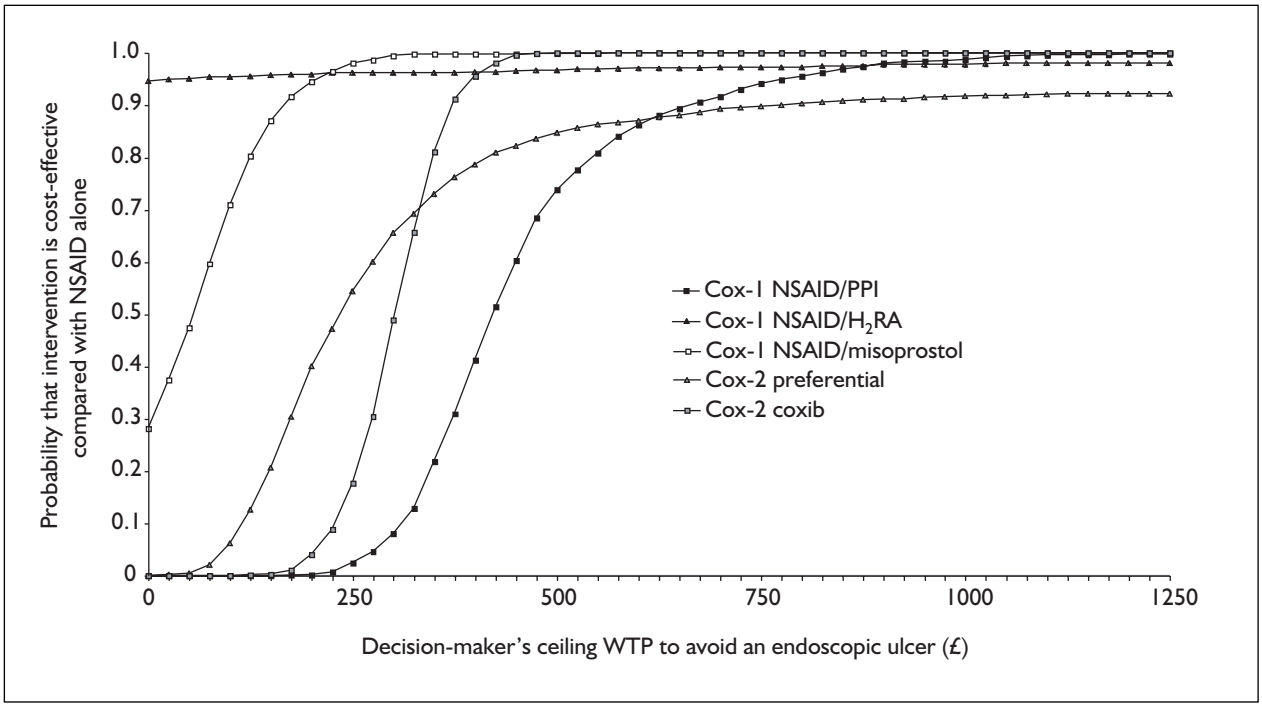

FIGURE 98 *CEACs for NSAID plus GPA, Cox-2 coxib or Cox-2 preferential inhibitor versus NSAID alone for cost per endoscopic ulcer avoided*

(less costly and more effective). There is a 95% probability that this intervention will be cost-effective if a decision-maker is willing to pay up to £210 with NSAID plus misoprostol to avoid an extra endoscopic ulcer, £770 with NSAID plus PPI and £400 with Cox-2 coxib inhibitors. Cox-2 preferential inhibitors reach only a 92% probability of cost-effectiveness at a ceiling value of £1250. The curve takes longer to reach $p = 1.0$ when there is more uncertainty around the data or the effectiveness of the intervention is not certain.

The optimal strategy is the intervention with the highest net benefit, whether we are choosing between two or six options, as in this study. In a multiple intervention decision such as in this analysis, the CEAC for each intervention can be established by calculating the proportion of the iterations from the simulation where that intervention is optimal over the other interventions, at a given cost per outcome. Repeating this process for each intervention and simultaneously plotting the CEAC curves allows the derivation of a cost-effectiveness acceptability frontier (CEAF).[207] A CEAF was generated for NSAID plus GPA, Cox-2 coxib or Cox-2 preferential inhibitor versus NSAID alone for cost per endoscopic ulcer avoided (*Figure 99*).

Figure 99 shows a family of CEACs. The CEAF is described by the uppermost combination of lines. The switch points on the frontier show where the optimal strategy changes, and is equivalent to the base ICER between these two options. If the decision-maker is willing to pay between £0 and £750, the optimal strategy is NSAID plus H_2RA. If the decision-maker is willing to pay over £750, the optimal strategy is NSAID plus misoprostol. Between £1900 and £3750, Cox-2 preferential inhibitors are optimal, and over £3750, Cox-2 coxib inhibitors become optimal. NSAID plus PPI is never the optimal strategy.

The data for endoscopic ulcers were the most robust outcome data obtained overall, although this base case analysis suggests that there is still an unacceptable level of uncertainty, as far as decision-making is concerned. However, they were not the most clinically relevant data. Therefore, the data for serious GI outcomes were used in an incremental economic analysis, although the higher levels of uncertainty generally found around these data meant that any findings would be more tentative.

Cost per serious GI event

ICERs were generated for serious GI event averted against total cost and bootstrapping was used to simulate the variance of these ICERs. The mean ICERs with 2.5th percentile and 97.5th percentile are reported in *Table 63*. *Figure 100* shows the distribution of the bootstrapped ICERs on the

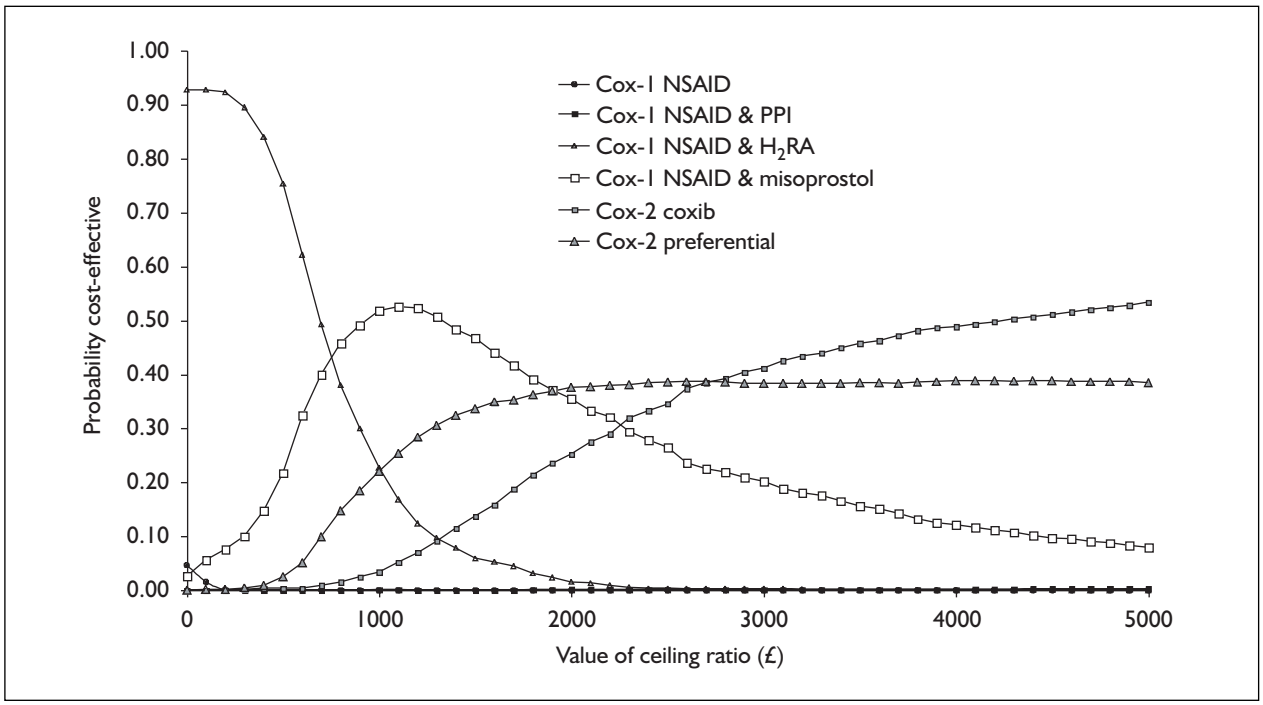

FIGURE 99 *CEAF for NSAID plus GPA, Cox-2 coxib or Cox-2 preferential inhibitor versus NSAID alone for cost per endoscopic ulcer avoided*

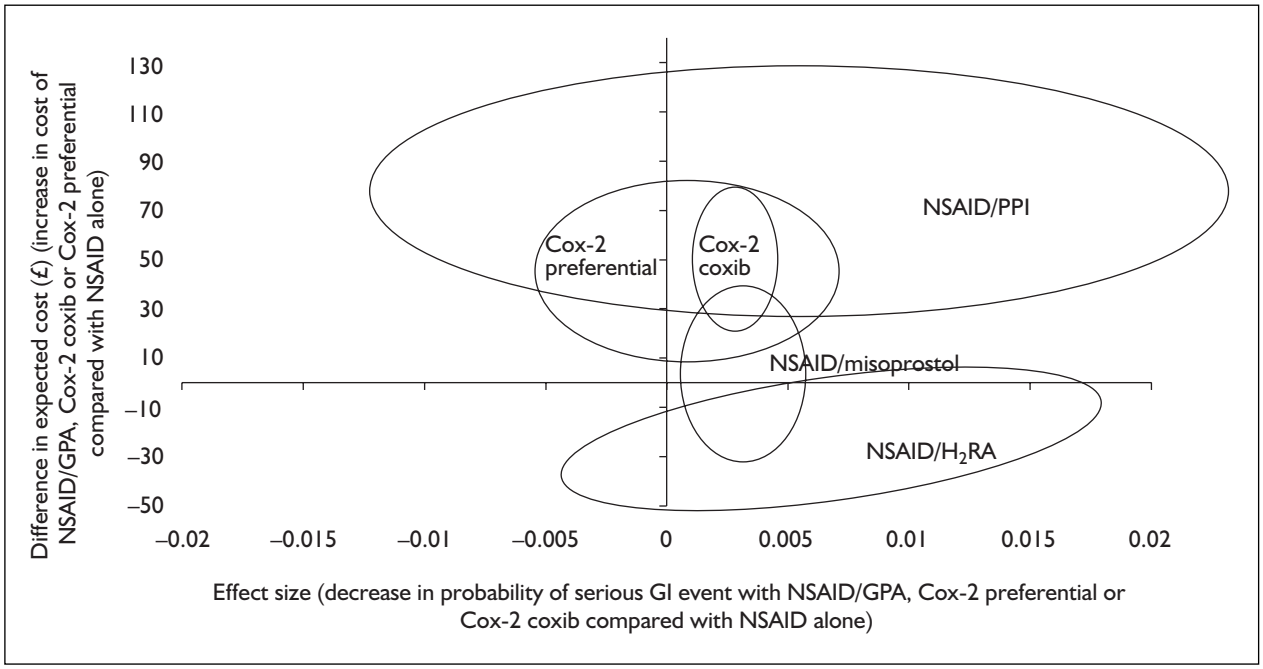

FIGURE 100 *Bootstrapped cost-effectiveness plane for NSAID plus GPA, Cox-2 coxib or Cox-2 preferential inhibitor versus NSAID alone for cost per serious GI event averted*

cost-effectiveness plane for cost per serious GI event avoided. It can be seen that most of the ICER point estimates are in the north-east and north-west quadrants, suggesting that all interventions are more costly than NSAIDs alone, but improvements in outcome are not always statistically significant, leading to an ICER distribution indicating both increased and decreased cost-effectiveness. NSAID plus H_2RA has the lowest ICER, followed by NSAID plus misoprostol, NSAID plus PPI, Cox-2 preferential inhibitors and Cox-2 coxib inhibitors with the highest ICER. *Figure 100* suggests that there is a degree of overlap between the ICER distributions

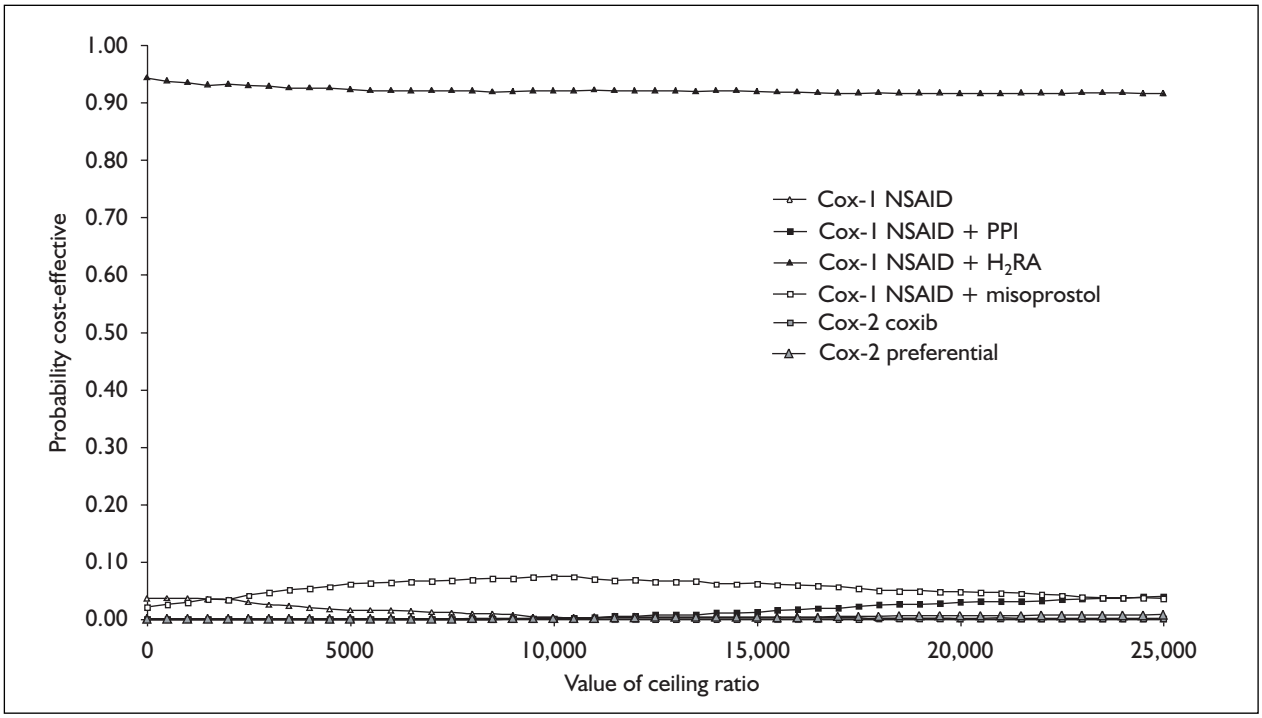

FIGURE 101 *CEAF for NSAID plus GPA, Cox-2 coxib or Cox-2 preferential inhibitor versus NSAID alone for cost per serious GI event averted*

of all arms. The wide spread of the ICERS, particularly for NSAID plus PPI and H_2RA, reflects the high level of uncertainty around the effectiveness measures.

The CEAF for NSAID plus GPA, Cox-2 coxib or Cox-2 preferential inhibitor versus NSAID alone for cost per serious GI event averted is shown in *Figure 101*. From this analysis, the frontier suggests the optimal strategy is NSAID plus H_2RA over a wide range of decision-makers' WTP.

Cost per LYG was calculated using the mean ages of the population presenting with upper GI bleeds.[2]

The mean ICERs with 2.5th percentile and 97.5th percentile are reported in *Table 63*. These follow the same order as cost per serious GI event averted.

Summary of base case analysis

1. Data on clinically significant outcomes, such as serious GI event averted or LYG, were associated with high levels of uncertainty, such that it is not possible to make recommendations for the optimal strategy based on these data.
2. Data on clinically significant outcomes not associated with GI outcomes, such as cardiac or renal outcomes, were absent, such that it is not possible to make recommendations for the optimal strategy based on these data.
3. Data on the less clinically significant outcome, endoscopic ulcers avoided, were associated with lower levels of uncertainty, such that the possible conclusions can be drawn.
   (a) All strategies (NSAID + H_2RA, NSAID + PPI, NSAID + misoprostol, Cox-2 preferential inhibitor or Cox-2 coxib inhibitor) are more effective options than NSAID alone.
   (b) There is 95% probability that NSAID + H_2RA is a dominant option compared with NSAIDs alone.
   (c) Comparison of mean ICERs suggests that NSAID + H_2RA and NSAID + misoprostol dominate NSAID + PPI, Cox-2 coxib inhibitor or Cox-2 preferential inhibitor, but this does not take into account uncertainty around the data.

Cost-effectiveness acceptability analysis partially supports this conclusion. If the decision-maker is only willing to pay less than a ceiling ratio of £750, the optimal strategy is NSAID + H_2RA. If the decision-maker is willing to pay over £750, the optimal strategy is NSAID + misoprostol. Between £1900 and £3750, Cox-2 preferential inhibitors are optimal, and over £3750, Cox-2 coxib inhibitors become optimal. NSAID + PPI is never the optimal strategy.

TABLE 64 *Missing data for subgroup analysis*

Basecase	Age <65 years	Age ⩾65 years	Group 1	Group 2	Group 3	Group 4
NA	No PPI	No PPI No Cox-2 coxib	No Cox-2 coxib No Cox-2 preferentials		No PPI No Cox-2 coxib No Cox-2 preferentials	No PPI No Cox-2 coxib No Cox-2 preferentials

NA, not applicable.

TABLE 65 *Probability of endoscopic ulcer generated from the subgroup analysis on age*

Analysis	Mean expected endoscopic ulcer (95% CI)					
	NSAID	NSAID + PPI	NSAID + H_2RA	NSAID + misoprostol	Cox-2 coxib	Cox-2 preferential
Base case	0.213 (0.204 to 0.223)	0.080 (0.063 to 0.098)	0.119 (0.093 to 0.149)	0.073 (0.060 to 0.087)	0.054 (0.044 to 0.064)	0.087 (0.021 to 0.210)
Age <65 years	0.216 (0.206 to 0.225)	Missing	0.126 (0.097 to 0.159)	0.072 (0.058 to 0.088)	0.054 (0.045 to 0.065)	0.101 (0.003 to 0.327)
Age ≥65 years	0.306 (0.289 to 0.324)	Missing	0.129 (0.061 to 0.236)	0.187 (0.064 to 0.435)	Missing	0.370 (0.000 to 1.000)

TABLE 66 *Expected costs generated from the subgroup analysis on age*

Analysis	Mean expected cost (95% CI)					
	NSAID	NSAID + PPI	NSAID + H_2RA	NSAID + misoprostol	Cox-2 coxib	Cox-2 preferential
Base case	139 (120 to 161)	200 (179 to 260)	122 (97 to 149)	147 (129 to 171)	187 (176 to 203)	175 (157 to 200)
Age <65 years	139 (118 to 161)	Missing	123 (97 to 170)	148 (130 to 174)	188 (177 to 202)	177 (156 to 208)
Age ≥65 years	150 (123 to 177)	Missing	123 (96 to 157)	161 (134 to 201)	Missing	196 (158 to 288)

Subgroup analysis

Subgroup analysis was severely affected by the lack of available data. For some subgroups there are no data at all. This is summarised in *Table 64*.

Even when there were data available, the small numbers remaining in each arm once subgrouping had been carried out led to very large ranges in probabilities.

Age

Probabilities were obtained in the MA for the age subgroups: <65 years and ≥65 years, where possible. *Table 65* reports the means and distributions for endoscopic ulcer. Data were not present for remaining outcome measures. *Table 66* summarises expected costs generated from the subgroup analysis on age.

ICERs were generated for the primary outcome measure (endoscopic ulcer) or against total cost and bootstrapping was used to simulate the variance of these ICERs. The mean ICERs with 2.5th percentile and 97.5th percentile are reported in *Table 67*.

These results suggest that NSAID plus H_2RA and NSAID plus misoprostol become more cost-effective (ICERs become lower) in the older age

TABLE 67 *Summary of incremental analysis for cost per endoscopic ulcer for 'under 65 years' and 'equal to or over 65 years' subgroups*

Treatment arm versus NSAID	Cost per endoscopic ulcers avoided (£) (2.5th percentile, 97.5th percentile)	
	⩽65 years	⩾65 years
NSAID plus PPI	No data	No data
NSAID plus H_2RA[a]	–170 (–564, 1542)	–220 (–803, 607)
NSAID plus misoprostol	70 (–82, 243)	51 (–620, 665)
Cox-2 coxib inhibitor	306 (194, 418)	No data
Cox-2 preferential inhibitor[b]	361 (–759, 1361)	–130 (–1303, 1287)

[a] Negative ICER due to reduced cost and increased effect.
[b] Negative ICER due to increased cost and reduced effect.

TABLE 68 *Probability of endoscopic ulcer generated from the subgroup analysis on GI risk*

Analysis	Mean expected endoscopic ulcer (95% CI)					
	NSAID	NSAID + PPI	NSAID + H_2RA	NSAID + misoprostol	Cox-2 coxib	Cox-2 preferential
Base case	0.213 (0.204 to 0.223)	0.080 (0.063 to 0.098)	0.119 (0.093 to 0.149)	0.073 (0.060 to 0.087)	0.054 (0.044 to 0.064)	0.087 (0.021 to 0.210)
Group 1	0.259 (0.242 to 0.276)	0.034 (0 to 0.169)	0.145 (0.074 to 0.256)	0.022 (0 to 0.101)	Missing	Missing
Group 2	0.177 (0.167 to 0.187)	0.076 (0.01 to 0.217)	0.110 0.082 to 0.144	0.057 (0.041 to 0.078)	0.045 (0.037 to 0.054)	0.051 (0.009 to 0.149)
Group 3	0.282 (0.268 to 0.297)	Missing	0.053 (0 to 0.287)	0.111 (0.084 to 0.142)	Missing	Missing
Group 4	0.336 (0.318 to 0.354)	0.124 (0.098 to 0.155)	0.159 (0.090 to 0.250)	0.123 (0.057 to 0.228)	Missing	Missing

group. No conclusions could be drawn for NSAID plus PPI or Cox-2 coxib inhibitor owing to a lack of data. The high levels of uncertainty around the Cox-2 preferential inhibitor data are reflected in the wide ranges for the ICER and the suggestion that this group are actually less effective than NSAIDs alone in the older age group. However, owing to the poor quality of the data, leading to high levels of uncertainty, and therefore wide ranges for ICERs, this conclusion is only tentatively drawn.

Previous GI disease

Probabilities were obtained in the MI for four GI risk groups, where possible. *Table 68* reports the means and distributions for endoscopic ulcer. Data were not present for remaining outcome measures. *Table 69* summarises expected costs generated from the subgroup analysis on GI risk.

ICERs were not generated for the primary outcome measure because the data were associated with too much uncertainty for meaningful analysis.

Summary of sensitivity and subgroup analysis

1. Data on clinically significant outcomes, such as serious GI event averted or LYG, were associated with high levels of uncertainty, such that it is not possible to make recommendations for the optimal strategy based on these data.
2. Data on the less clinically significant outcome, endoscopic ulcers avoided, were associated with lower levels of uncertainty. However, in some sections of the subgroup analysis, lack of these data rendered incremental economic analysis of limited use.

TABLE 69 *Expected costs generated from the subgroup analysis on GI risk*

Analysis	Mean expected cost (95% CI)					
	NSAID	**NSAID + PPI**	**NSAID + H_2RA**	**NSAID + misoprostol**	**Cox-2 coxib**	**Cox-2 preferential**
Base case	139 (120 to 161)	200 (179 to 260)	122 (97 to 149)	147 (129 to 171)	187 (176 to 203)	175 (157 to 200)
Group 1	142 (121 to 166)	195 (174 to 249)	126 (97 to 145)	142 (124 to 169)	Missing	Missing
Group 2	135 (118 to 155)	198 (177 to 261)	121 (97 to 170)	147 (128 to 170)	186 (176 to 203)	172 (156 to 195)
Group 3	146 (121 to 171)	Missing	113 (90 to 161)	153 (132 to 176)	Missing	Missing
Group 4	153 (124 to 183)	205 (182 to 265)	126 (99 to 160)	155 (133 to 181)	Missing	Missing

3. The impact of age on cost-effectiveness could only be examined tentatively owing to poor age-specific outcome data from the trials. These results suggest that NSAID plus H_2RA and NSAID plus misoprostol become more cost-effective in the older age group. No conclusions could be drawn for NSAID plus PPI or Cox-2 coxib inhibitors owing to a lack of data. The high levels of uncertainty around the Cox-2 preferential inhibitor data are reflected in the wide ranges for the ICER and the suggestion that this group are actually less effective than NSAIDs alone in the older age group.
4. The impact of baseline GI risk on cost-effectiveness could not be examined quantitatively owing to poor risk group-specific outcome data from the trials.

Chapter 24

Discussion

Systematic review summary

Overall, relevant published trials were of poor quality and there were few data on this review's primary outcomes: serious GI complications, symptomatic ulcers, serious cardiovascular or renal disease, QoL and deaths. When we compared the four gastroprotective strategies against placebo, we found that:

- There was no evidence of the effectiveness of H_2RAs against any of these primary outcomes, but they do appear to reduce the risk of endoscopic ulcers.
- PPIs also reduced the risk of endoscopic ulcers and appeared to reduce symptomatic ulcers, GI symptoms and drop-outs due to GI symptoms.
- Misoprostol reduced the risk of symptomatic ulcers and endoscopic ulcers, but increased the risk of drop-outs and drop-outs due to GI symptoms.
- Cox-2 coxibs reduced the risk of serious GI events, symptomatic ulcers, endoscopic ulcers and anaemia and may have reduced GI symptoms, drop-outs and drop-outs due to GI symptoms.
- Cox-2 preferentials reduced the risk of symptomatic ulcers, GI symptoms, total drop-outs and drop-outs due to GI symptoms.

When we compared gastroprotective strategies against each other, the evidence was even weaker, but showed that:

- Cox-2 coxibs appeared more effective than misoprostol at preventing serious GI complications.
- PPIs were likely to be better at preventing symptomatic ulcers than Cox-2 coxibs (but this only comes from indirect comparisons).
- H_2RAs and Cox-2 coxibs and preferentials were better than misoprostol at preventing GI symptoms (from direct comparisons) and PPIs appeared better than Cox-2 coxibs or misoprostol at reducing the risk of GI symptoms (from indirect comparisons).
- Misoprostol was better than Cox-2 coxibs or H_2RAs and PPIs were better than H_2RAs at preventing endoscopic ulcers (all by direct comparisons).
- PPIs, misoprostol and Cox-2 coxibs all appeared better than H_2RAs at reducing the risk of endoscopic ulcers and Cox-2 coxibs appeared better than PPIs, but these were all from indirect comparisons.
- All other strategies were better than misoprostol at reducing the risk of total drop-outs or drop-outs due to GI symptoms.

MA results for the five gastroprotective strategies are summarised in *Table 70*.

Limitations of the systematic review

The most obvious limitation of these reviews is the lack of reporting in RCTs of the primary outcomes of interest: symptomatic ulcers, serious GI events, cardiovascular and renal illness, QoL and deaths. Many studies did not report the presence or absence of these outcomes and, perhaps worse, may have mentioned several events in an ad hoc manner, so that when we collected these few events we may not have reflected their actual level of occurrence.

We attempted to collect further primary outcome data by contacting authors of the primary studies. Unfortunately, the response rate was very low so we were only rarely able to augment the available data with more complete information on event numbers or trial quality. A common response from contact authors who did reply was that all the relevant data were with the sponsoring pharmaceutical company and therefore unavailable to the author. In view of the recent withdrawal of rofecoxib on the basis of suggested increased cardiovascular events, it may be significant that so few authors or pharmaceutical companies provided data on these important outcomes. This suggests that regulation may be needed to ensure such important outcomes are gathered centrally and made available for research synthesis of such issues. In the UK, legislation for the reporting and collection of such outcomes is now in place, but the availability of such data for use in systematic reviews is also imperative.

Although there is a very large body of evidence comparing Cox-2 coxibs and preferential NSAIDs

TABLE 70 *MA results for the five gastroprotective strategies on primary and secondary health outcomes, showing significant relationships (at the 5% significance level), RRs (95% CIs) and number of events*[a]

	H_2RA vs placebo	PPI vs placebo	Misoprostol vs placebo	Cox-2 preferential vs Cox-1	Cox-2 coxib vs Cox-1
Primary outcomes					
Total number of trial participants	2621	1358	16945	28178	25564
Serious GI complications	0.33 (0.0 to 8.1), 1	0.46 (0.1 to 2.9), 3	✓✓ 0.57 (0.4 to 0.9), 75	0.61 (0.3 to 1.1), 43	✓ 0.55 (0.4 to 0.8), 114
Symptomatic ulcers	1.46 (0.1 to 35.5), 1	✓ 0.09 (0.0 to 0.5), 18	✓✓ 0.36 (0.2 to 0.7), 54	✓✓ 0.41 (0.3 to 0.7), 82	✓✓ 0.49 (0.4 to 0.6), 281
Serious CV or renal events	0.53 (0.1 to 3.5), 5	0.78 (0.1 to 6.3), 3	1.78 (0.3 to 12.1), 4	0.95 (0.6 to 1.7), 48	1.19 (0.8 to 1.8), 241
Mortality	3.00 (0.1 to 68.3), 1	0.17 (0.0 to 4.1), 1	0.89 (0.5 to 1.7), 35	0.68 (0.3 to 1.6), 19	1.02 (0.6 to 1.9), 78
Health-related QoL				WMD –0.10 (–1.0 to 0.8)	
Secondary outcomes					
GI symptoms	✓ 0.72 (0.6 to 0.9), 201	✓✓ 0.43 (0.2 to 0.8), 45	0.97 (0.7 to 1.4), 1218	✓✓ 0.73 (0.7 to 0.8), 3894	✓✓ 0.81 (0.7 to 0.9), 5184
Endoscopic ulcers	✓✓ 0.55 (0.4 to 0.7), 250	✓✓ 0.37 (0.3 to 0.5), 281	✓✓ 0.33 (0.3 to 0.4), 658	0.41 (0.2 to 1.1), 24	✓✓ 0.25 (0.2 to 0.3), 522
Anaemia	3.00 (0.1 to 73.3), 1		2.66 (0.1 to 63.8), 1	0.30 (0.1 to 1.3), 6	✓ 0.62 (0.5 to 0.7), 464
Occult bleeding			RR 0.46 (0.2 to 1.3), 16	RR 0.86 (0.3 to 2.2), 17	
Total drop-outs	0.97 (0.8 to 1.1), 362	0.98 (0.6 to 1.5), 116	× 1.11 (1.0 to 1.2), 4772	✓✓ 0.93 (0.9 to 1.0), 4274	✓ 0.82 (0.7 to 0.9), 9510
Drop-outs due to GI symptoms	0.71 (0.4 to 1.2), 57	✓✓ 0.45 (0.3 to 0.8), 48	×× 1.36 (1.3 to 1.5), 2332	✓✓ 0.63 (0.6 to 0.7), 1174	✓ 0.69 (0.6 to 0.8), 2171

✓✓, Statistically significant protective relationship, no heterogeneity and significance not lost on sensitivity analysis;
✓, Statistically significant protective relationship, but significant heterogeneity or significance lost on sensitivity analysis;
×, Statistically significant harmful relationship, but significant heterogeneity or significance lost on sensitivity analysis;
××, Statistically significant harmful relationship, no heterogeneity and significance not lost on sensitivity analysis.
[a] Blank entries imply that no data were available for MA.

with Cox-1 NSAIDs, this is not matched by studies of the other types of gastroprotectors or by studies directly comparing active gastroprotective strategies. This lack of direct comparisons led us to attempt to use indirect comparisons to help understand the relative efficacy of these strategies. Indirect evidence in itself is weak and was also hampered by lack of evidence in the underlying studies (where the gastroprotectors were compared with placebo).

Many aspects of trial quality were routinely poorly reported. In the few instances where we did receive more information about study quality, it almost invariably improved the study's quality ratings. We were left with very few studies which

we knew were adequately concealed at allocation or where outcome assessors were blind to treatment. It is likely that more trials were, in reality, of better methodological quality than that indicated by our ratings, owing to a lack of clear reporting. A recent review of celecoxib studies by Deeks[208] accessed detailed manufacturer reports and rated all nine included studies highly.

Funding of studies was usually either overtly by pharmaceutical companies or such funding was indicated by employment of trial authors or provision of support to the trial. Extremely few studies stated funding sources that did not include a pharmaceutical company. This may have resulted in an increased tendency to report preferentially those outcomes that 'look good' for the sponsoring drug company, and may have led to considerable bias in an area where so few hard outcomes either occurred or were reported.

It was difficult to ensure that individual trial participants were included only once in the analysis for each outcome. Large multicentre international trials sometimes produced multiple publications where it was possible that particular populations were published several times in different groupings. We scrupulously married up multiple publications and attempted to check with authors, but cannot guarantee that some people did not appear more than once.

All these issues limited the conclusions that can be drawn from this review, and this should be borne in mind when making clinical or policy decisions based on this evidence.

Comparisons with other literature

This systematic review has built on an earlier published review of effectiveness conducted by Rostom and colleagues.[18,21]

Both reviews demonstrate significant reduced RR of developing endoscopic ulcers in people prescribed H_2RA, PPI and misoprostol compared with placebo. In head-to-head comparisons, both reviews showed that PPI and misoprostol are better than H_2RA at preventing endoscopic ulcers. Both reviews showed no difference between misoprostol compared to PPI in preventing endoscopic ulcers.

With regard to total number of drop-outs from trials, both reviews demonstrate significant increased RR of dropping out in misoprostol groups compared with placebo groups. Both reviews showed no difference in total number of drop-outs between H_2RA and placebo and between PPI and placebo. In head-to-head comparisons, both reviews showed no difference between misoprostol and H_2RA in total number of drop-outs.

The review by Rostom and colleagues found that one study showed a significantly reduced RR of developing ulcer complications in misoprostol compared with placebo. The significant results of this study in favour of misoprostol are lost on meta-analysis in this current review. This current review only found a significantly reduced RR of developing serious GI complications in misoprostol compared with placebo on SA (where Cox-2 preferentials were removed). Two of the three studies that favoured placebo in the meta-analysis compared a Cox-1 NSAID plus misoprostol with a Cox-2 preferential. Cox-2 preferentials (nabumetone in particular) may provide more protection against a serious GI complication than a Cox-1 NSAID plus misoprostol.

It should be noted that this current review included all trials that reported a serious GI event even if this was not the primary outcome measure of the trial and included melaena as an outcome that could indicate a serious GI complication. Further differences in data analysis between the two reviews should also be noted: one of the two studies[145] that compared a Cox-1 NSAID plus misoprostol with a Cox-2 preferential was excluded in the review by Rostom and colleagues. Another short-term study[67] included in this review was not found in the search by Rostom and colleagues.[18]

Of the remaining five studies providing data regarding serious GI complications used in this review, Rostom and colleagues[18,21] used only two of these studies (although including all five in the report) in the meta-analysis of 'clinical ulcers'. This may be due to the difference between definitions of serious GI events used in both reports. Data extracted from the same two studies[6,77] also differs between the two reports. In one study,[77] this review combined the two arms using misoprostol at differing doses (within the recommended range) whereas the review by Rostom and colleagues uses only one of these arms in comparison to placebo. This review included melaena as a serious GI event, which explains why this review extracted a larger number of events from the study by Silverstein and colleagues.[6]

Economic evaluation summary

As a baseline estimate, our economic analysis suggested Cox-1 NSAIDs plus H_2RAs may reduce the risk of endoscopic ulcer at a lower overall cost to the healthcare provider than NSAIDs alone. Cox-1 NSAIDs plus PPIs or misoprostol and Cox-2 coxibs may reduce the risk of endoscopic ulcer at an increased overall cost to the healthcare provider than NSAIDs alone. The data for endoscopic ulcers were the most robust outcome data obtained overall, although this analysis suggests that there is still an unacceptable level of uncertainty as far as decision-making is concerned. However, this was not the most clinically relevant outcome measure because most endoscopic ulcers do not develop into clinically significant ulcers or bleeds.[11]

In our systematic review, only 138 deaths and 248 serious GI events were reported for 74,666 participants in 112 trials. It is likely that serious GI outcomes are under-reported in trials as patients may be withdrawn before events occur. Therefore, the data for serious GI outcomes were used in an incremental economic analysis, although the higher levels of uncertainty generally found around these data meant that any findings would be more tentative.

Limitations of the economic evaluation

The model was constructed to provide a conservative estimate of cost-effectiveness. We did not extend the effect of treatment beyond the length of the trials, although benefits may continue to accrue. We were not able to assess the effect of baseline risk on cost-effectiveness, such as age or previous GI morbidity, owing to the poor quality of subgroup reporting in the trials in the meta-analysis.

Despite the large body of evidence in this area, there is very little information on the relative effectiveness of the five strategies owing to lack of head-to-head studies. This meant using indirect comparisons in the economic analysis, a method that can provide useful results,[31] but not as robust as direct comparisons.

Direct healthcare costs were available only as reported estimates from clinicians.[167] There is little or no patient-based information about the resource use consequences of NSAID-related GI events. Other economic evaluations of gastroprotective strategies in NSAID therapy have used data synthesis and modelling, other than one primary economic evaluation based on the MUCOSA trial.[11] We used a simple, conservative, static model design, with probabilistic data distributions to allow quantification of uncertainty. We did not use a more complex model structure because the data were not available to populate such a model. We did not want to weaken the model by application of an excessive number of assumptions about treatment pathways, probabilities and data distributions. The use of this model has generated useful results in the light of poor data quality, and indicates clearly where more primary data generation is required.

Comparisons of economic evaluation with other literature

There has been no head-to-head trial of gastroprotective strategies that has included an economic evaluation that collects patient-based observational data. All nine head-to-head economic analyses found in this review were modelling, or secondary economic evaluations, synthesising clinical and cost data from a range of sources. Some of these studies used robust and considered methods, and provide useful answers within their own context. There were no UK head-to-head economic analyses, so these studies have limited applicability to the UK context. Of the 35 economic evaluations reviewed, 26 studies were funded by pharmaceutical manufacturers and 23 found in favour of their product, the remaining three reporting neutral results. Our economic evaluation found in favour of use of Cox-1 NSAIDs plus H_2RAs despite the poorer quality of clinical data associated with this gastroprotective strategy.

Chapter 25
Conclusions

Recommendations for healthcare

Physicians prescribing NSAIDs need to be aware of the potential of serious GI toxicity and of the risk factors which enhance the incidence of such adverse events. The most effective way of avoiding NSAID-induced GI symptoms is not to take the NSAID but to use simple analgesia instead. Patients who are in the highest risk groups should certainly have a trial of simple analgesia before proceeding to an NSAID. However, for many patients with RA or more severe OA, simple analgesia is not sufficient to control their pain and stiffness. Patients who are in the highest risk groups should either be co-prescribed a GPA or a Cox-2 NSAID. Based on the clinical results of this systematic review, there is little justification for co-prescribing an H_2RA over the other three strategies. Misoprostol is not so well tolerated as either PPIs (plus a Cox-1 NSAID) or a Cox-2. PPIs are probably more effective at reducing the incidence of GI symptoms but not necessarily at reducing the risk of serious GI complications compared with a Cox-2 NSAID.

When costs are taken into consideration (and focusing solely on the prevention of endoscopic ulcers), there may actually be a case for co-prescribing H_2RA for all patients receiving a Cox-1 NSAID since H_2RAs are inexpensive and (based on economic modelling) likely to be associated with cost saving. If the decision-maker is willing to pay up to £750 to prevent an endoscopic ulcer, then the optimal strategy is to use Cox-1 plus H_2RA. If the decision-maker is willing to pay over £750, the optimal strategy is NSAID plus misoprostol. For WTP between £1900 and £3750, Cox-2 preferential inhibitors are optimal, and over £3750, Cox-2 coxibs become optimal. NSAID plus PPI is never the optimal strategy. However, this modelling was based on endoscopic ulcers – which are not what patients complain of or the most serious or costly outcome. Unfortunately, the data were too sparse to comment on the other more relevant outcomes.

Misoprostol is an effective gastroprotective strategy, but has a very high incidence of GI side-effects. Despite including a 10% withdrawal rate in our model to account for these side-effects, misoprostol was the optimal strategy above a decision-maker's WTP of £750. However, the extent to which prescribers are using misoprostol in the UK is decreasing, so it is not likely that recommendations to use this agent will be followed.

From our systematic review, we were not able to identify an increased cardiovascular risk associated with individual agents or classes of agents owing to very poor reporting of all outcomes, including cardiovascular outcomes. Our model could not examine differential cardiovascular risk between the strategies under consideration, owing to this lack of data. The recent events around the increased cardiovascular risk associated with rofecoxib compared with NSAIDs alone have led to scrutiny of all Cox-2 coxibs. So far, this increased risk appears to be associated with rofecoxib alone, rather than being a 'class effect'. This suggests that our results are applicable to gastroprotective strategies, including Cox-2 coxibs other than rofecoxib. If future data suggest that there is a 'class effect', it is likely that Cox-2 coxibs will not be recommended for patients with cardiovascular problems, and may be withdrawn if the risk is sufficiently high. However, exclusion of cardiovascular effects in our model, which assumes an equal cardiovascular risk between strategies, does not lead to Cox-2 coxibs becoming an optimal strategy.

Implications for further research

1. This study has highlighted the importance of reporting major outcomes, and also important patient-centred outcomes such as QoL, even where individual trials may not be powered to evaluate them – ideally such data would be centrally collected (as is now occurring in the UK) and openly available for use in meta-analysis to assess harms and benefits of treatments.
2. In future trials, the numbers of participants invited to participate, the number who agree and are randomised, the number who drop out (with reasons) and the number not analysed (with reasons) should all be clearly

reported. At present, assessing this information from published studies is generally impossible.

3. Future trials need to randomise in a way that ensures adequate allocation concealment and masking of participants, clinicians, statisticians and outcome assessors, and the procedures used should be clearly reported.
4. Funding of studies, and vested interests, should be clearly declared in all publications.
5. The primary investigator should retain trial data and have full access to this data at all times. It is not appropriate to hand the total set of study data over to pharmaceutical companies or to claim that, as primary author, one does not have access to it.
6. Further large independently funded RCTs, directly comparing various gastroprotective strategies, with sufficient power to report on symptomatic ulcers are clearly needed.
7. Such further studies should include those patients who have definite indications for NSAID use but also have other risk factors (e.g. elderly or one steroids). Economic analyses should be based on primary data when they are available, rather than adding to the large number of modelling studies.
8. Increased follow-up of patients who experience adverse events with prescription medicines including Cox-2 inhibitors is needed to allow a clearer understanding of, and provide better quality data on, incidence rates and to practice patterns after mild and major side-effects.
9. Assessment of practice such as:
   (a) the extent of use of H_2RAs and PPIs with Cox-2 coxibs
   (b) willingness to use misoprostol
   (c) patient risk factors affecting individual prescribers' use of preferential and Cox-2 coxibs
   (d) recent events around rofecoxib affecting attitudes to Cox-2 coxibs.
10. Exploration of patients' preferences around the optimal strategy, understanding of risks and benefits of NSAIDs and Cox-2 inhibitors, wish for involvement in decision-making and reaction to recent events around rofecoxib.

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Contribution of the authors

Alaa Rostom (Assistant Professor) was involved in performing previous work that was the foundation of the current study, securing funding for the review and economic analysis, providing a clinical perspective, providing general advice on the review and economic analysis and editing the report. Chris Roberts (Senior Lecturer in Medical Statistics) was involved in designing the review and economic analysis, securing funding for the review and economic analysis, providing statistical support and advice on the review and economic analysis and editing the report. Deborah Symmons (Professor of Rheumatology and Musculoskeletal Epidemiology) was involved in the conception of the review, designing the review and economic analysis, coordinating the work, securing funding for the review and economic analysis, abstracting data from papers, interpreting data, providing a clinical perspective, providing general advice on the review and economic analysis, editing the report and writing the executive summary. Katherine Payne (Research Fellow) was involved in developing the model for the economic analysis, constructing a decision-analytic model in Excel and Data, liaison with the project team for generation of clinical data from meta-analysis, generation of simulated clinical and economic data to generate probabilistic cost-effectiveness ratios, sensitivity analysis, appraising the quality of economics papers and tabulation of review of economic evaluations, writing of economic chapters of the review and providing an economic perspective. Lee Hooper (Lecturer in Evidence Based Care and Systematic Review) was involved in designing, coordinating and securing funding for the review, designing and running the electronic search strategies, screening search results, screening retrieved papers against inclusion criteria, appraising the quality of papers, abstracting data from papers, writing to authors of papers for additional information, performing meta-regressions, meta-analysis and subgrouping of absolute risk reductions, kappa score calculations, interpretation of the data, providing a methodological perspective, joint writing of the first draft of the report on the systematic review, incorporation of the edits of others, final editing of the report and writing two articles for publication in other journals. Rachel Elliott (Clinical Senior Lecturer) was involved in designing, coordinating and securing funding for the review and economic analysis, designing electronic search strategies, screening economic search results, screening retrieved economics papers against inclusion criteria, appraising the quality of economics papers, abstracting data from economics papers and other sources, writing to authors for additional information, designing a decision-analytic model, designing, coordinating and carrying out the economic analysis, synthesising clinical and economic data to

generate probabilistic cost-effectiveness ratios and cost-effectiveness acceptability curves and frontiers, sensitivity analysis, writing of economic chapters of the review, two abstracts for the British Society of Rheumatology and one article for publication providing an economic perspective. Roger Webb (Research Associate) was involved in the conception of the review, designing the review, coordinating the review in its early stages, securing funding for the review, providing general advice on the review, providing a methodological perspective and editing the report. Tamara Brown (Research Assistant) was involved in screening search results, checking bibliographies for further studies, organising retrieval of papers for the review and economic analysis, screening retrieved papers against inclusion criteria, appraising the quality of papers, abstracting data from papers, writing to authors of papers for additional information, data management for the review, performing meta-analysis and sensitivity analyses of relative risks, liaising between the review and the economic analysis parts of the project, organising project team meetings and telephone meetings with external advisors, keeping minutes of meetings, joint writing of the first draft of the report on the systematic review, editing the report and writing an abstract for the Cochrane Colloquium in Barcelona.

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The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@hta.ac.uk
http://www.hta.ac.uk

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