

Coxibs and traditional NSAIDs:

Systematic overviews of the randomised evidence for the effects of traditional non-steroidal anti-inflammatory drugs and selective inhibitors of cyclo-oxygenase-2 on vascular and upper gastrointestinal outcomes

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A thesis submitted for the degree of Doctor of Philosophy

Hilary term, 2013

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Word count (prose): 29694

Pages (prose): 129

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FOREWORD

Between August 2007 and September 2011, I joined Professor Colin Baigent and the Vascular Overviews Group at the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) in Oxford. I was extremely fortunate to help develop and coordinate one of the projects there: the Coxib and traditional NSAID Trialists' (CNT) Collaboration. This was a large-scale meta-analysis of individual participant data to assess the vascular and upper gastrointestinal effects in unconfounded randomised comparisons of selective inhibitors of cyclo-oxygenase-2 (coxibs) and traditional non-steroidal anti-inflammatory drugs (NSAIDs). The results of this systematic overview, which are now being prepared for publication, have come about from a substantial collaborative effort, involving hundreds of researchers and hundreds of thousands of participants in randomised trials.

I took on the day-to-day coordination of the CNT Collaboration, under the supervision of Prof. Colin Baigent. This involved supervising a team in Oxford (including research assistants, computer programmers, and administrative staff). It also involved interactions with clinical, statistical and corporate collaborators, both in Oxford and around the world.

My other contributions included:

1. Drafting and developing the study protocol, including requests for individual participant and tabular data, for the project along with my supervisor. I also developed the list of unadjudicated outcomes using the Medical Dictionary for Regulatory Affairs (MedDRA).
2. Project planning, including obtaining personal funding via the Medical Research Council Population Health funding stream
3. Conducting electronic searches with the CNT Secretariat, including undertaking the first check for relevant papers by title/abstract and then reviewing the full paper of thousands of references.

4. I organised meetings of the Steering Committee of the CNT Collaboration for strategic advice, which were carried out by teleconference as well as a Preliminary Results Meeting in person at Oxford in January 2011.
5. I communicated with collaborating sponsors and trialists for the CNT Collaboration throughout the project, including the initial invitation to collaborate, and subsequent negotiations.
6. Once data was provided, I took responsibility for checking the data, particularly baseline characteristics and the number and types of outcomes. Working with the Vascular Overviews Group computer programmers, the individual participant (and where not available, tabular) data was converted, checked, corrected and harmonised appropriately. I also ensured that collaborating trialists signed off on data presented for their individual study.
7. I also worked with statisticians on the calculation and presentation of the overall results, including the tables and figures enclosed in this thesis (Chapters 5-8).

Although there will be some further minor data corrections between the final formal publication of these results, these are not anticipated to materially influence the results presented in this thesis. The discussion, interpretation and implications of this work are my own.

ACKNOWLEDGEMENTS

Dr Jonathan Emberson – for being an outstanding scientist, probably the most organised person I know (including rapid precise turnover giving some comments on chapters), and a good friend to boot.

Mrs Heather Halls – for constantly keeping up my spirits and that of the team, and for many of your unsung contributions to work at CTSU.

Dr Lisa Holland – for being a wonderful colleague, an expert at unruffling feathers and reminding me about the need to practice good science.

Dr Amal Merhi – the work presented is really about interactions between clinicians and statisticians, and you and Jon worked hard on this project with me – thank you for your efforts.

Dr Kate Bird, Felicity Yau, Kelly Davies, Christina Reith and Lisa Blackwell – for all their hard work in the VOG office, which has provided the foundations of the various overviews. Your good spirits, in spite of the various trials and tribulations, definitely made the job easier.

Prof Carlo Patrono and other CNT collaborators – for the scientific and political clout to help navigate some of the challenges around this project. In particular, I would like to thank Carlo, who shaped much of the biological understanding of this project and kindly gave comments on my thesis.

Contributing trialists, sponsors and participants – although this project includes hundreds of trials and hundreds of thousands of participants, if it was not for individual participants taking part, and the responsible investigators/sponsors providing data, none of this would have been possible.

Dr Sarah Lewington – for giving me many hours of mentorship and lots of sensible advice, as well as dear friendship.

Dr Gary Whitlock – for your unique perspective on medical research and the world in general, and for introducing me to the kiwi sense of humour.

To my examiners Dr Robert Clarke, Dr Andrew Moore and Prof Ian Roberts for pushing me further on this topic and their valuable insights into the realities of academic medicine.

Prof Richard Peto – for the opportunity to work with a sheer epitome of academic, genius and great humanitarian to boot, as well as your insights into how we can prevent premature mortality and illness on a large scale.

Other colleagues at CTSU – for the countless chats and support which have left a big mark on my thinking – it has been a pleasure working with many of you. I would like to particularly thank Carolyn Taylor (a wonderful officemate) and other lunch companions.

Friends and previous mentors, too many to mention – thanks for your support.

Family – Dr BalMukund, Dr Aruna and Rajiv Bhala – from a humble background in India, my parents have always emphasised the value of education. Thank you for providing me with all the opportunities I have had to date from childhood, school and medical school: everything I am I owe to you.

To my wife Dr Francesca Crowe – living with a fellow epidemiologist certainly helped me with writing my thesis. Thanks for our discussions, your patience, and keeping me on the straight and narrow.

Prof Colin Baigent – for having the vision and ambition to put this project together, and for your wealth of knowledge and expertise, which you have contributed to this project. I know that learning from your ability to distil the important questions and implement science to test hypotheses will put me in good stead for the future.

Systematic overviews of the randomised evidence for the effects of traditional non-steroidal anti-inflammatory drugs and selective inhibitors of cyclo-oxygenase-2 (coxibs) on vascular and upper gastrointestinal outcomes

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A thesis submitted for the degree of Doctor of Philosophy

Hilary term, 2013

Background: Comparative assessments of the vascular and upper gastrointestinal risks of different regimens of non-steroidal anti-inflammatory drugs (NSAIDs) are required.

Methods: Meta-analyses were conducted, using individual participant data where possible, of placebo-controlled trials of a selective cyclo-oxygenase [COX]-2 inhibitor ('coxib') or traditional NSAID, or randomised trials of a coxib versus traditional NSAIDs. A prespecified subdivision of traditional NSAID regimens of those with antiplatelet activity (mainly naproxen) and those without (mainly diclofenac) was made. Primary outcomes were major vascular events (MVEs; nonfatal myocardial infarction, nonfatal stroke or vascular death) and upper gastrointestinal complications (UGICs; perforation, obstruction or bleed).

Findings: Searches identified 788 trials: 200 comparisons of a coxib vs placebo (88,604 participants, mean follow-up 0.60 years), 206 comparisons of a traditional NSAID vs placebo (43,482 participants, 0.46 years) and 149 comparisons of a coxib vs traditional NSAID (137,466 participants, mean follow-up 0.95 years).

Compared to placebo, allocation to a coxib increased the risk of MVEs (rate ratio 1.38, 95% CI 1.14-1.66), vascular mortality (1.58, 1.11-2.24) and UGICs (1.81, 1.17-2.81). Overall, in the population studied, coxibs were associated with three additional major vascular events (one fatal) and two (rarely fatal) upper gastrointestinal complications per 1000 person-years exposure. There was no evidence of heterogeneity by duration of follow-up, coxib type, dose (other than for celecoxib), or patient characteristics, for the primary outcomes.

The risk of MVEs for traditional NSAIDs without antiplatelet activity (mostly diclofenac 75mg bd or ibuprofen 800mg tds) were comparable to coxibs (1.40, 1.15-1.72); but the risk of UGICs (1.98, 1.39-2.84) was significantly greater. For traditional NSAIDs with antiplatelet activity (mostly naproxen 500mg bd) there were no significant excess of MVEs (0.84, 0.66-1.08), but UGICs were substantially increased (4.06, 2.85-5.78). Both coxibs and traditional NSAIDs increased risk of hospitalisation for heart failure by about two-fold.

Interpretation: The vascular and upper gastrointestinal risks of coxibs and high-dose tNSAID regimens can be predicted, allowing the choice of analgesia to be tailored for particular patients.

Word count: 300 words

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- 1.3 Upper gastrointestinal effects of traditional NSAIDs
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1.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs, usually abbreviated to NSAIDs, are drugs with analgesic (pain-reducing) and antipyretic (fever-reducing) effects and which have, in higher doses, prostaglandin-mediated anti-inflammatory effects. (Burke, Smythe, & FitzGerald 2005) The term "non-steroidal" is used to distinguish these drugs from steroids, which, amongst other effects, also have an anti-inflammatory action.

NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. NSAIDs are generally prescribed for the symptomatic relief of long-term rheumatological conditions, e.g., osteoarthritis, rheumatoid arthritis, and inflammatory arthropathies (e.g., ankylosing spondylitis). NSAIDs are also used in shorter courses for acute conditions, for example, gout, dysmenorrhoea (menstrual pain), headache, migraine, postoperatively and in mild-to-moderate pain (eg, due to a sports injury). Furthermore, as well as being used in analgesia for cancer-related pain, research continues into the potential use for NSAIDs in the prevention and treatment of neoplasia itself, especially for colorectal adenomas (polyps), the predominant precursors of colorectal carcinoma.

In comparison to opioid-based analgesic treatments, traditional NSAIDs differ as analgesics in that they are non-narcotic. The most commonly prescribed NSAIDs, which were developed in the 1960s and 1970s (and are often labelled as 'traditional NSAIDs'), were diclofenac, ibuprofen, and naproxen. These traditional NSAIDs are available as prescribed medications for long-term conditions throughout the world, and some are also accessible without prescription ('over-the-counter') in many countries (such as the United Kingdom). Table 1.1 lists the pharmacological features of some commonly used traditional NSAIDs. (Burke, Smythe, & FitzGerald 2005)

Aspirin, the only NSAID able to irreversibly inhibit COX-1 (by acetylating a serine residue), inhibits thromboxane A₂ production, which leads to reduced platelet aggregation. Due to these antiplatelet properties, aspirin is now used predominantly in the management of occlusive vascular disease rather than as a long-term analgesic *per se*. Hence, due to the different indication for which it is used, and the fact it has

been extensively studied in previous meta-analyses, its direct comparisons are outwith the remit of this thesis. (Antithrombotic Trialists' (ATT) Collaboration 2002; Baigent et al. 2009)

Aspirin aside, the prescribing costs of other oral traditional NSAID were around £30 million per year in the period from 2003 to 2008 in the United Kingdom, which corresponds to more than 4.5 million items per year. (NHS Business Services Authority 2008) Diclofenac was the most commonly prescribed NSAID, accounting for 44% of all such prescriptions, with ibuprofen accounting for 25% and naproxen accounting for 10%. These numbers substantially underestimate the actual use of NSAIDs, because they do not account for over-the-counter medications (eg, of diclofenac and ibuprofen, which are both available in the UK).

Despite being widely used throughout the world, traditional NSAIDs have a number of adverse events associated with their use. Although traditional NSAIDs can have effects on the lower gastrointestinal (GI) tract, the most common effects are those of the upper GI tract, specifically of the stomach and duodenum. Traditional NSAIDs can cause peptic ulcer disease, which leads to a spectrum of clinical issues ranging from upper GI symptoms (eg, dyspepsia and heartburn) to potentially life-threatening complications (eg, bleeding of the upper GI tract).

1.2 Cyclo-oxygenase (COX) inhibition

Most traditional NSAIDs act as non-selective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. COX, also known as prostaglandin G/H synthase, is the key enzyme in prostaglandin biosynthesis, and catalyzes the first step in the formation of prostaglandins and thromboxane from arachidonic acid (released from the cellular phospholipid bilayer by the action of phospholipase A₂). Prostaglandins act (among other roles) as messenger molecules in the process of inflammation. (Burke, Smythe, & FitzGerald 2005) A schematic for COX-related activity is shown in Figure 1.1.

In terms of their molecular biology, COX-1 and COX-2 are of similar molecular weight, approximately 70 and 72 kDa, respectively, and have near-identical catalytic sites and approximately 65% of the same amino acid sequences. (FitzGerald & Patrono 2001) Both COX isoenzymes are differentially regulated by relevant cytokines and growth factors, which affect their regulation of expression and tissue distribution. The key structural difference between the isoenzymes is that the substitution of isoleucine at position 523 in COX-1 with valine in COX-2 means that a hydrophobic side-pocket in the COX-2 enzyme is exposed. The key mechanistic difference is the predominantly homeostatic (constitutive) role played by the COX-1 isoenzyme, as compared to the predominantly inflammation-mediated (inducible) role of the COX-2 isoenzyme.

COX-1 promotes the production of the natural mucus lining that protects the inner stomach, contributing to reduced acid secretion and reduced pepsin content. (FitzGerald & Patrono 2001) COX-1 is normally constitutively present in a variety of other tissues of the body, including platelets. (Rocca et al. 1999; Smith et al. 1997) In contrast, the synthesis of COX-2 is normally inducible following an inflammatory or mitogenic stimulus (but it is also constitutively expressed in some tissues, e.g., the kidney and brain). COX-2 becomes abundant in activated macrophages and other cells at sites of inflammation: expression of COX-2 has also been shown to be up-regulated in various cancers (eg, colorectal carcinoma). (Mann et al. 2001) From these findings, COX-2 has been hypothesised to be pathophysiologically relevant for such cancers.

1.3 Upper gastrointestinal effects of traditional NSAIDs

Peptic ulcer disease is a pathophysiological condition in which an ulcer (often defined as mucosal erosions equal to or greater than 5 millimetres) of the upper gastrointestinal (GI) tract occurs. (Malfertheiner, Chan, & McColl 2009) Symptoms of a peptic ulcer can be: (i) epigastric abdominal pain, classically with severity relating to mealtimes; (ii) bloating and abdominal fullness; (iii) nausea, and copious vomiting; or (iv) loss of appetite and weight loss. The identification of an uncomplicated ulcer can also be made by upper GI endoscopy in the absence of overt symptoms. Peptic ulcers

arise in the gastric antrum (body of the stomach) and in the duodenum (first part of the small intestine or just after the stomach). Ulcers are often associated with (and caused by) infection by *Helicobacter pylori*, a Gram-negative spiral-shaped bacterium that is well adapted to the acidic environment of the stomach. NSAIDs are another important cause of ulcers due to their effects on prostaglandins, secondary to COX-1 inhibition.

The gastric mucosa protects itself from hydrochloric acid (released from the parietal cells) with a layer of mucus, the secretion of which is stimulated by certain prostaglandins. NSAIDs cause a dual insult on the upper GI tract: the acidic molecules directly irritate the gastric mucosa, and the inhibition of COX-1 and COX-2 reduces the levels of protective prostaglandins. (Burke, Smythe, & FitzGerald 2005) Inhibition of prostaglandin synthesis in the upper GI tract causes increased gastric acid secretion, diminished bicarbonate secretion, diminished mucus secretion and diminished trophic effects on epithelial mucosa. By blocking COX-1 activity, which is essential for the production of the cytoprotective mucosal prostaglandin E₂, traditional NSAIDs can induce peptic ulceration. Hence, it was postulated that NSAIDs, which had more of a sparing effect on COX-1 inhibition, might cause less peptic ulceration.

Whilst uncomplicated symptomatic ulcers are common and can be managed relatively easily, upper GI complications are a more serious clinical concern. The most frequent complication is upper GI bleeding, which occurs when the ulcer erodes one of the blood vessels, such as the gastroduodenal artery, and can be potentially life-threatening. Bleeding can present with melaena (tarry, foul-smelling faeces due to oxidised iron from haemoglobin) or haematemesis (vomiting of blood).

Other complications include 'perforation', when an ulcer creates a hole in the wall of the stomach, which can cause a spillage of stomach contents into the abdominal cavity, presenting clinically as acute peritonitis. Scarring and swelling caused by ulcers can also cause 'obstruction', or narrowing in the duodenum and gastric outlet, which can present clinically with persistent vomiting. Both of these ulcer complications may require surgical treatment, as would bleeding in some cases.

In the United Kingdom, the incidence of peptic ulcers has declined dramatically during the last 30 years, partly due to a lower incidence of *H. pylori* infection because of improved standards of living. (Malfertheiner, Chan, & McColl 2009) Since the 1980s, the development and widespread use of gastroprotectant therapies (eg, proton pump inhibitors and histamine-2 receptor antagonists) have also contributed to this substantial decline in peptic ulcer disease. However, in both developed and emerging economies, ageing populations already contribute to a large and increasing global burden of arthritides and other musculoskeletal conditions that require analgesia. (Bijlsma, Berenbaum, & Lafeber 2011) Therefore, even with increasing gastroprotectant therapy use and the diminishing incidence of *H. pylori*, a greater proportion of upper GI ulcers are likely to be caused by analgesic NSAID use.

1.4 Coxibs or “selective inhibitors of the COX-2 enzyme”

Historically, the main adverse drug reactions associated with traditional NSAIDs were thought to be upper GI events, mediated predominantly by inhibition of COX-1. Hence, it was hypothesised that pharmaceutical compounds which had more of an effect on inhibition of COX-2 (which does not play a major role in protecting the gastric mucosa) might result in a reduced risk of upper GI ulcers compared to traditional NSAIDs. (FitzGerald & Patrono 2001) As such drugs would also be expected to maintain equivalent anti-inflammatory (and analgesic) efficacy to traditional NSAIDs, this was the driver for the intensive pharmaceutical development of selective COX-2 inhibitors soon after the COX-2 enzyme was discovered in 1988. (Hawkey 2005)

Although these drugs which selectively inhibit COX-2 came to be known as ‘coxibs’ (which is the terminology that will be used for the remainder of this thesis), it is important to note that a better description would have been COX-1 sparing NSAIDs, as traditional NSAIDs also mediate their anti-inflammatory effects by inhibiting COX-2. (Vane & Warner 2000) A schematic for the different effects of coxibs and traditional NSAIDs on a particular inflammatory mediator, prostaglandin E₂ is shown in Figure 1.2 and the structures of some coxibs are shown in Figure 1.2. Coxibs achieve sufficient

brain concentrations to have a central analgesic effect, but, as they are distributed widely throughout the body, they also act peripherally by reducing prostaglandin formation in inflamed joints. (Burke, Smythe, & FitzGerald 2005) Estimates of peak concentration and half-lives do, however, differ between the coxibs, as presented in Table 1.2. Moreover, as COX-2 selectivity of different drug regimens is a continuous variable, there is some overlap between coxibs and traditional NSAIDs.

1.5 Upper gastrointestinal effects of coxibs

Ever since their discovery in the 1960's, traditional NSAIDs were evaluated in randomised controlled trials (typically of tens or hundreds of patients followed up for weeks or months), particularly to assess their upper gastrointestinal effects. As many of these trials were traditional NSAID versus other traditional NSAID comparisons designed to assess similar efficacy, only small sample sizes were required to detect differences. Moreover, the magnitude of upper gastrointestinal effects meant that other study designs such as case-control studies were able to detect differences. (Langman et al. 1994)

Unlike the traditional NSAIDs that preceded them, however, coxibs required reliable evaluation in larger randomised trials (ideally of thousands of participants followed up for many months or years). This was important for both clinical and scientific evidence but also as a part of pharmaceutical regulatory approval of coxibs. Moreover, in the context of similar efficacy of coxibs and traditional NSAIDs, the hypothesis of a safety benefit in upper GI effects was one of the main aims of these randomised trials: the detection of moderate differences between coxibs and traditional NSAIDs required randomisation of more patients (thousands rather than hundreds) followed up for longer (many months/years rather than weeks/months).

Celecoxib was the first selective COX-2 inhibitor marketed to treat patients with arthritis, and was first evaluated in the Celecoxib Long-term Arthritis Safety Study (CLASS) trial (versus the traditional NSAIDs ibuprofen and diclofenac). (Silverstein et al.

2000) A total of 8053 patients with osteoarthritis or rheumatoid arthritis were randomly assigned to receive celecoxib 400 mg twice per day, ibuprofen 800 mg three times per day, or diclofenac 75 mg twice per day. The main outcome measures were the incidence of prospectively defined symptomatic upper GI ulcers and ulcer complications (bleeding, perforation, and obstruction) and other adverse effects. The annualized incidence rates of upper GI ulcer complications combined with symptomatic ulcers were 2.08% for those allocated celecoxib versus 3.54% for those allocated traditional NSAIDs ($P=0.02$).

Rofecoxib was the second selective COX-2 inhibitor to be marketed, and was assessed in the Vioxx in Gastrointestinal Outcomes Research (VIGOR) trial in which 8076 rheumatoid arthritis patients were randomly assigned to receive either 50 mg of rofecoxib daily or 500 mg of naproxen twice daily, with similar efficacy between the two drugs. (Bombardier et al. 2000) The primary end point was confirmed clinical upper GI events (gastroduodenal perforation or obstruction, upper GI bleeding, and symptomatic gastroduodenal ulcers). During a median follow-up of 9.0 months, 2.1 confirmed GI events per 100 patient-years occurred with rofecoxib, as compared with 4.5 confirmed GI events per 100 patient-years with naproxen (relative risk [RR], 0.5; 95 percent confidence interval [CI], 0.3 to 0.6; $P<0.001$).

1.6 The hypothesis of vascular effects associated with rofecoxib generated in the VIGOR study

Larger randomised trials such as CLASS and VIGOR were important in proving that, compared to traditional NSAIDs, both celecoxib and rofecoxib were associated with a lower risk of upper GI events, particularly complications. This evidence base was a key reason for the widespread prescription of these coxibs in preference to older traditional NSAIDs for arthritis patients at the start of the 21st century. (Juni 2002) However, although it was primarily designed to assess upper GI effects, the VIGOR study (involving 8,076 rheumatoid arthritis patients), showed, unexpectedly, that those allocated to receive a daily dose of 50 mg of rofecoxib experienced a higher risk

of major vascular events than those allocated to receive 500 mg of naproxen twice daily. This excess of major vascular events was almost entirely accounted for by a difference in the incidence of myocardial infarction (20 events among patients allocated rofecoxib versus 4 among patients allocated naproxen; RR 5.00, 95% CI 1.72–14.29). (Bombardier et al. 2006)

A number of mechanistic explanations have been proposed for this observed excess (Baigent & Patrono 2003; FitzGerald & Patrono 2001): (i) persistent antiplatelet activity of naproxen and other NSAIDs; (ii) prothrombotic alteration of the prostacyclin/thromboxane ratio; (iii) cardiorenal effects on prostaglandins affecting blood pressure; (iv) other considerations, including the role of random error. These are considered in further detail below:

1.6.1 The persistent antiplatelet activity of naproxen and other NSAIDs

When used in doses of 500 mg twice daily (as used in VIGOR), naproxen – which inhibits COX-1 and has a relatively long half-life (~14 hours) - inhibits more than 90% of platelet thromboxane A₂ (TXA₂) production throughout its dosing interval. (Capone et al. 2004) Since naproxen may have antiplatelet activity similar to that of low-dose aspirin, it was suggested that naproxen might reduce myocardial infarction by up to one-fifth compared to the effects of rofecoxib. (Baigent and Patrono 2003) However, prior to the VIGOR study, there were only small randomised trials directly assessing the effects of naproxen on myocardial infarction and other vascular events. It is unlikely that an antiplatelet effect alone could explain the five-fold relative difference in risk of myocardial infarction (20 versus 4 events) reported in the VIGOR trial, even allowing for statistical imprecision. Taking this finding into account along with the pharmacological evidence that the inhibition of TXA₂ by naproxen is not as consistent as that of low-dose aspirin, the overall effects on major vascular events of traditional NSAIDs such as naproxen (and other NSAIDs with similar effects on platelet TXA₂ [eg, flurbiprofen and indobufen]) could be neutral rather than protective *per se*. (Baigent & Patrono 2003; Brochier 1993; Fornaro et al. 1993)

1.6.2 Prothrombotic alteration of the prostacyclin/thromboxane ratio

The platelet-aggregating and vasoconstricting actions of thromboxane A₂ (TXA₂) are antagonised by prostacyclin, which is a platelet anti-aggregant and vasodilator. Since naproxen inhibits the synthesis of both TXA₂ and prostacyclin, but rofecoxib inhibits the synthesis of COX-2–dependent prostacyclin only, it was suggested that rofecoxib might cause arterial thrombosis because of an accumulation of unopposed TXA₂ (which is prothrombotic) at the platelet–vascular endothelial interface, thus favouring occlusive thrombus formation. (FitzGerald, Cheng, & Austin 2001) Therefore, alteration of the homeostatic balance of endothelial prostacyclin and platelet-derived TXA₂ by rofecoxib (and other coxibs) by means of unopposed COX-2 inhibition was hypothesised to explain the higher risk of myocardial infarction among patients on coxibs in the VIGOR study.

1.6.3 Cardiorenal effects on prostaglandins affecting blood pressure

Through their effects on renal prostaglandins, traditional NSAIDs and coxibs both induce an increase in blood pressure, which is another important risk factor for vascular outcomes. (FitzGerald & Patrono 2001) Moreover, results from the VIGOR study showed that participants assigned to rofecoxib had a mean increase in the systolic blood pressure of 3.6 mmHg in comparison with those assigned naproxen, and this was maintained for just under one year. (Bombardier et al. 2000) Extrapolation from the available epidemiologic evidence in the Prospective Studies Collaboration meta-analyses, (Lewington et al. 2002) suggests that this increment in blood pressure would cause around a 10% higher risk of myocardial infarction, and around a 20% increased risk of stroke and congestive heart failure for rofecoxib versus naproxen in the VIGOR study.

1.6.4 Other considerations, including the role of random error

Other factors may also play a role in explaining the vascular findings of the VIGOR study. For example, the daily dose of the coxib or traditional NSAID also determines the extent of COX-2 inhibition, which is pertinent when supratherapeutic doses were

used. Compare, for example, the 50mg dose of rofecoxib used in VIGOR with the smaller licensed doses at the time (Table 1.4). Other potential pharmacological variables contributing to different COX-2–dependent effects would include the half-life and dosing interval of the drug. Moreover, as the vascular results were not a primary outcome of the VIGOR study, they need to be interpreted with a degree of caution. Although the randomised trial design of VIGOR would be able to avoid significant biases, the relative risk (RR = 5.00) estimate is still imprecise, as is indicated by the wide confidence intervals (95% CI 1.72-14.29).

Hence, although the mechanistic causes of the excess vascular risk of rofecoxib could not be fully established by the experimental design of the VIGOR study, a combination of the persistent antiplatelet activity of naproxen, a prothrombotic COX-2 dependent effect of rofecoxib, a cardiorenal prostaglandin-mediated effect, as well as the role of the play of chance, could all be contributory factors.

1.7 Placebo-controlled randomised trials which tested the hypothesis of coxibs causing vascular effects

Although the VIGOR result generated the hypothesis of rofecoxib being associated with an increased risk of major vascular events versus naproxen, such an effect cannot be reliably assessed in a direct comparison of a coxib versus a traditional NSAID, because traditional NSAIDs may have unrecognised vascular effects themselves. Hence, in order to test the hypothesis of vascular effects of rofecoxib, the necessary experimental study design would be a large randomised trial of rofecoxib versus placebo. However, in the context of pain management, such a placebo-controlled trial would not be appropriate, since arthritis patients require some type of analgesia.

As it happens, however, such placebo-controlled trials were conducted, because cyclo-oxygenase-2 activity was hypothesised to have a role in cancer prevention, particularly on the adenoma-carcinoma sequence in the large bowel. (Mann et al. 2001) On this premise, long-term randomised trials of rofecoxib and celecoxib versus placebo were

undertaken to evaluate the effect of COX-2 inhibition among people with colorectal polyps. (Bresalier et al. 2005) By serendipity, these relatively large coxib versus placebo trials involved the appropriate experimental design to test whether coxibs themselves were associated with increased vascular hazards.

The results of the first of these trials, the adenomatous polyp prevention on Vioxx (APPROVe) trial, indicated that rofecoxib increased the risk of major vascular events (myocardial infarction, strokes and vascular death) by about twofold in 2586 participants with colonic polyps. (Bresalier et al. 2005) A total of 46 patients in the rofecoxib group had a confirmed thrombotic event compared with 26 patients in the placebo group, with a corresponding relative risk of 1.92 (95% CI 1.19 to 3.11; $P=0.008$). These results primarily reflected a greater number of myocardial infarctions and ischaemic cerebrovascular events in the rofecoxib group. The results of the APPROVe trial, reported in September 2004, confirmed that rofecoxib had a role in causing moderate vascular harms, particularly on coronary events, effectively confirming the hypothesis-generating VIGOR study result. This led to the worldwide withdrawal of rofecoxib from the marketplace by its pharmaceutical sponsor Merck on 30th September 2004.

Soon afterwards, similar findings for major vascular events were reported in placebo-controlled trials involving the other first-generation coxib (celecoxib). In the adenoma prevention with celecoxib (APC) trial, 2035 patients with a history of colorectal neoplasia were randomised to either two doses of celecoxib or placebo. Compared to placebo, a composite vascular endpoint was 2.3-fold higher in those receiving 200 mg of celecoxib twice daily (95% CI, 0.9 to 5.5) and 3.4-fold higher in those receiving 400 mg of celecoxib twice daily (95% CI, 1.4 to 7.8). At about the same time, the results of the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trials in 1561 patients with colonic polyps also supported the findings of a moderate vascular effect of celecoxib 400 mg daily versus placebo (RR 1.3; 95% CI 0.7 to 2.6). (Arber et al. 2006; Bertagnolli et al. 2006) In view of the reports of the vascular hazards associated with rofecoxib from VIGOR and APPROVe, the APC and PreSAP data provided evidence that coxibs might increase the risk of major vascular events as a class effect.

1.8 Other randomised trials of coxibs versus traditional NSAIDs which focused on the vascular and upper gastrointestinal effects

Due to the concerns about vascular risks, other ongoing rofecoxib and celecoxib versus placebo trials were closely monitored for vascular events or stopped early, eg, the ADAPT, VICTOR and VIP trials. (Kerr et al. 2007; Lyketsos et al. 2007; van Adelsberg et al. 2007) Moreover, as a consequence of the knowledge generated about atherothrombotic effects from VIGOR, subsequent large randomised trials comparing coxibs and traditional NSAIDs, the majority of which were for arthritis, assessed vascular as well as upper gastrointestinal effects (eg, the ADVANTAGE and SUCCESS trials). (Lisse et al. 2003; Singh et al. 2006)

As well as rofecoxib and celecoxib, other coxibs developed were also evaluated in randomised trials, particularly related to vascular as well as upper gastrointestinal safety. Lumiracoxib, a second-generation coxib, was assessed (versus ibuprofen and naproxen) in the TARGET study. (Farkouh et al. 2004; Schnitzer et al. 2004) Parecoxib is a water-soluble inactive prodrug of valdecoxib, a second-generation coxib, although no long-term large trials of this drug have been conducted. An experimental compound called GW403681 was developed and tested in a few randomised trials, but has never been formally approved for use. Etoricoxib is the most recent coxib developed and marketed, and has undergone evaluation (versus diclofenac) in the MEDAL programme, which is the largest coxib trial programme to date. (Cannon et al. 2006; Laine et al. 2007) The characteristics of several of the large coxib trials mentioned, comprising thousands of patients followed up for months, are shown in Table 1.3.

1.9 Persisting uncertainties about the effects of traditional NSAIDs as well as coxibs

The unexpected finding of an increased risk of vascular disease caused by coxibs, also marked a watershed in concerns about the reporting of adverse events in drug trials.

The concern about vascular risks with coxibs, which were by now widely used therapies throughout the world, affected the regulatory authorities, clinicians (via the medical press) and patients (via the popular press). Coxibs, initially hailed as a pharmaceutical breakthrough, were now treated with considerable suspicion: this led to many members of the public being 'switched over' from coxibs to older traditional NSAIDs, either of their own volition or that of their prescribing clinician. (Sukel et al. 2008)

In light of the results of large randomised trials (eg, VIGOR, APPROVe and APC) and the subsequent withdrawal of rofecoxib, there was considerable public and professional uncertainty about the extent of any vascular hazards of coxibs for individual patients. These concerns applied particularly to those who required continued pain relief, such as those with chronic rheumatological conditions (eg, arthritis). This was at least partly due to a lack of understanding by clinicians about putting the relative risks of the different coxibs on the relevant vascular and upper gastrointestinal events in the context of the absolute risk of the individual patient.

Some coxibs (eg, celecoxib and etoricoxib in the UK) still remain on the market, particularly for patients with rheumatological indications. Although many patients previously on coxibs were switched over to traditional NSAIDs, these drugs have not undergone the same rigor of evaluation in large randomised trials. Moreover, despite this paucity of evidence, traditional NSAIDs (both with and without antiplatelet activity) are still amongst the most widely used medical therapies, particularly for arthritis and analgesia.

Hence, although much of the controversy relates to the hypotheses of vascular effects of coxibs (unexpectedly generated in the VIGOR study), both coxibs and traditional NSAIDs require evaluation to understand their role in mediating both vascular and upper gastrointestinal outcomes. Putting these iatrogenic hazards into context has clinical implications in therapeutic management for the individual patient, and, given the widespread use of these medications, resultant effects on the health of the wider population.

Figure 1.1: Schematic of the effects of coxibs and traditional NSAIDs on prostaglandin E₂

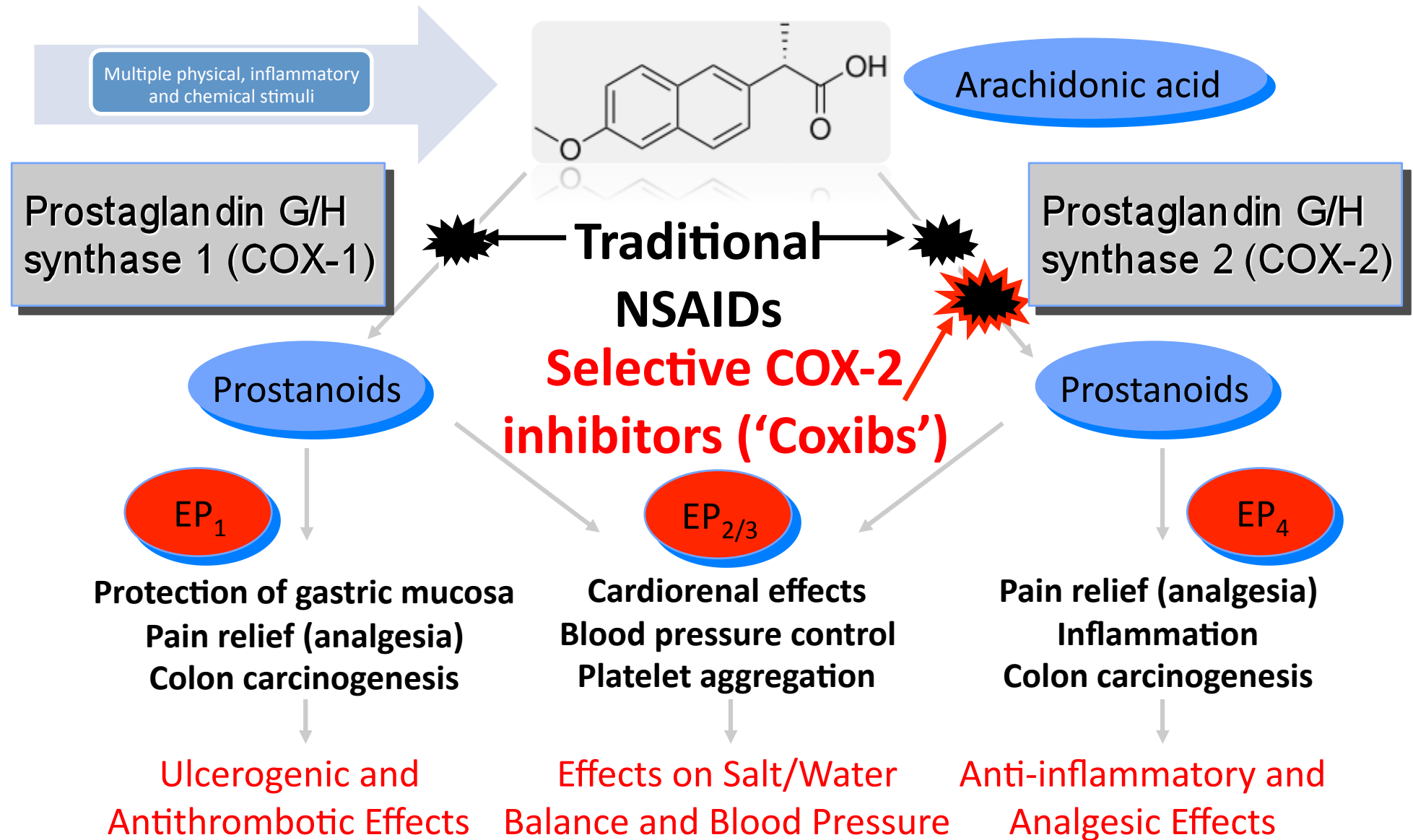
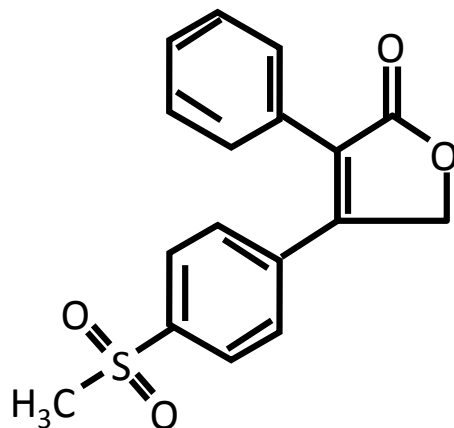


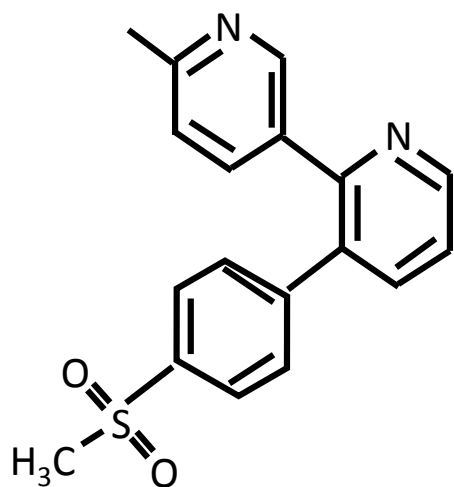
Figure 1.2 Selective inhibitors of cyclo-oxygenase-2 (coxibs) , by drug class

Methyl Sulphones

Rofecoxib

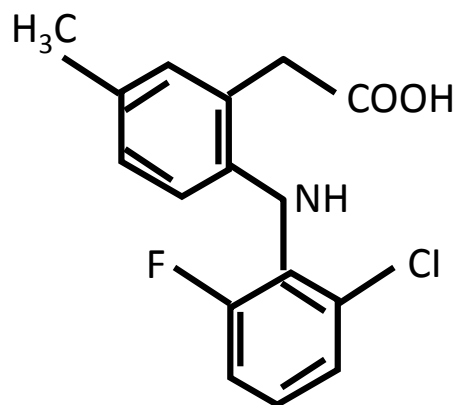


Etoricoxib



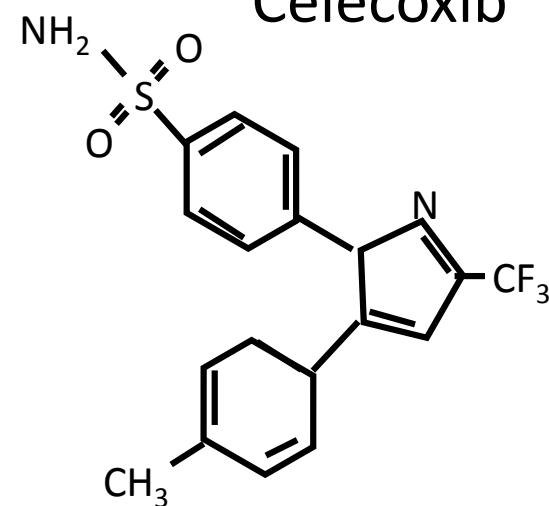
Carboxylic Acid

Lumiracoxib

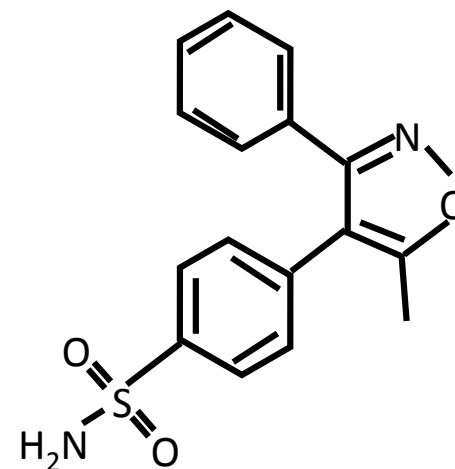


Sulphonamides

Celecoxib



Valdecoxib



CHAPTER 2: Rationale for a meta-analysis of individual participant data from randomised trials

- 2.1 The advantages of a meta-analysis of randomised trials to evaluate the available evidence
- 2.2 The tabular meta-analysis of randomised trials of coxibs and traditional NSAIDs to evaluate effects on major vascular events
- 2.3 Outstanding questions relevant to coxibs and traditional NSAIDs
- 2.4 The need for an updated collaborative meta-analysis of individual participant data

TABLES

Table 2.1 Requirements for reliable assessment of moderate effects when conducting meta-analyses of randomised trials

Table 2.2 Summary of the tabular meta-analysis of randomised trials assessing the effects of coxibs (and traditional NSAIDs on major vascular events)

Table 2.3 Outstanding questions relevant to coxibs and traditional NSAIDs (and how they can be explored reliably using meta-analysis of individual participant data)

2.1 The advantages of a meta-analysis of randomised trials to evaluate the available evidence

The simplest measure to evaluate the effects of a medication is if a single very large (mega) randomised trial, ideally involving tens of thousands of participants, is carried out. However, when many smaller randomised trials have been conducted which have all addressed much the same question, the traditional scenario that only a few of these becoming widely known may be a source of serious bias. For example, smaller trials, usually with larger effect sizes, may become well known and widely cited, but these results could be heavily influenced by random error.

In order to evaluate the evidence from randomised trials as thoroughly as possible, a quantitative overview of all the available evidence is required. Meta-analysis is a method that uses statistical techniques for systematically combining results from different studies of the same type, in order to obtain a quantitative estimate of the overall relative and absolute effects of a particular intervention on a defined outcome. (Collins and MacMahon 2000)

Meta-analyses can minimise random errors in the assessment of treatment since, in general, far more patients are involved in a meta-analysis than in any contributing individual trial (see Table 2.1). (Baigent et al. 2010) It also avoids the bias of selective emphasis on the results of particular trials, as inference is based chiefly on the results from all of the available trials that have addressed a particular type of question (or at least an unbiased subset of such trials), and not on some potentially biased subset of these trials. Moreover, collecting information from unpublished trials can avoid selective emphasis on published data alone (publication bias). As well as providing statistically reliable results, providing adequate data exists, meta-analyses can also help generate future research questions by providing an estimate of the variation (heterogeneity), for example, when contradictory results exist.

As well as those larger randomised trials of coxibs mentioned in Chapter 1, many smaller trials assessing the clinical outcomes for coxibs have been carried out. Moreover, in addition to comparisons involving a coxib, many hundreds of small short-

term trials, which evaluated traditional NSAIDs alone have also been conducted for clinical outcomes. Evidence from these smaller randomised trials also need to be incorporated when conducting a meta-analysis to reliably evaluate the effects of both coxibs and traditional NSAIDs.

Rather than simply pooling the data into one group, in order to demonstrate the quantitative strength of the evidence, contributing studies are organised into types of comparisons (eg, organising trials into coxib versus placebo or traditional NSAID versus placebo). This systematic approach is of specific importance when considering the comparisons of coxibs versus traditional NSAIDs with and without antiplatelet activity, making a meta-analysis of all the randomised evidence a valuable methodology for the evaluation of the effects of both coxibs and traditional NSAIDs.

2.2 The tabular meta-analysis of randomised trials of coxibs and traditional NSAIDs to evaluate effects on major vascular events

In order to assess the effects of coxibs and traditional NSAIDs on the risk of occlusive vascular events, colleagues at the Clinical Trial Service Unit conducted a tabular meta-analysis of all the published and unpublished randomised studies carried out up to 2005. (Kearney et al. 2006) Studies that were eligible to be included were randomised trials that included a comparison of a coxib versus placebo or a coxib versus a traditional NSAID, of at least four weeks' duration, with information on major vascular events (defined as myocardial infarction, stroke, or vascular death). Individual investigators and manufacturers provided information on the number of patients randomised, numbers of vascular events, and the person time of follow-up for each randomised group. In all, data from 138 randomised trials reporting up to 2005 were analysed, comprising around 145,000 participants.

In comparison to placebo, allocation to a coxib was associated with a 42% relative increase in the incidence of major vascular events (1.2% per year vs 0.9% per year; rate ratio 1.42, 95% CI 1.13 to 1.78; $P = 0.003$), with no significant heterogeneity among the various types of coxibs. This was chiefly attributable to an increased risk of

myocardial infarction (0.6% per year vs 0.3% per year; RR 1.86, 1.33 to 2.59; $P = 0.0003$), with little difference between coxib and placebo in other major vascular outcomes.

Overall, the incidence of major vascular events was similar, among those allocated to a coxib or any traditional NSAID, with no good evidence of a difference (1.0%/year v 0.9%/year; RR 1.16, 0.97 to 1.38; $P = 0.1$). However, due to the known persistent antiplatelet activity of naproxen from pharmacological studies, it was pre-specified to test effects separately from other traditional NSAIDs. There was strong evidence of heterogeneity ($P = 0.001$) found between trials of a coxib versus naproxen (RR 1.57, 1.21 to 2.03) and of a coxib versus non-naproxen NSAIDs (RR 0.88, 0.69 to 1.12).

Due to the paucity of larger longer-term randomised trials involving a comparison of traditional NSAIDs versus placebo, reliable direct estimates of the effects of traditional NSAIDs were not available. However, by utilising the available larger evidence from comparisons involving a coxib, indirect comparisons (using both the coxib versus placebo and coxib versus traditional NSAID comparisons) were possible to estimate the effects of traditional NSAIDs. The summary rate ratio for major vascular events, for naproxen compared with placebo, was 0.92 (0.67 to 1.26), implying a neutral effect. Corresponding summary rate ratios versus placebo were 1.51 (0.96 to 2.37) for ibuprofen and 1.63 (1.12 to 2.37) for diclofenac respectively, suggesting a similar increase for major vascular effects for these traditional NSAIDs as coxibs (Table 2.2).

Results from this large tabular meta-analysis confirmed that coxibs were associated with a moderate increase in the risk of major vascular events (predominantly myocardial infarction). In addition, they suggested that some high-dose regimens of traditional NSAIDs (eg, ibuprofen and diclofenac) might be associated with similar vascular risks, but that naproxen, likely due to its antiplatelet activity, was not associated with such an excess.

2.3 Outstanding questions relevant to coxibs and traditional NSAIDs

There were some advantages of incorporating more recently completed randomised trials since the tabular meta-analysis reported in 2006. For example, there have been multiple large randomised studies published, including the largest coxib trials to date, the MEDAL programme of etoricoxib versus diclofenac. (Cannon et al. 2006) In addition, trials of traditional NSAIDs alone (of which there are many, albeit these studies are much smaller and of shorter duration, so there is less corresponding evidence) were not formally evaluated in the previous tabular meta-analysis.

1. An updated study would be able to provide **more accurate estimates of major vascular events** (eg, more detailed information on stroke subtypes and other vascular complications, eg, heart failure) for both coxibs and traditional NSAIDs.
2. Moreover, an updated study would also provide **reliable estimates of the risk of outcomes such as upper GI complications and other ulcer events** for both coxibs and traditional NSAIDs.

Although the tabular meta-analysis has been widely used by regulatory authorities in informing treatment choices for the public, there are several outstanding important questions relevant to coxibs and traditional NSAIDs:

1. Given that initial analyses from the APPROVe trial of rofecoxib versus placebo raised the hypothesis that coxibs may have a latent effect on vascular events, (Bresalier et al. 2005) **do hazards occur soon** after drug initiation, or do they only occur with prolonged exposure?
2. In particular, do these analyses support the hypothesis, first raised by the Cross Trial Safety Assessment Group in celecoxib versus placebo trials, (Solomon et al. 2008b) that there is a trend towards larger **proportional increases in risk** with higher dose and higher baseline risk of major vascular events (and, in addition, do similar proportional increases also apply to upper GI ulcers)?

3. Do the **proportional effects** on vascular events and upper GI complications **vary** amongst patient subgroups, for example **by clinically important factors** such as age, gender, aspirin use etc.? Strong evidence of such heterogeneity in subgroups would be clinically relevant; moreover, if it existed, this would also have implications for predicting absolute risks of coxibs and traditional NSAIDs on primary outcomes.

(Conversely, if there is no strong evidence of heterogeneity for multiple subgroups, proportional and absolute effects are likely to be more reliable for different patients. As no overt heterogeneity was anticipated, no subgroup analyses were pre-specified *per se* to have a positive or negative effect, with the exception of *a-priori* differences in the effects of coxibs and traditional NSAIDs, with and without antiplatelet activity).

4. Although **risk factors** that underlie vascular disease are well established, those determinants most relevant to the risk of NSAID-induced upper GI disease are not as well understood, so using analyses of detailed data can help assess this.

5. Finally, what are the **balance of benefits and risks** of different coxibs and traditional NSAIDs in terms of absolute effects on major vascular and upper GI events among different types of patients?

2.4 The need for an updated collaborative meta-analysis of individual participant data

Tabular meta-analysis does, however, have methodological shortcomings that limit its reliability to assess the outstanding questions listed above. For example, by using aggregated (summary) data from each trial, a tabular meta-analysis does not allow reliable assessment of whether the proportional effects of treatment differ among prognostic subgroups of individuals (for example, absolute risks of both vascular and upper gastrointestinal events differ substantially between a younger person with no co-morbidity and an older person with multiple co-morbidities).

Hence, for both vascular and upper gastrointestinal events, the effects of factors such as age, gender, baseline absolute risk and concomitant aspirin use cannot be assessed reliably in a tabular meta-analysis. In addition, analyses of summary data in tabular meta-analyses cannot reliably assess the temporal relationship of therapies (for example, is there good evidence of a latent period after which effects occur).

Rather than utilising tabular data from the randomised trials alone, conducting meta-analysis including individual participant data would have distinct methodological advantages in order to reliably assess these outstanding questions. Incorporating evidence to the level of detail of the randomised individual allows better standardisation and harmonisation of information, including the baseline characteristics of participants for appropriate categorisation. Detailed data-checking of outcomes can be verified against the results presented in the trial publications or study reports (eg, ensuring the quality of follow-up and randomisation). As well as standardisation of analyses (eg, 'intention-to-treat'), a particular strength of individual participant data meta-analysis is reliable assessment of time-to-event analyses. Robust evaluation of any proposed time-to-event (latent interval) and dose response effects have important clinical and biological implications for these medications.

The most important benefits of obtaining this patient-level of detail are the ability to understand, by placing results in context, variability in the effects of different drugs. For example, meta-analyses incorporating individual participant data can evaluate in more detail the effects of individual baseline characteristics at randomisation (eg, the age of the participant and whether they took concomitant aspirin). Moreover, the detailed analyses allow the ability to develop judgements about the balance of benefits and risks for particular drug regimens used in different populations. Hence, an updated meta-analysis with more detail (ie, collecting data on each individual participant themselves in the trials) would be substantially more informative than simply expanding the tabular data.

In order to collect detailed reliable evidence to explore these questions, the pharmaceutical sponsors of coxib trials and their investigators agreed to provide data on individual participants to facilitate a meta-analysis of all such randomised studies.

This collaboration of randomised trials, guided by an independent academic Steering Committee, has assembled a database of individual participant data from all unconfounded randomised trials, which involve a coxib or a traditional NSAID. This will incorporate published and unpublished studies, of at least four weeks duration, and will focus on vascular and upper gastrointestinal outcomes. This thesis is carried out as part of a comprehensive collaborative meta-analysis of individual participant data from randomised trials of these medications: the Coxib and traditional NSAID Trialists' (CNT) Collaboration.

Table 2.1 Requirements for reliable assessment of moderate effects when conducting meta-analyses of randomised trials

Limiting biases (i.e., guaranteed avoidance of moderate biases)
1. Proper randomisation (non-randomised methods might suffer moderate biases) 2. Analysis by allocated treatment (including all randomised patients in statistical analyses) 3. Chief emphasis on overall results (no unduly data-dependent emphasis on particular subgroups) 4. Systematic overview of all relevant randomised trials (no unduly data-dependent emphasis on particular studies)
Reducing random errors (i.e., guaranteed avoidance of moderate fluctuations by the play of chance) 5. Large numbers in any new trials (to be really large, trials can be simple or ‘streamlined’ in design) 6. Systematic overview of all relevant randomised trials (which yields the largest possible total numbers)

Adapted from Baigent et al. 2010

Table 2.2 Summary of an earlier tabular meta-analysis of randomised trials assessing the effects of coxibs on major vascular events

Type of drug	Effect on outcome and estimated relative risk versus placebo (absolute risk for average-risk individuals from Kearney et al.)	
	Major vascular events	95% confidence interval
COXIB	↑ 1.42-fold (3 per 1000py)	(1.13 to 1.78)
Naproxen (traditional NSAID <u>with</u> antiplatelet activity)	↔ neutral (0.92) (no effect)	(0.67 to 1.26)
Diclofenac (traditional NSAID <u>without</u> antiplatelet activity)	↑ 1.63-fold (3 per 1000py)	(1.12 to 2.37)
Ibuprofen (traditional NSAID <u>without</u> antiplatelet activity)	↑ 1.51-fold (3 per 1000py)	(0.96 to 2.37)

Adapted from Kearney et al. BMJ 2006

Table 2.3 Outstanding questions relevant to coxibs and traditional NSAIDs (and how they can be explored reliably using meta-analysis of individual participant data)

-
1. **What are reliable estimates of the effects of coxibs and traditional NSAIDs on major vascular events, other vascular complications (eg, heart failure) and, particularly, upper GI complications?**
(reliable and detailed analyses of outcomes)
 2. **Do coxibs and traditional NSAIDs have evidence of latent effects on vascular and upper GI events?**
(reliable time-to-event analyses can be conducted)
 3. **Do the proportional effects of coxibs and traditional NSAIDs on vascular and upper GI events vary amongst patient subgroups (eg, age, gender etc.)?**
(reliable and detailed subgroup analyses can be conducted, especially as any heterogeneity of these could affect absolute risks)
 4. **What are the risk factors that increase the risk of vascular and upper GI outcomes for coxibs and traditional NSAIDs?**
(reliable and detailed assessment of risk factors)
 5. **Are there trends towards larger proportional increases in vascular and upper GI events with higher baseline absolute risks and higher coxib/traditional NSAID doses?**
(reliable and detailed assessment of risk categories and doses)
 6. **What are the balance of benefits and risks of different coxibs and traditional NSAIDs in terms of absolute effects on vascular and upper GI events among different types of patients?**
(reliable and detailed risk-modelling)
-

CHAPTER 3: Study protocol and procedures

3.1 Trial eligibility

3.2 Search strategy

3.3 Comparisons studied

3.3.1 Traditional NSAIDs with and without antiplatelet activity

3.4 Data collection

3.4.1 Invitation to collaborate

3.4.2 Individual participant data

3.4.3 Tabular data

3.5 Data checking

3.5.1 Definition of primary outcome measures

3.5.2 Definition of secondary outcome measures

3.5.3 Adjudicated and unadjudicated outcomes

3.5.4 Assessments of type of drug, dose response and effects over time

3.5.5 Other subgroup analyses

3.6 Interim and summary checks for collaborators

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Table 1.1 Search strategy for published and unpublished trials

Table 1.2 Data request for individual participant data

Table 1.3 Sample output summary report used for data-checking

3.1 TRIAL ELIGIBILITY

The Coxib and traditional NSAID Trialists' (CNT) Collaboration was set up to obtain reliable estimates of the common vascular and upper gastrointestinal effects of these medications. Hence, data were sought from all unconfounded published and unpublished randomised trials of at least four weeks' duration which have involved a coxib or traditional NSAID. Sponsors and trialists agreed to form a collaborative database to assess the available randomised evidence for final study reports which were available by January 2010.

Trials of humans were included if they were randomised in a manner that precluded prior knowledge of the next treatment (eg, where allocation was not alternate). Only unconfounded comparisons were assessed: for example, a trial in which a coxib plus proton pump inhibitor (PPI) was compared with a traditional NSAID plus PPI would be included, whereas a trial of coxib alone versus traditional NSAID plus PPI would not. Those trials that were less than four weeks in duration were excluded, as they were unlikely to contribute much additional information, as were the second-phases of any crossover trials. However, information from shorter-term trials carried out in participants with overt vascular disease (eg, coronary artery bypass grafts) was collected for sensitivity analyses. Trials that were stopped early, from which useful outcome data were collected, were included, although those planned or never started, or those that had not reported by January 2010 were excluded. The CNT protocol (included in the Appendix) was circulated and agreed upon by all collaborators before the analysis of any data.

3.2 SEARCH STRATEGY

A series of searches were carried out to maximise the number of relevant published and unpublished unconfounded randomised trials. (Table 3.1) First, computer-aided literature searches (Medline/EMBASE/CENTRAL) were conducted using the modified Cochrane strategy. Reference lists of randomised trials, meta-analyses and reviews, including the previous tabular meta-analysis, (Kearney et al. 2006) were scrutinised for

further studies. Clinical trial registers (eg, clinicaltrials.gov, clinicalstudyresults.org) and websites (eg, the Food and Drug Administration) were searched for completed studies. The manufacturers of coxibs were also approached for completed published and unpublished trials: Pfizer (celecoxib, valdecoxib), Merck (etoricoxib, rofecoxib), Novartis (lumiracoxib) and GlaxoSmithKline (GW403681). For traditional NSAIDs, most of which are now available generically (eg, naproxen, diclofenac, ibuprofen etc.) companies were also approached (there was, however, no response from those companies). The only exception to this was newer agents that are currently undergoing trials, eg, naproxcinod (NicOx), who could not contribute individual participant data due to regulatory submissions (but for which tabular data are still available). Finally, inquiry was also made amongst contributing trialists (and other sponsors, eg, academic institutions) about additional trials that they were aware of. Whilst it is possible that some unpublished studies in particular could have been missed (and there would be no reliable method for checking such an eventuality), using multiple search methods meant that included published and unpublished trials could be verified.

3.3 COMPARISONS STUDIED

Requests were made to collect available information for relevant unconfounded comparisons of coxibs and traditional NSAIDs. Although there were many more randomised trials of traditional NSAIDs, those trials involving coxibs were typically much larger and of longer duration, and therefore contributed more evidence.

- i. Coxib versus placebo (or open control);
- ii. coxib versus traditional NSAID;
- iii. traditional NSAID versus placebo (or open control);
- iv. one coxib versus another coxib;
- v. one traditional NSAID versus another traditional NSAID; and
- vi. dose comparisons for coxibs/traditional NSAIDs.

3.3.1 *Traditional NSAIDs with and without antiplatelet activity*

In combination with the established pharmacokinetic and pharmacodynamic properties of the traditional NSAIDs studied, results from an earlier tabular meta-analysis of randomised trials (Kearney et al. 2006) provided evidence that naproxen has persistent antiplatelet activity, which translates to different vascular effects from other traditional NSAIDs. Therefore, we prospectively specified *a priori* that analyses involving traditional NSAIDs would be subdivided into those involving traditional NSAIDs with persistent antiplatelet activity (naproxen, indobufen, and flurbiprofen) and those without. The latter category includes ibuprofen (which has known short-lived antiplatelet activity, albeit not *persistent*), diclofenac, and other traditional NSAIDs (some of which are listed in Table 1.3).

3.4 DATA COLLECTION

3.4.1 *Invitation to collaborate*

Formal invitations to collaborate were sent to identified trialists by email, post, facsimile and/or telephone. In the event of no response, repeat mailings were sent to recent addresses and/or alternative authors/sponsors. More than 2000 mailings were sent to more than 30 countries in six continents for potential randomised studies carried out from the 1960s to 2010.

3.4.2 *Individual participant data*

Individual participant data (IPD) were requested for each participant enrolled in a study for a number of baseline features, included on a data request (Table 3.2):

- demographic characteristics (eg, age, gender);
- medical history (eg, atherosclerosis, diabetes, upper GI ulcers);
- smoking and alcohol status;
- concomitant medications (eg, aspirin, gastroprotectant medication);
- physical measures (eg, blood pressure, body mass index);
- biochemical measures (eg, Haemoglobin);

- other measures (eg, *Helicobacter pylori* status); and
- indication for treatment.

The details of the randomly allocated treatments (ie, drugs used, doses used, dates commenced and stopped) were collected. Finally, information on vascular, upper gastrointestinal and cause-specific mortality outcomes, explained in more depth in *Outcome measures*, and their dates of occurrence were also collected. For “extension trials” (where a short-term often placebo-controlled period, sometimes with several different doses, was followed by an often longer comparison of a coxib vs a traditional NSAID) outcomes were collected for all periods in which a valid randomised comparison was assessed (see *Chapter 4: Statistical Methods and presentation* for an expanded description).

3.4.3 Tabular data

If trialists were unable to supply IPD (eg, due to a lack of records) tabular data were still sought. This consisted of confirming data derived from the publication and/or additional unpublished data on the numbers of participants, study duration and primary outcomes. For all studies, information was collected on the method of randomisation (including allocation concealment and blinding), as well as other logistical information, eg, up-to-date contact details.

3.5 Outcome measures

3.5.1 Definition of primary outcome measures

The two primary outcomes were:

- 1). **Major Vascular Events (MVE)**, a composite of non-fatal myocardial infarction (MI), non-fatal stroke, or vascular death; and
- 2). **Upper gastrointestinal complications (UGIC)**, a composite of upper GI perforation, obstruction or bleed.

The definitions for all outcomes were as defined by the trial investigator, but for those trials where adjudication had not taken place, definitions and relevant codes were supplied in the Study Protocol (enclosed in the Appendix). For all events, only the first definite or “probable” (but not “possible”) event was utilised. For example, a participant could have suffered more than one type of event, eg, a MI followed by a stroke, but only the first event would count in the primary outcome above.

Confirmation of myocardial infarction used the World Health Organisation definition (a history of chest pain, electrocardiogram changes, or cardiac enzyme [eg, troponin] measurements although verification of these were not required). Strokes were defined clinically as 'a neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours', and, where possible, confirmation of aetiology (that is, ischaemic or haemorrhagic) was obtained. Upper GI complications were defined anatomically as including and being proximal to the duodenum (i.e., the ligament of Treitz). If a patient had a symptomatic ulcer diagnosed without perforation, obstruction or bleed occurring, it was defined as uncomplicated (i.e., a symptomatic UGI ulcer).

3.5.2 Definition of secondary outcome measures

Information on the individual components of the MVEs (MI, stroke and vascular death) were collected. For studies that supplied individual participant data, further outcomes were also collected. Stroke was subdivided into ischaemic, haemorrhagic (including subarachnoid haemorrhage) and unknown aetiology. Transient ischaemic attacks (TIA) were not included because of the criteria that neurological deficit needed to last more than 24 hours. Individual components of upper GI complications (perforation, obstruction or bleed) were also collected, as were data on symptomatic (uncomplicated) ulcers. These included symptomatic ulcers diagnosed clinically or confirmed endoscopically, according to the study design of each individual trial.

Data were also collected on other vascular complications, including time of event:

- coronary revascularisation;
- pulmonary embolus;
- peripheral arterial disease events;
- hospitalisation for unstable angina; and
- hospitalisation for heart failure.

For each event, further information was sought on whether it was “non-fatal” or “fatal”. In addition to vascular deaths (as part of the primary vascular outcome), data on more detailed cause-specific mortality were also collected. For all recorded deaths, trialists were asked for International Classification of Disease (ICD) version 9 or 10 codes (although this was not possible in all cases).

Analyses of mortality were grouped as follows:

- vascular (subdivided by coronary, stroke-related or other vascular);
- non-vascular (subdivided by upper gastrointestinal, cancer, other non-vascular); or unknown causes.

3.5.3 Adjudicated and unadjudicated outcomes

Where adjudication had been carried out, particularly in the more recent large-scale trials, these outcomes were preferentially used. Where this was not possible, unadjudicated outcomes were used, in which case, the Medical Dictionary of Regulatory Authorities (MedDRA) codes for outcomes were supplied in the CNT protocol to guide trialists in coding their outcomes (see Appendix). The main point is that comparisons were only made within trials, so although adjudication may safeguard against erroneous outcomes being included, it should not change the relative effect substantially. There were differences between studies in the definitions of outcome measures, but because retrospective classifications would have been potentially biased (and impractical for all trials), the categorisation of outcomes used by the original trial investigators were retained. Any non-differential misclassification of vascular outcomes in those trials without independent adjudication would tend to

bias the results towards the null, but as most of the vascular events occurred in trials that were adjudicated, the potential for this to greatly affect the overall findings was likely to be minimal. (Kearney et al. 2006) Nevertheless, sensitivity analyses were also carried out to test the effect that differences in adjudication might have on outcomes.

3.5.4 Assessment of type of drug, dose response and effects over time

For the primary outcomes listed, formal subgroup analyses were conducted for each comparison, and these methods are explained in the statistical methods chapter. These include assessments for heterogeneity (and trend, where appropriate) for:

- (i) type of drug (eg, separate coxibs versus placebo)
- (ii) dose response (eg, for rofecoxib versus placebo)
- (iii) time-to-event (principally using individual participant data)

Differences between per-protocol and intention-to-treat analyses were also assessed where possible (e.g., in the APPROVe trial). (Bresalier et al. 2005; Baron et al. 2008)

3.5.5 Assessment of other subgroup analyses

Other subgroup analyses included assessments of effects on the primary outcomes among categories defined by:

- (i) baseline demographic features (e.g., age, sex, etc.);
- (ii) baseline past medical history (e.g., atherosclerosis, upper GI ulcer, diabetes etc.);
- (iii) baseline physical features (e.g., body mass index, blood pressure etc.);
- (iv) concomitant treatments at baseline (e.g. aspirin, gastroprotectants etc.);
- (v) baseline laboratory features
- (vi) participants at low-, intermediate-, and high-risk of major vascular events;
- (vii) participants at low-, intermediate-, and high-risk of upper gastrointestinal complications;
- (viii) particular indications for an anti-inflammatory drug (e.g. osteoarthritis, rheumatoid arthritis, cancer prevention etc.)

3.6 Interim and summary checks for collaborators

When data were sent to the Secretariat (often a long process for IPD which involved protracted discussions and, in some cases, legal contracts), extensive checks were carried out. It should be noted that data-checking does not take place to centrally police trials or to expose fraud, but purely to check that the clinical and methodological details are correct. (Clarke & Stewart 1994) The aim was to carry out standardised analyses for all outcomes among all the participants who had been randomised in all the trials. Summary report tables for each randomised trial were checked by multiple members of the CNT Secretariat for internal consistency, other anomalies (eg, logic and range checks) and completeness. (Table 3.3)

The most important assessment was ensuring that the primary and secondary outcomes (vascular, upper gastrointestinal and cause-specific mortality outcomes) for each trial were correct, including the number of fatal/non-fatal events and subtypes (eg, ischaemic stroke, upper GI perforation etc.). In addition, dates of events were checked to ensure that they matched the trial randomisation and follow-up dates.

The data received were scrutinised to ensure it yielded identical results to those presented previously in study reports/protocols/publications (and, if not, to ensure that explanations for any discrepancies were available). The total numbers randomised (including subsequent randomisations in extension studies) and allocated treatment were examined, as was the integrity of the randomisation and follow-up procedures (which may have been longer in the data provided than the publication). Study reports were also checked for baseline characteristics (including demographics, indication for treatment, past history, other medication use, physical and laboratory measures), as were details on study discontinuation and follow-up.

Numbers of events or relevant percentages for characteristics were presented in the standardised summary reports, with means, standard deviations and ranges as well as any missing data. Anomalies (logic checks) and extreme values (range checks) in the data were also highlighted to the collaborating trialists in a standardised form. As well

as extensive double-checks of the data received, further efforts were also made to capture additional unpublished information. This included requests for missing data on outcomes, baseline demographics and intention-to-treat data (ensuring data on events occurring after patients discontinued study treatment), where this was not publicly available.

Queries were referred back to the corresponding investigator or sponsor, along with summary reports for review and confirmation. In some cases, this process involved protracted discussions and correspondence, with repeated data checking, in order to ensure that the data were as reliable as possible. Finally, the principal investigators and sponsors were asked to confirm the corresponding data for their trial, especially the outcomes, were correct in a formal sign-off.

TABLE 3.1: SEARCH STRATEGY FOR PUBLISHED AND UNPUBLISHED TRIALS

-
1. Computer-aided literature searches (Medline/EMBASE/CENTRAL) conducted
 2. 138 published and unpublished trials from the tabular meta-analysis
 3. Searches of reference lists of randomised trials, meta-analyses and reviews
 4. Clinical trial registers (eg, clinicaltrials.gov, clinicalstudyresults.org)
 5. Other relevant websites (eg, United States Food and Drug Administration)
 6. Manufacturers of coxibs and traditional NSAIDs (eg, Merck, Novartis, Pfizer, GlaxoSmithKline, Nicox etc.)
 7. Inquiries amongst contributing trialists and sponsors for additional studies
-

TABLE 3.2: DATA REQUEST FOR INDIVIDUAL PARTICIPANT DATA [Full request with notes and explanation in Appendix]

A. Baseline data recorded PRIOR to randomisation	Coding
Patient identifier	
Gender	1 = male 2 = female
Ethnicity	1 = caucasian 2 = other
Date of birth <i>or</i> age at randomisation	
Indication for treatment	1 = rheumatoid arthritis 2 = osteoarthritis 3 = back pain 4 = gout 5 = cancer treatment 6 = cancer prevention 7 = treatment/prevention of Alzheimer's disease 8 = other condition 9 = unknown
History of atherosclerosis (coronary heart disease, cerebrovascular disease or other arterial disease)	1 = yes 0 = no
History of diabetes mellitus	1 = yes 0 = no
History of upper gastrointestinal ulcer	1 = yes 0 = no
<i>Helicobacter pylori</i> status at baseline	1 = positive 0 = negative
Height (cm)	
Weight (kg)	
Current cigarette smoker	1 = yes 0 = no
Current drinker of alcohol	1 = yes 0 = no
Current user of aspirin	1 = yes 0 = no
Current user of gastroprotective agent	1 = proton pump inhibitor 2 = histamine 2 receptor blockers 3 = misoprostol 9 = other 0 = no

Baseline haemoglobin (g/dl)	
Baseline total cholesterol (mmol/L)	
Baseline creatinine (μ mol/l)	
Baseline systolic blood pressure (mm Hg)	
Baseline diastolic blood pressure (mm Hg)	
B. Randomisation and treatment allocation	
Date of randomisation	
Date commenced <i>first</i> treatment	
First randomised treatment allocation	
Date ended first treatment	
Date commenced <i>second</i> treatment	
Second randomised treatment allocation	
Date ended second treatment	
C. Cardiovascular events occurring AFTER randomisation (record information on first event of each type)	
First myocardial infarction (MI) <i>after</i> randomisation	1 = yes 0 = no
Date of first MI	
Whether MI was fatal or non-fatal	1 = fatal 0 = non-fatal
First stroke <i>after</i> randomisation	1 = yes 0 = no
Type of stroke <i>after</i> randomisation	1 = intracerebral haemorrhage 2 = subarachnoid haemorrhage 3 = subdural haematoma 4 = ischaemic (including embolic) stroke 9 = unknown
Date of first stroke	
Whether stroke was fatal or non-fatal	1 = fatal 0 = non-fatal
First episode of heart failure requiring hospitalisation <i>after</i> randomisation	1 = yes 0 = no
Date of first heart failure event	
Whether heart failure event was fatal or non-fatal	1 = fatal 0 = non-fatal

First pulmonary embolus (PE) <i>after</i> randomisation	1 = yes 0 = no
Date of first PE	
Whether PE was fatal or non-fatal	1 = fatal 0 = non-fatal
First peripheral arterial disease event <i>after</i> randomisation	1 = yes 0 = no
Date of first peripheral arterial disease event	
Whether peripheral arterial disease event was fatal or non-fatal	1 = fatal 0 = non-fatal
First coronary revascularisation <i>after</i> randomisation	1 = yes 0 = no
Date of first coronary revascularisation	
Whether coronary revascularisation was fatal or non-fatal	1 = fatal 0 = non-fatal
First resuscitated cardiac arrest <i>after</i> randomisation	1 = yes 0 = no
Date of first resuscitated cardiac arrest	
Whether resuscitated cardiac arrest was fatal or non-fatal	1 = fatal 0 = non-fatal
First episode of unstable angina <i>after</i> randomisation	1 = yes 0 = no
Date of first unstable angina event	
Whether unstable angina was fatal or non-fatal	1 = fatal 0 = non-fatal
D. Upper gastrointestinal (UGI) events occurring AFTER randomisation (record information on first event of each type)	
First symptomatic (but <u>un</u> complicated) UGI ulcer <i>after</i> randomisation	1 = yes 0 = no
Date of first symptomatic (but <u>un</u> complicated) UGI ulcer	
First upper gastrointestinal UGI ulcer complication <i>after</i> randomisation	1 = yes 0 = no
Date of first UGI ulcer complication	
Type of UGI ulcer complication	1 = UGI haemorrhage 2 = UGI obstruction 3 = UGI perforation 4 = other 9 = unknown

Whether UGI ulcer complication was fatal or non-fatal	1 = fatal 0 = non-fatal
E. Study discontinuation	
Study treatment discontinued permanently prior to scheduled end	1 = yes 0 = no
Date study treatment discontinued if prior to scheduled end	
F. Follow-up information	
Date of scheduled end of treatment	
Date of last follow-up for cardiovascular events	
Date of last follow-up for gastrointestinal events	
Date of last follow-up for vital status	
Vital status on that date	1 = dead 0 = alive
ICD (or other code) for death	

TABLE 3.3: SAMPLE OUTPUT SUMMARY REPORT USED FOR DATA-CHECKING (USING VIGOR TRIAL [FULL REPORT IN APPENDIX])

	n (%)	Missing data	Mean (SD)	1st - 99th percentile	Range
Number randomised	8076				
A. Baseline characteristics					
Number of men	1638 (20.3%)	-			
Number of caucasians	5511 (68.2%)	-			
Age, years	8076 (100.0%)	-	58.1 (9.5)	(40 - 80)	(34 - 89)
Indication for treatment					
Rheumatoid arthritis	8076 (100.0%)	-			
History of atherosclerosis	321 (4.0%)	-			
History of diabetes mellitus	502 (6.2%)	-			
History of upper GI ulcer	630 (7.8%)	-			
Positive <i>H. pylori</i> status	3452 (42.7%)	120 (1.5%)			
Height, cms		40 (0.5%)	161.8 (10)	(140 - 188)	(115 - 203)
Weight, kg		4 (0.0%)	72.1 (17)	(42 - 125)	(31 - 193)
Current cigarette smoker	1569 (19.4%)	-			
Current drinker of alcohol	2097 (26.0%)	1 (0.0%)			
Current user of aspirin	0 (0.0%)	-			
Current user of gastroprotective agent					
Proton pump inhibitor	49 (0.6%)	-			
Histamine 2 receptor blocker	707 (8.8%)	-			
Misoprostol	0 (0.0%)	-			
Combination of gastroprotectants	5 (0.1%)	-			
Unknown or other known drug	15 (0.2%)	-			
Haemoglobin, g/dl		36 (0.4%)	13.2 (1.3)	(10 - 16)	(8 - 18)
Total cholesterol, mmol/L		ALL MISSING	-	-	-
Creatinine, umol/l		23 (0.3%)	64.1 (17.5)	(35 - 115)	(18 - 221)
Systolic BP, mm Hg		2 (0.0%)	128.7 (15.5)	(98 - 165)	(80 - 190)
Diastolic BP, mm Hg		3 (0.0%)	78.2 (8.6)	(60 - 95)	(50 - 110)
B. Randomisation and treatment allocation					
Date of randomisation	8076 (100.0%)	-		(Jan 1999 - Jul 1999)	
Duration of FIRST treatment, weeks	8076 (100.0%)	-	34.2 (14.3)	(0.6 - 53)	(0 - 56)
Date commenced first treatment	8076 (100.0%)	-		(Jan 1999 - Jul 1999)	
First treatment allocation = Rofecoxib 50mg	4047				
First treatment allocation = Naproxen 1000mg	4029				
Date ended first treatment	8076 (100.0%)	-		(Feb 1999 - Mar 2000)	

	n (%)	Missing data	Mean (SD)	1st - 99th percentile Range
C. Cardiovascular events occurring AFTER randomisation				
First myocardial infarction (MI)				
No. patients that had an MI	24	-		
Date of first MI	24 (100.0%)	-		(Apr 1999 - Feb 2000)
First MI fatal, no. (%)	2 (8.3%)	-		
First stroke				
No. patients that had a stroke	20	-		
Intracerebral haemorrhage	3	-		
Subarachnoid haemorrhage	0	-		
Subdural haematoma	0	-		
Ischaemic (including embolic)	17	-		
Unknown type	0	-		
Date of first stroke	20 (100.0%)	-		(Apr 1999 - Feb 2000)
First stroke fatal, no. (%)	3 (15.0%)	-		
First heart failure				
No. patients that had heart failure	28	-		
Date of first heart failure	28 (100.0%)	-		(Mar 1999 - Feb 2000)
First heart failure fatal, no. (%)	1 (3.6%)	-		
First pulmonary embolism (PE)				
No. patients that had PE	0	-		
First peripheral arterial event (PAD)				
No. patients that had PAD	1	-		
Date of first PAD	1 (100.0%)	-		(Dec 1999 - Dec 1999)
First PAD fatal, no. (%)	0 (0.0%)	-		
First coronary revascularisation (CRV)				
No. patients that had CRV	0	-		
First resuscitated cardiac arrest (RCA)				
No. patients that had RCA	0	-		
First unstable angina				
No. patients that had unstable angina	8	-		
Date of first unstable angina	8 (100.0%)	-		(Apr 1999 - Dec 1999)
First unstable angina fatal, no. (%)	0 (0.0%)	-		

	n (%)	Missing data	Mean (SD)	1st - 99th percentile Range
D. Gastrointestinal events occurring AFTER randomisation				
First symptomatic (but uncomplicated) gastroduodenal ulcer				
No. patients that had event	132	-		
Date of first uncomplicated gastroduodenal ulcer	132 (100.0%)	-		(Mar 1999 - Mar 2000)
First upper gastrointestinal (UGI) complication				
No. patients that had event	61	-		
Gastroduodenal haemorrhage	52	-		
Gastric outlet obstruction	1	-		
Gastroduodenal perforation	7	-		
Other	0	-		
Unknown	1	-		
Date of first UGI complication	61 (100.0%)	-		(Mar 1999 - Mar 2000)
First UGI complication fatal, no. (%)	5 (8.2%)	-		
E. Study discontinuation				
Treatment discontinued prior to scheduled end	2334 (28.9%)	-		
Date of discontinuation (if prior to scheduled end)	2334 (100.0%)	-		(Feb 1999 - Mar 2000)
F. Follow-up information				
Date of scheduled end of treatment	8076 (100.0%)	-		(Feb 1999 - Mar 2000)
Date of last follow up for cardiovascular events	8076 (100.0%)	-		(Apr 1999 - May 2000)
Date of last follow up for gastrointestinal events	8076 (100.0%)	-		(Apr 1999 - Dec 2000)
Date of last follow up for vital status	8076 (100.0%)	-		(Apr 1999 - Dec 2000)
Number (%) of deaths during trial	37 (0.5%)	-		
ICD cause of death provided (or could be derived)	19 (51.4%)	18 (48.6%)		
Cause of death				
Cardiac	10	-		
Stroke	3	-		
Other vascular	1	-		
GI ulcer complication	5	-		
Other GI / hepatic	0	-		
Cancer	0	-		
Other known non-vascular cause	0	-		
Unknown cause	18	-		

CHAPTER 4: Statistical methods and presentation

- 4.1 Calculating the event rate ratio for a single trial
- 4.2 Combining rate ratios across several trials in a “meta-analysis”
- 4.3 Forest plots
- 4.4 Proportional and absolute effects of treatment
- 4.5 Estimating effects using direct and indirect methods
- 4.6 Effects in specific subgroup categories
- 4.7 Effects in studies with more than one comparison
- 4.8 Identifying risk factors and risk-modelling

TABLES

Table 4.1 Calculation of the risk ratio, odds ratio, observed minus expected and its variance applied to the VIGOR study

Table 4.2 Principle of unbiased combination of information applied to major vascular events in three large-scale rofecoxib versus placebo trials

FIGURES

Figure 4.1 Comparison of effects of different coxibs versus placebo on major vascular events in the previous tabular meta-analysis

Figure 4.2 Estimating the effects of coxibs directly

Figure 4.3 Estimating the effects of naproxen

Figure 4.4 Identifying properly randomised comparisons within extension studies

4.1 Calculating the event rate ratio for a single trial

To estimate the effect of an intervention on a particular outcome, the first step is an evaluation of the direction and strength of effect for each individual randomised comparison in the trial, summarised in this case by an “event rate ratio”. For each valid randomised comparison in each trial, the log-rank “observed minus expected” statistic $o - e$ (and its variance v) was estimated. As its name suggests, the $o - e$ statistic is the extent to which the *observed* number of disease cases among patients allocated active treatment in the trial (o) differs from what would have been *expected* (e) if active treatment had no effect on disease outcome. (If treatment has no effect, then the $o - e$ statistic differs only randomly from zero, whilst its variance v always increases as the study size increases). The process involves estimation of a separate $o - e$ and v statistic at every point in time at which an event occurs.

The summation of all the separate $o - e$'s yields the overall log-rank $o - e$ statistic for the trial (and the summation of all the separate v 's provide its overall variance). (Peto et al. 1977) The “one-step” estimate of the log event rate ratio is then provided by the formula $b = (o - e) / v$, its 95% confidence interval is given by the formula $b \pm 1.96 / \sqrt{v}$, and its associated 2-sided p-value (ie, the log-rank test) is provided by comparing the statistic $(o - e)^2 / v$ against a chi-squared (χ^2) distribution with 1 degree of freedom. In all trials for which individual participant (rather than tabular) data were available, such time-to-event analyses were conducted.

Since calculation of the log-rank event rate ratio requires detailed knowledge of the timing of every outcome in the trial, it can only be calculated when individual patient data are available. For trials where only tabular data were available, approximate $o - e$ and v statistics for the trial were generated instead from the overall numbers of patients randomised and numbers of first events using standard formulae for 2x2 contingency tables (which were then used to derive the “one-step” estimate of the odds ratio using the same formulae shown above). While the log-rank method provides an improvement in sensitivity over such cruder tabular methods, this can be limited in trials (including those involving coxibs) in which most participants would be

expected to survive. Table 4.1, for instance, illustrates how application of this tabular method for major vascular events in the VIGOR trial (Bombardier et al. 2000) results in an odds ratio estimate that is very similar to the log-rank event rate ratio calculated from the individual patient data. The real advantage in having access to individual patient data, therefore, is not so much in the overall estimate of treatment effect it provides, but in allowing examination of how effects vary between different types of patient (as well as how risks/benefits emerge over time when contiguous time periods, eg, six-monthly, are examined).

4.2 Combining rate ratios across several trials in a “meta-analysis”

To calculate the overall event rate ratio across all trials that have provided a given randomised comparison, the log-rank $o - e$ values from each such comparison (or equivalent $o - e$ statistic derived from tabular data) are summed to produce a grand total G and the variances v from each such comparison summed to produce a grand total V . (Event rates were only calculated among trials in which at least one relevant event occurred). The log-rank event rate ratio across all trials is then provided by the statistic G/V , its 95% confidence interval is given by the formula $G/V \pm 1.96 / \sqrt{V}$, and its associated 2-sided p -value is provided by comparing the statistic G^2/V against a chi-square distribution with 1 degree of freedom. If the treatment had no effect in every trial, then each $o - e$ value would differ only randomly from zero, and, therefore, so would G . This method of combining the results across different trials means that patients in one trial are *never* directly compared with patients in another trial.

Table 4.2 illustrates the application of these statistical methods to combine the results from three different large-scale rofecoxib versus placebo trials. (Antiplatelet Trialists' Collaboration 1994) Within each separate trial the standard quantity log rank $o - e$, together with its v , has been calculated for the numbers of major vascular events (MVEs) among treatment allocated patients. Although the total for log-rank $o - e$ in the VIP trial was 0.0 (as there were 11 vs 11 MVEs), for the three large-scale rofecoxib versus placebo trials together, the grand total (G) of the individual log-rank $O-E$ values in the three trials was 9.7. The positive sign indicates a greater number of MVEs in the

patients allocated coxib therapy than in the controls, and the numerical value suggests (very approximately due to a doubling of the O-E) that about 20 extra MVEs were attributable to allocation to coxib therapy in these three studies.

This method of meta-analysis is often referred to as being a "fixed effect" method, but this terminology is unsatisfactory, for it misleadingly suggests that any heterogeneity between the true effects of treatment in different trials is assumed to be zero (whereas no such unjustified assumptions are involved) (Yusuf et al. 1985). The overall result is merely the weighted average of the "like-with-like" comparisons from each trial, with larger trials contributing more weight than smaller trials, and so a better description would be to refer to it as an "assumption-free" method.

A fuller description of the statistical methods used for the meta-analysis of trials and of why they are used in preference to other methods (eg, random effect methods) has been given elsewhere (Early Breast Cancer Trialists' Collaborative Group 1990) and applied in a number of other such overviews. (Antiplatelet Trialists' Collaboration 1994; Antithrombotic Trialists' (ATT) Collaboration 2002; Baigent et al. 2009; Cholesterol Treatment Trialists' (CTT) Collaboration 2005; Cholesterol Treatment Trialists' (CTT) Collaboration 2010; Kearney et al. 2006)

4.3 Forest plots

Forest plots are a graphical display designed to illustrate the proportional strength of treatment effects in multiple randomised controlled trials. For example, in Figure 4.1, which displays the effects of different coxibs on major vascular events in trials comparing a particular coxib versus placebo, the left-hand column gives the type of coxib, with the subsequent columns showing the number of trials that supplied data, and the events/person-years for those participants allocated a coxib or placebo. The right-hand column is a plot of the measure of effect (in this case a rate ratio) for each of the results of relevant studies (represented by a square) incorporating confidence intervals (represented by horizontal lines). The area of each square is proportional to the variance of the sum of the o-e statistics for the trials represented in each row (as

this is the amount of “statistical information” provided by those trials). (Early Breast Cancer Trialists' Collaborative Group 1990)

In the present analyses, 99% confidence intervals (obtained by replacing 1.96 in the formulas above with 2.576) have been used for individual subgroups (eg, type of coxib), whilst 95% confidence intervals have been used for subtotals. The measure of overall effect is commonly plotted as a diamond, the lateral points of which indicate confidence intervals for this estimate. A vertical line representing the null hypothesis of no effect is also plotted (in this case a rate ratio of 1.0). If the confidence intervals for individual trials and points of the diamond overlap with this, this means that at the given level of confidence, there is no evidence to reject the null hypothesis of no true treatment effect. As well as rate ratios, absolute rates are presented in brackets below the subtotals, and the absolute effects in this case can be estimated from the difference in annual event rates in the events/person-years columns. Heterogeneity between the types of drugs in this example were calculated using a chi-squared test (χ^2), with corresponding degrees of freedom (df) and a corresponding p-value.

4.4 Proportional and absolute effects of treatment

The rate ratios calculated are described in the results as relative or proportional effects. Both proportional and absolute effects in clinical events can help in describing the size of any treatment effects. For example, in the results of the tabular meta-analysis presented in Figure 4.1, (Kearney et al. 2006) among 121 placebo controlled trials, 216 major vascular events occurred during 18 490 person years of exposure to a coxib (1.2%/year) compared with 112 during 12 639 person years of placebo (0.9%/year), corresponding to a 42% proportional increase in the incidence of a first MVE (rate ratio 1.42, 95% confidence interval 1.13 to 1.78; P = 0.003). This proportional risk increase corresponds to an absolute increase of 0.3% per year (that is, about 3 additional MVEs per 1000 people for one year treated) taking coxib therapy (compared to placebo) for the average participant in these randomised trials.

Proportional reductions may be more widely generalisable to different medical circumstances, while absolute reductions may be more directly relevant to deciding whether to use treatment in particular medical circumstances. For example, the absolute baseline risk clearly differs substantially between a young well person with a sports injury, or an older person with multiple comorbidities. For these reasons both proportional and absolute reductions are presented.

4.5 Estimating effects using direct and indirect methods

Where the majority of the available data were available from a direct comparison, eg, coxib versus placebo, estimates of the effects of coxibs can be obtained directly by analyses from this comparison (see Figure 4.2). For traditional NSAIDs, however, the amount of data available from the direct comparisons was likely to be limited due to lack of statistical power (fewer patients, shorter follow-up, and hence fewer outcomes, compared with the coxib trials), so the most reliable estimate of their effect comes from a weighted combination of both direct and indirect comparisons. For example, the best estimate of naproxen's effects uses a weighted combination of the: (i) direct comparison (ie, naproxen versus placebo) and (ii) the indirect comparison (ie, coxib versus placebo and coxib versus naproxen)(see Figure 4.3).

When assessing traditional NSAIDs, using indirect comparisons in conjunction with the available direct evidence has been suggested as a methodology previously (Gotzsche 1993) and was conducted in an earlier tabular meta-analysis. (Kearney et al. 2006) Hence, it was pre-specified to estimate the effects of traditional NSAIDs by combining the direct and indirect evidence using a linear regression model. Specifically, for trial $k(i,j)$ comparing the effects of treatments i and j , the following linear regression model was fitted: $Y_{ijk(i,j)} \sim N(\mu_i - \mu_j, \sigma^2_{ijk(i,j)})$ where $Y_{ijk(i,j)}$ is the log rate ratio for the k th trial comparing treatments i and j (given by $(o_i - e_i)/v_i$ above), μ_i and μ_j are the unknown mean effects of treatments i and j , and $\sigma^2_{ijk(i,j)}$ is the assumed known variance of the log rate ratio (equal to $1/v_i$ above). (see Appendix ...)

However, although using indirect methods in a regression model can improve statistical power considerably, it does make assumptions which could introduce bias. For example, are there substantial baseline differences between participants in the coxib versus placebo and coxib versus naproxen comparisons, which might bias results of the indirect comparison of naproxen? Evaluating detailed baseline characteristics of the participants in various comparisons, as is available with individual participant data, can be used to assess whether risk of such methodological bias exists. (Glenny et al. 2005; Song et al. 2003)

4.6 Effects in specific subgroup categories

In addition to the primary and secondary outcomes, pre-specified subgroup tests were conducted using the information collected in the data request (eg, subtypes of drug and baseline characteristics at randomisation). This included assessments of the chi-squared (χ^2) test statistic for heterogeneity between n trials (χ^2_{n-1}), provided by $S - (G^2/V)$, where S is the sum over all the trials of $(o_i - e_i)^2/v_i$, which is then tested against a χ^2 distribution with $n - 1$ degrees of freedom. Where it is possible to order trials (e.g. by coxib dose and time-to-first event), tests for trend were performed by calculating $T = GB/V$, where $T = \sum i(o_i - e_i)$ and $B = \sum i v_i$, and testing against a χ^2 distribution with 1 degree of freedom. Note that in the presence of such a trend, the overall event rate ratio is still valid; it merely represents the summary (or "typical") rate ratio over the relevant trend.

The heterogeneity of rate ratios among multiple subgroups defined by baseline characteristics is investigated by a global heterogeneity test, which helps to avoid misinterpreting false positive results arising from multiple comparisons. (For each characteristic [eg, age], a χ^2 test for trend on 1 degree of freedom is carried out. If there are 10 different χ^2 tests, and none of the trends is real, then their sum has expectation 10, and has a variance at least as great as χ^2_{10}). In other words, even if conventionally significant heterogeneity was present, groups of patients in whom treatment is relatively hazardous or safer can be difficult to identify reliably and the power of these tests of heterogeneity need to be interpreted cautiously.

Findings from multiple subgroup analyses may be misleading, especially as subgroup analyses are observational by nature and are not based on randomized comparisons. False negative and false positive significance tests increase in likelihood rapidly as more subgroup analyses are performed. Given multiple testing, especially where very small numbers of patients in a subgroup have been assessed (increasing the role of random error), it is important that “lack of evidence of an effect” is not misinterpreted as “evidence of lack of an effect”. The relevant question in each subgroup is whether there is convincing evidence that there is any material difference in the subgroup from the overall effect. If subgroup findings are presented as definitive conclusions there is clearly a risk of patients being denied an effective intervention or treated with an ineffective (or even harmful) intervention. Nevertheless, even though the low power of heterogeneity tests mean that individual subgroup results needs to be interpreted cautiously on their own, homogeneity of multiple subgroups suggests that the proportional effects are more reliable, especially when assessing absolute effects.

4.7 Assessing effects in studies with more than one comparison

For studies that involved more than one randomised comparison at the same time (eg, coxib versus NSAID versus placebo), these were each considered separately (ie, coxib versus NSAID; coxib versus placebo; NSAID versus placebo). For crossover trials, only the first part of the trial was incorporated into analyses. Where trials involved more than one randomisation (eg, extension studies), separate randomised comparisons were split out on the basis of the study design. For example, suppose a study initially randomised patients to coxib versus traditional NSAID versus placebo, and then, at some later point, re-randomised the placebo arm to coxib versus traditional NSAID (whilst other patients continued on their original treatment). For the first part of the trial, valid randomised comparisons would include: (i). coxib versus tNSAID (first part only); (ii). coxib versus placebo (first part only); and (iii). tNSAID versus placebo (first part only). For the second part of the trial, valid randomised comparisons would include this portion of time only and would include: (iv). coxib versus tNSAID (among patients initially randomised to placebo); and (v). coxib versus tNSAID (among patients who continued on their original treatment allocation). (This last comparison is *only*

valid when considered together with comparison (i) from the first part of the trial [see how the o-e's and v's need to be combined below]) This is demonstrated graphically in Figure 4.4. For such a trial, the overall estimate of the effect of coxib vs tNSAID would be provided by summing the three separate o – e's (and three separate v's) obtained from the separate analyses of the first part of the trial (one o – e and one v) and the second part of the trial (two o – e's and two v's). An advantage of having individual participant data is being able to assess extension studies more reliably than is possible using aggregate data.

4.8 Identifying risk factors and risk-modelling

To identify risk factors for the primary outcomes (major vascular events and upper GI complications) among participants in the randomised trials, Poisson regression was used. (Cholesterol Treatment Trialists' (CTT) Collaboration 2005) The estimate of the common linear dependence of the natural logarithm of the event rate on baseline measures was calculated. The results from this model for major vascular events and upper GI complications were used to classify the baseline risks (presented in Chapter 8) of all participants (including those allocated placebo, coxib and traditional NSAID). These baseline risks were divided into: low (predicted 5-year risk of events <5%), medium (predicted 5-year risk 5-10%) and high (predicted 5-year risk >10%) for major vascular events and upper GI complications.

TABLE 4.1 – Calculation of the log-rank rate ratio, crude odds ratio, observed minus expected (O-E) and its variance applied to the VIGOR study

	Rofecoxib group	Naproxen group	TOTAL
MVEs	35	18	53 = D
No MVEs	4012	4011	8023
Total	4047	4029	8076 = N

N = 8076 subjects; p = probability of allocation to first treatment (ie, rofecoxib) ~ 0.5 (50%); D = total number having a major vascular event (MVE) = 53

O-E is calculated only for the active treatment group: O = 35; E = 26.5 (53/2); difference (O-E) = 8.5. In an evenly balanced study such as this, an O-E of 8.5 corresponds to an apparent increase in MVEs of 17. The variance of O-E may be calculated by standard statistical formula $E(1-p)(N-D)/(N-1)$. For the VIGOR study, this is 13.2. The log odds ratio is therefore equal to $O-E/V = 8.5/13.2$: giving an odds ratio (95% CI) of 1.90 (1.11-3.26). By contrast, the event rate ratio for this trial calculated using the log-rank method is 1.88 (95% CI 1.10-3.22).

TABLE 4.2 – Principle of unbiased combination of information applied to major vascular events in three large-scale rofecoxib versus placebo trials

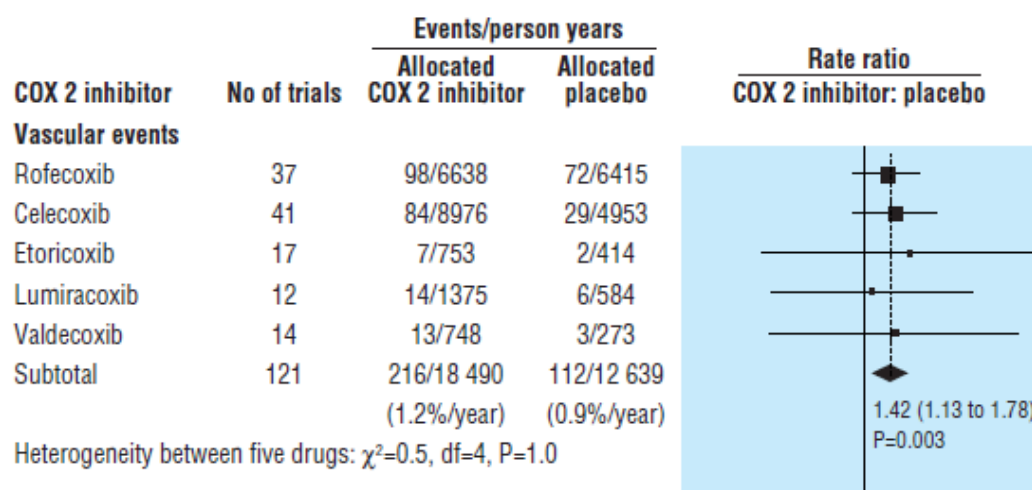
	Major Vascular Events (%pa)		Log-rank	
	COXIB	PLACEBO	O-E	Variance
APPROVe	48 (1.06)	28 (0.61)	10.3	19.0
VICTOR	9 (0.31)	5 (0.17)	2.0	3.5
VIP	11 (0.90)	11 (0.90)	0.0	5.5
Grand total (G)	68	44	12.3	28.0

Abbreviations: %pa = percentage per annum; O-E = observed minus expected

APPROVe = Adenomatous Polyp Prevention on Vioxx Trial (Bresalier et al. 2005);
 VICTOR = Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime Trial (Kerr et al. 2007); VIP = VIOXX in Prostate Cancer Prevention study (van Adelsberg et al. 2007)

The overall event rate ratio equals 12.3/28.0, giving an estimated event rate ratio across the three trials of 1.55 (95% CI 1.07-2.25), implying that rofecoxib is associated with ~55% increased risk of MVEs versus placebo in these 3 studies.

Figure 4.1 Comparison of effects of different coxibs versus placebo on major vascular events in an earlier tabular meta-analysis.



Event numbers and person-years of exposure, with corresponding mean annual event rates in parenthesis, are presented for patients allocated to coxib and placebo. Event rate ratios for subtotals, with 95% confidence intervals, are indicated by a diamond, and presented with a p-value; rate ratios for individual coxibs, with 99% confidence intervals, are indicated by a square and horizontal line. Diamonds to the right of the solid line indicate hazard with a coxib compared with placebo (this is conventionally significant, as in this case, if the diamond does not overlap the solid line). (Kearney et al. 2006)

Figure 4.2: Estimating the effects of coxibs directly

Estimate of effects of coxibs obtained directly from particular coxib versus placebo comparisons by stratified analyses, ie, rate ratio of A vs B

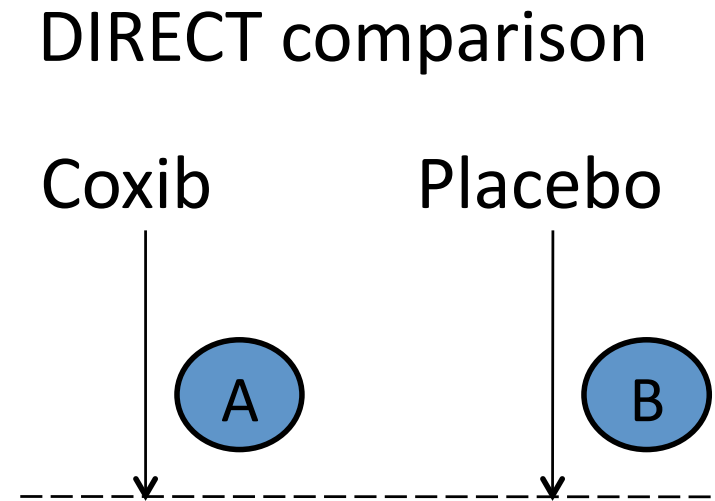
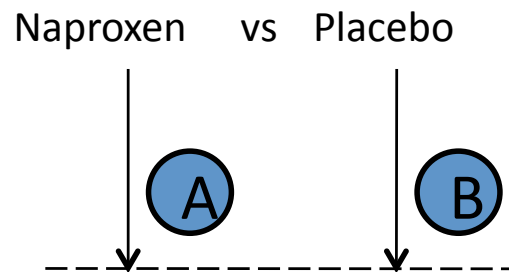


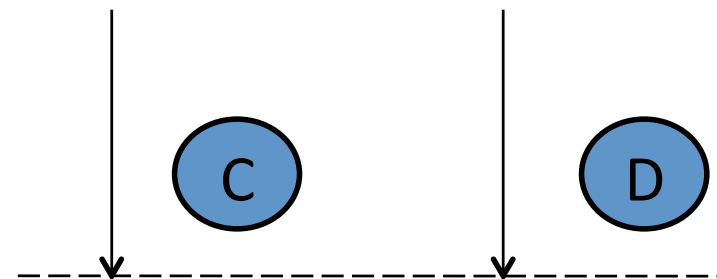
Figure 4.3: Estimating the effects of naproxen

DIRECT comparison



INDIRECT comparison

Coxib vs Placebo



The estimate of the effect of naproxen is a weighted combination of the stratified analyses of all the rate ratios for:
(A vs B) and (C vs D) = (E vs F)

Coxib vs Naproxen

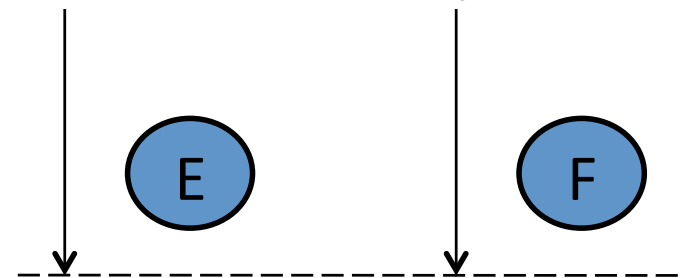
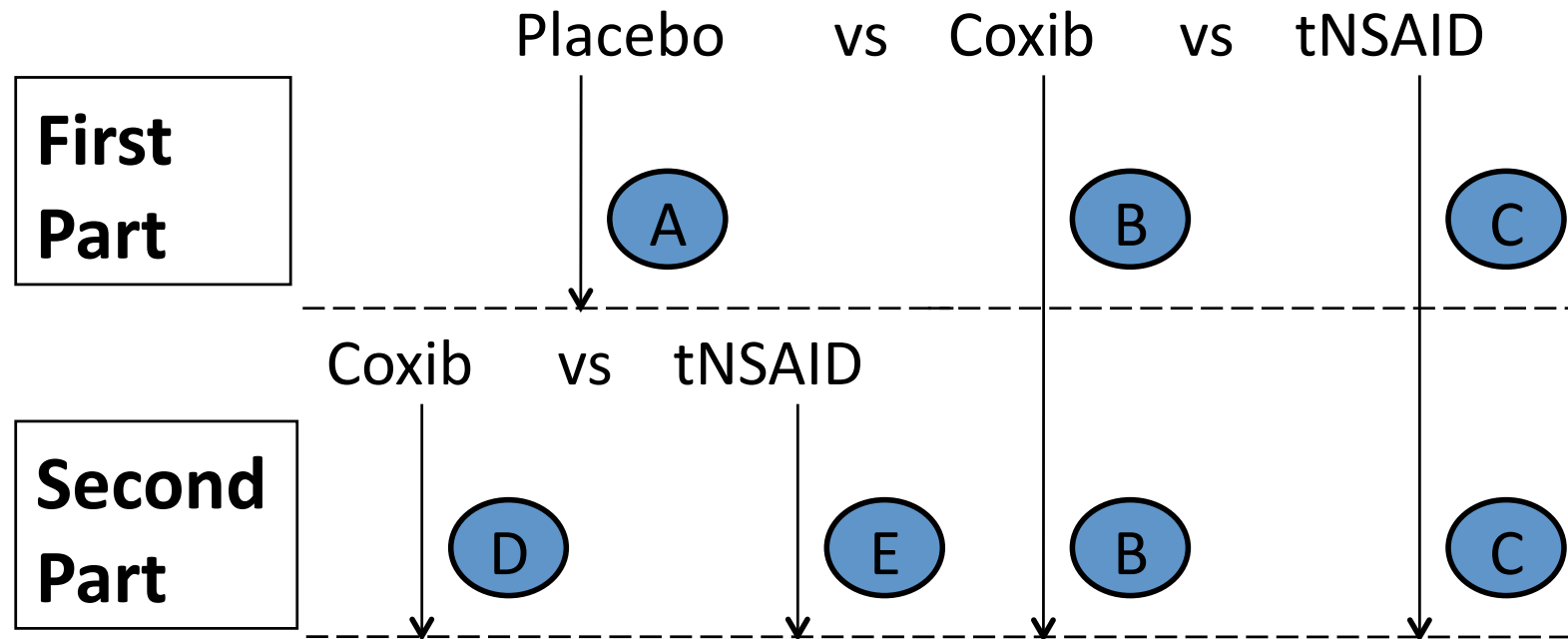


Figure 4.4: Identifying properly randomised comparisons within extension studies



Comparisons available to study

First part:	A vs B	A vs C	B vs C (1 st part)
Second part:		D vs E	B vs C (2 nd part)

CHAPTER 5: Baseline features of included studies

5.1 Study population

5.1.1 Results of electronic searches

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5.2.2 Coxib versus traditional NSAID

5.2.3 Traditional NSAID versus placebo

5.2.4 NSAIDs with antiplatelet effects versus NSAIDs without antiplatelet effects

5.2.5 Coxib versus another coxib

5.2.6 One coxib versus same coxib (high dose versus low dose)

5.2.7 Typical doses used

5.2.8 Summary of available data by comparisons

5.3 Baseline characteristics of study participants for which IPD available

5.3.1 Age, demographics and indication for treatment

5.3.2 Prior medical history, smoking status and concomitant medication use

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5.4 Summary of baseline data for IPD

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Table 5.1 Available data, by comparison

Table 5.2 Unpublished data, by comparison

Table 5.3 Baseline characteristics of trial participants for which individual participant data was available

Table 5.4 Baseline characteristics of trial participants for selected large-scale trials

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Figure 5.1 Flow diagram for electronic literature searches

5.1 Study population

5.1.1 *Results of electronic searches*

The study searches found a total of 25285 reports (titles and abstracts) from multiple sources. Figure 5.1 shows the flow diagram from the literature search and full details of the electronic searches are provided in Appendix 1. After 2107 duplicate reports were removed, 21110 reports were excluded by double-checking from myself and a member of the CNT Secretariat based on title and abstract. Reasons for exclusion included: not a study of a coxib or tNSAID (n=11978); not being a randomised trial (n=6520); being less than 4 weeks (n=1585); being a study of topical/ocular therapy (n=119); not being adult human (n=847); confounded study design (n=50) and being a secondary study report (n=11).

In total, 2068 potentially relevant reports retrieved for full text review. 1280 studies were excluded because eligibility criteria were not met: not being a coxib or NSAID (n=590); not being a randomised trial (n=201); being less than 4 weeks (n=108); confounded study design (n=183); and being a duplicate/secondary study report (n=98).

In total, 788 published and unpublished trials were identified: 287 involving a coxib, and 501 trials involving a traditional NSAID (but not a coxib). Information from these trials were then organised into relevant comparisons, with some trials contributing to more than one comparison. All studies were cross-checked against publications, clinical study reports or abstracts to ensure there was no duplication of results, correct numbers of participants and events: if there was no such corresponding information, such comparisons were considered unpublished and the relevant investigator/company/sponsor were asked to confirm outcomes. As mentioned previously, the pharmaceutical manufacturers of coxibs (Pfizer, Novartis, Merck and GlaxoSmithKline) all provided individual participant data for studies they sponsored, with the exception of valdecoxib from the former. Tabular data for studies of this drug and a newer traditional NSAID, naproxinod were included in subsequent analyses.

5.2 Comparisons

Data from the randomised trials were grouped according to the comparison being tested. These were split into those that supplied individual participant data, those for which tabular data were available (the combination of these data comprised total available data for analyses) and trials for which no data on either numbers of patients randomised or outcomes could be extracted. A full list of the individual trials, including – for each trial - the treatments tested, the number of patients and key outcomes reported, and whether individual participant data were available is presented in the Appendix Tables 1-6. A summary of these trials, total numbers of participants and person-years by randomised comparisons is provided below (Table 5.1).

5.2.1 *Coxib versus placebo*

Among the 151 trials involving a comparison of a coxib versus placebo, there were a total of 200 comparisons, incorporating data available on 87,741 participants and 52,099 person-years. Individual participant data were available for 84% of the participants, corresponding to 89% of the person-time. Data were available from 184 (92%) of the relevant comparisons (only 16 comparisons were missing), corresponding to around 99.5% of the person-time. These statistics are summarised in Table 5.1 and the detail for each comparison is shown in Appendix Table 1. Unpublished data contributed 43 of the comparisons (23.4%), corresponding to 10.9% of the participants and 5.1% of the person-time (Table 5.2).

5.2.2 *Coxib versus traditional NSAID*

Among the 120 trials involving a comparison of a coxib versus a traditional NSAID, there were a total of 149 comparisons, incorporating data available on 136,535 participants and 126,106 person-years. Individual participant data were available for 92% of the participants, corresponding to 98% of the person-time. In total, data were available from 96% of the relevant comparisons (only 6 comparisons were missing), corresponding to 99.9% of the person-time. These statistics are summarised in Table 5.1 and the detail for each comparison is shown in Appendix Table 2. Unpublished data

contributed 22 of the comparisons (15.4%), corresponding to 5.0% of the participants and 1.9% of the person-time (Table 5.2).

As pre-specified, this comparison was divided into coxibs versus traditional NSAIDs with persistent antiplatelet activity (all naproxen) *and* traditional NSAIDs without persistent antiplatelet activity (predominantly diclofenac and ibuprofen). The latter comprised the majority of available data by participants (48,441 and 88,198 persons respectively) and person-years (25,125 and 100,994 person-years respectively).

5.2.3 Traditional NSAID versus placebo

Among the 132 trials involving a comparison of a traditional NSAID versus placebo, there were a total of 162 comparisons, incorporating data available on 37,640 participants and 17,496 person-years. Individual participant data were available for 48% of the participants, corresponding to 47% of the person-time. In total, data were available from 79% of the relevant comparisons (44 comparisons were missing), corresponding to around 94% of the person-time. Unpublished data contributed 11 of the comparisons (7%). These statistics are summarised in Table 5.1 and the detail for each comparison is shown in Appendix Table 3.

5.2.4 Traditional NSAID with antiplatelet effects versus traditional NSAID without antiplatelet effects

Among the 129 trials involving a comparison of a traditional NSAID with antiplatelet activity versus traditional NSAID without antiplatelet activity, there were a total of 143 comparisons, incorporating data available on 21,472 participants and 5,091 person-years. Individual participant data were not available for any of these comparisons. Data were available from 83% of the relevant comparisons (24 comparisons were missing), corresponding to 90% of the person-time. Unpublished data contributed 4 of the comparisons (3%). These statistics are summarised in Table 5.1 and the detail for each comparison is shown in Appendix Table 4.

5.2.5 One coxib versus another coxib

Among the 36 trials involving a comparison of a coxib versus another coxib, there were a total of 68 comparisons, incorporating data available on 35,817 participants and 11,113 person-years. Individual participant data were available for 99% of the participants, corresponding to 99% of the person-time. In total, data were available from 97% of the relevant comparisons (only 2 were missing), corresponding to all of the known person-time. Unpublished data contributed 17 of the comparisons (25%). These statistics are summarised in Table 5.1 and the detail for each comparison is shown in Appendix Table 5.

5.2.6 One coxib versus same coxib (high dose versus low dose)

Among the 60 trials involving a comparison of a coxib versus the same coxib (high dose versus low dose), there were a total of 77 comparisons, incorporating data available on 32,787 participants and 30,848 person-years. Individual participant data were available for 90% of the participants, corresponding to 97% of the person-time. In total, data were available from 98% of the relevant comparisons (only 3 comparisons were missing), corresponding to 99% of the known person-time. Unpublished data contributed 18 of the comparisons (30%). These statistics are summarised in Table 5.1 and the detail for each comparison is shown in Appendix Table 6.

5.2.7 Typical doses utilised

Standard daily doses utilised in the trials varied slightly, but were most commonly: celecoxib 400-800 mg; etoricoxib 60-90 mg; lumiracoxib 400 mg; rofecoxib 25-50 mg; diclofenac 150 mg; ibuprofen 2400 mg; and naproxen 1000 mg.

5.2.8 Summary of available data by comparisons

Individual participant data were available from 156 randomised trials involving a comparison of a coxib versus placebo or versus a traditional NSAID (or both), in which there were a total of 192 981 participants. As outlined in Table 5.1, the majority of the available data (by person-years) comes from the coxib trials, for which the vast majority of the data is available for individual participants. Unpublished data

contributed a fraction of the main comparisons, and an even smaller proportion of participants and person-years.

Although there are many more traditional NSAID studies without a coxib, these had far fewer participants and were much shorter than the coxib trials, so the data for direct NSAID comparisons versus placebo or other traditional NSAIDs are relatively sparse compared to that for NSAIDs versus coxibs. It is important to note, however, that the numbers of the primary outcomes in the comparisons listed, which provide the power for primary statistical analyses, are presented in Chapters 6 and 7.

5.3 Baseline characteristics of study participants for which IPD available

Baseline characteristics of the participants for which IPD were available are shown, by comparisons, in Tables 5.3. The characteristics in the selected large-scale trials are shown in Table 5.4.

5.3.1 *Age, demographics and indication for treatment*

The mean age was 61.2 years (standard deviation [SD] 11.3), with around two thirds (68%) of participants being female and most (79%) being Caucasian. The indication for treatment was predominantly arthritis (79%), of which osteoarthritis was the major aetiology (60%). Cancer prevention and treatment were the indication for 17% of the coxib versus placebo comparison (Table 5.3).

5.3.2 *Prior medical history, smoking status and concomitant medication*

Apart from the arthritis which was the indication for the randomised trial, other past medical history of disease was present at baseline for a minority of participants: any prior atherosclerosis (including any previous occlusive vascular disease [9%]); diabetes mellitus (7%) and any prior upper GI ulcer (7%). At baseline, 8% of participants were current smokers. At baseline, 14% of participants used aspirin and 11% used

gastroprotectants (although these were more widely used in recent large studies, eg, MEDAL) (Table 5.3).

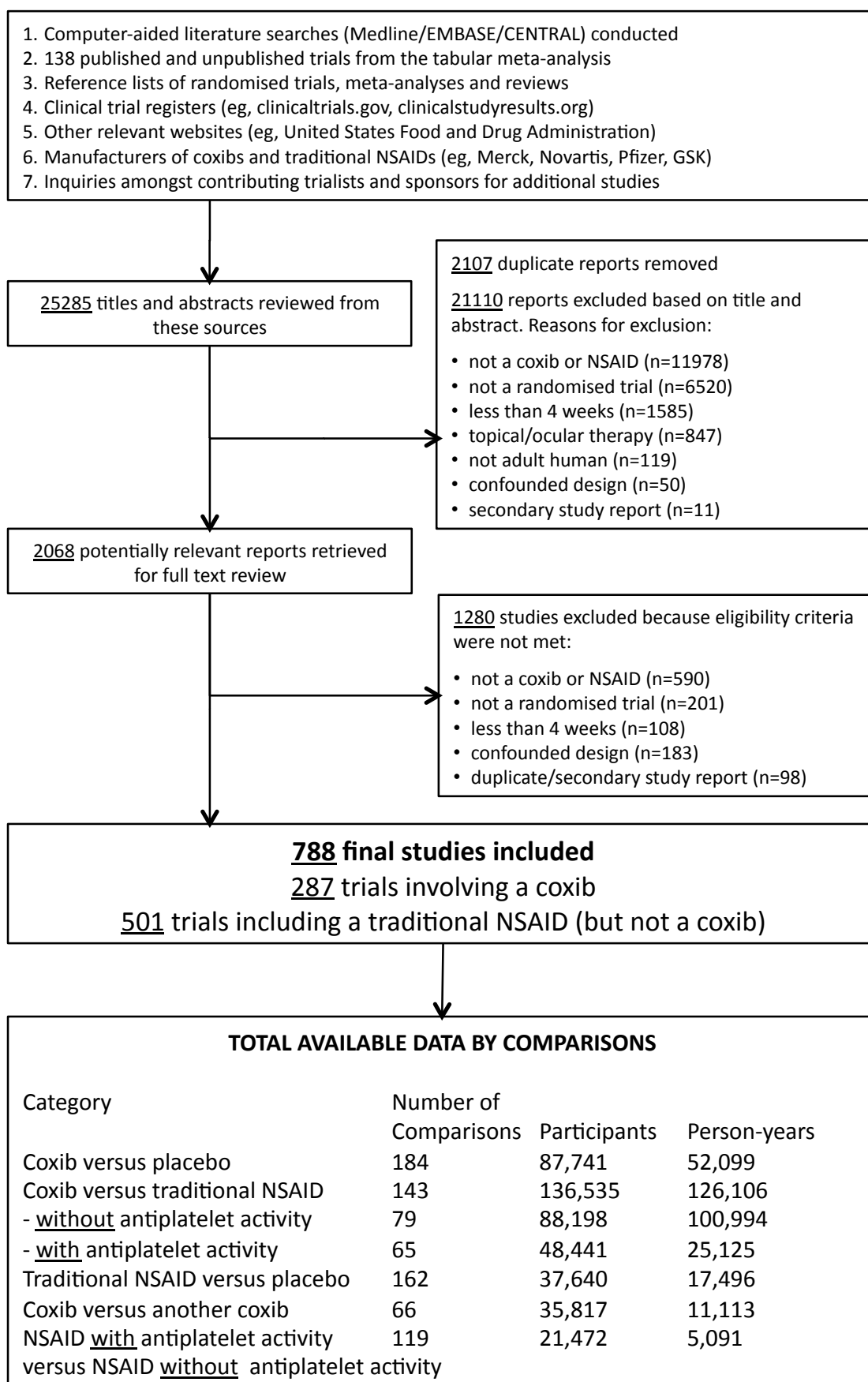
5.3.3 *Physical and laboratory measures*

There were no marked differences between the different comparisons in physical measures: the mean body mass index was 29.3 kg/m², with a mean blood pressure of 132/79 mmHg. There were also no marked differences for biochemical measures: the mean haemoglobin was 13.7 g/dL, the serum creatinine was 79 umol/L and total cholesterol was 5.3 mmol/L (Table 5.3).

5.4 Summary of baseline data for IPD

One advantage of IPD is that robust evaluation of these baseline characteristics can be carried out. In summary, the typical participant in the randomised trials for which IPD was available (the vast majority of trials) was a middle-aged Caucasian (two thirds of whom were women). Although participants typically required a coxib or traditional NSAID for arthritis, only a small proportion had other comorbidities or utilised concomitant aspirin or gastroprotectant therapies. Apart from a slightly higher than expected body mass index, average physical measures were in the normal ranges. These baseline data from the IPD are relevant to put into context the participants who went on to subsequently have the primary outcomes (major vascular events and upper gastrointestinal complications) presented in the next two chapters. Moreover, the fact that the baseline characteristics were remarkably similar for all the coxib versus placebo and coxib versus NSAID comparisons provides justification when carrying out indirect comparisons in subsequent analyses.

Figure 5.1: Flow-diagram of electronic literature searches



CHAPTER 6: Vascular effects of coxibs and traditional NSAIDs

6.1 Comparison of a coxib versus placebo

- 6.1.1 Major vascular events
- 6.1.2 Type and dose of coxib
- 6.1.3 Heart failure and other vascular complications
- 6.1.4 Stroke subtypes
- 6.1.5 Cause-specific mortality
- 6.1.6 Effects by time to first major vascular event
- 6.1.7 Subgroup analyses

6.2 Comparisons of a coxib versus a traditional NSAID

6.3 Comparisons of a coxib versus a traditional NSAID with antiplatelet activity (all naproxen)

- 6.3.1 Major vascular events
- 6.3.2 Type and dose of coxib
- 6.3.3 Heart failure and other vascular complications
- 6.3.4 Stroke subtypes
- 6.3.5 Cause-specific mortality
- 6.3.6 Effects by time to first major vascular event
- 6.3.7 Subgroup analyses

6.4 Comparisons of a coxib versus a traditional NSAID without antiplatelet activity (predominantly diclofenac and ibuprofen)

- 6.4.1 Major vascular events
- 6.4.2 Type and dose of coxib
- 6.4.3 Heart failure and other vascular complications
- 6.4.4 Stroke subtypes
- 6.4.5 Cause-specific mortality
- 6.4.6 Effects by first major vascular event
- 6.4.7 Subgroup analyses

6.5 Comparisons of a traditional NSAID versus placebo

6.5.1 Direct estimates for major vascular events

6.5 Combining direct and indirect comparisons for estimates of major vascular events

6.6 Considering VIGOR as the hypothesis-generating study for vascular effects

6.7 Summary of the vascular effects of coxibs and traditional NSAIDs

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Table 6.2 Overall estimates of effects of major vascular events and heart failure, by type of drug

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Figure 6.1 Effects of COXIBS versus PLACEBO on primary outcome of major vascular events (myocardial infarction, stroke or vascular death)

Figure 6.2 Effect of COXIBS versus PLACEBO on major vascular events, by type of coxib

Figure 6.3 Effects of CELECOXIB versus PLACEBO on major vascular events, by dose

Figure 6.4 Effects of ROFECOXIB versus PLACEBO on major vascular events, by dose

Figure 6.5 Effects of COXIBS versus PLACEBO on heart failure and other vascular complications

Figure 6.6 Effects of COXIBS versus PLACEBO on stroke subtypes (ischaemic, haemorrhagic or unknown)

Figure 6.7 Effects of COXIBS versus PLACEBO on cause-specific mortality

Figure 6.8 Effects of COXIBS versus PLACEBO on major vascular events, by time to first event

Figure 6.9 Effects of COXIBS versus PLACEBO on major vascular events, by baseline characteristics

Figure 6.10 Effects of COXIBS versus PLACEBO on major vascular events, by baseline physical/laboratory measures

Figure 6.11 Effects of COXIBS versus PLACEBO on major vascular events, by selected large-scale trials

Figure 6.12 Effects of COXIBS on primary outcome of major vascular events by type of NSAID (with or without antiplatelet activity)

Figure 6.13 Effects of COXIBS versus NSAIDs with antiplatelet activity on primary outcome of major vascular events (myocardial infarction, stroke or vascular death)

Figure 6.14 Effects of COXIBS versus NSAIDs with antiplatelet activity on heart failure and other vascular complications

Figure 6.15 Effects of COXIBS versus NSAIDs with antiplatelet activity on stroke subtypes (ischaemic, haemorrhagic or unknown)

Figure 6.16 Effects of COXIBS versus NSAIDs with antiplatelet activity on cause-specific mortality

Figure 6.17 Effects of COXIBS versus NSAIDs without antiplatelet activity on primary outcome of major vascular events (myocardial infarction, stroke or vascular death)

Figure 6.18 Effects of COXIBS versus NSAIDs without antiplatelet activity on heart failure and other vascular complications

Figure 6.19 Effects of COXIBS versus NSAIDs without antiplatelet activity on stroke subtypes (ischaemic, haemorrhagic or unknown)

Figure 6.20 Effects of COXIBS versus NSAIDs without antiplatelet activity on cause-specific mortality

Figure 6.21 Effects of NSAIDs with antiplatelet activity versus PLACEBO on primary outcome of major vascular events (myocardial infarction, stroke or vascular death)

Figure 6.22 Effects of NSAIDs without antiplatelet activity versus PLACEBO on primary outcome of major vascular events (myocardial infarction, stroke or vascular death)

Figure 6.23 Effects of COXIBS on primary outcome of major vascular events (MI, stroke or vascular death), by type of comparator

Figure 6.24 Effects of COXIBS versus NSAIDs with antiplatelet activity on major vascular events and myocardial infarctions (excluding the hypothesis-generating VIGOR study)

Figure 6.25 Effects of COXIBS on primary outcome of major vascular events, by type of comparator (excluding the hypothesis-generating VIGOR study)

6.1 COMPARISONS OF A COXIB VERSUS PLACEBO

6.1.1 *Major vascular events*

Overall, 480 first major vascular events (ie, non-fatal myocardial infarction [MI], stroke or vascular death) occurred among 89 placebo-controlled comparisons during 48 078 person years follow-up, 306 during 26 733 person years of exposure to a coxib (1.14%/year) compared with 174 during 21 345 person years of placebo (0.82%/year) (Figure 6.1). This corresponded to a 38% proportional increase in the incidence of a first major vascular event (rate ratio [RR] 1.38, 95% confidence interval [CI] 1.14 to 1.66; $P < 0.001$), reflecting a definite 76% proportional increase in the risk of MI or coronary heart disease (CHD) death (RR 1.76, 1.31 to 2.37; $P < 0.001$), a non-significant difference in the incidence of stroke (RR 1.09, 0.78 to 1.52; $P = 0.64$) and a 54% non-significant increase in other vascular death (RR 1.54, 0.99 to 2.42; $P = 0.06$). The proportional increase in major vascular events corresponded to an annual absolute excess of about 3 (95% CI 1 to 5) major vascular events per 1000 patients allocated a coxib instead of placebo.

6.1.2 *Type and dose of coxib*

There was no evidence that the proportional excess incidence of major vascular events varied among the different coxibs studied (χ^2 for heterogeneity = 1.7, degrees of freedom (df) = 5; $P = 0.89$) (Figure 6.2). However, as only two coxibs (rofecoxib and celecoxib) had recorded appreciable numbers of such outcomes, the power to identify any real differences that might exist between coxibs was limited. Nonetheless, there was no significant difference between these two coxibs in the rate ratio for major vascular events (χ^2 for heterogeneity = 0.0, $P = 0.9$).

Too few major vascular events were available to reliably assess dose-response in placebo-controlled trials of etoricoxib, lumiracoxib, or valdecoxib. For celecoxib, there was evidence of a trend towards an increasing rate ratio for a major vascular event with higher daily doses (trend $\chi^2 = 6.3$; $P = 0.01$) (Figure 6.3). For rofecoxib, 90% of major vascular events occurred at a dose of 25 mg daily, with few events at lower or

higher daily doses, so dose dependence could not be evaluated reliably (trend $\chi^2 = 0.0$; $P = 0.83$) (Figure 6.4).

6.1.3 Heart failure and other vascular complications

In coxibs versus placebo comparisons that supplied IPD, 157 patients had a report of first hospitalisation for heart failure during 33 069 person-years follow-up (Figure 6.5). Overall, allocation to a coxib compared with placebo was associated with a 2.3-fold increased risk of heart failure (RR 2.28, 1.62 to 3.20; $P < 0.001$) corresponding to an absolute annual excess of 4 (95% CI 1 to 7) people with heart failure per 1000 allocated to a coxib. In these trials, 133 patients with a report of heart failure (85%) had no other vascular event recorded during the trial.

In coxibs versus placebo comparisons that supplied IPD, there were a total of 244 patients who had some other vascular complication (coronary revascularisation, pulmonary embolus, peripheral arterial event, resuscitated cardiac arrest or hospitalisation for unstable angina) during 40 813 person years follow-up (Figure 6.5). Overall, there was no significant difference in the risk of any other vascular complications between patients allocated a coxib and patients allocated placebo (RR 1.00, 0.76 to 1.32; $P = 1.0$).

6.1.4 Stroke subtypes

In coxibs versus placebo comparisons that supplied IPD, there were a total of 104 ischaemic strokes, 24 haemorrhagic strokes and 33 strokes of unknown aetiology, during 40 338 person years follow-up (Figure 6.6). Allocation to a coxib had no significant effect on any stroke (RR 1.09, 95% CI 0.78-1.52) and there was no significant heterogeneity ($c^2 = 0.81$, $P = 0.67$) among the rate ratios for ischaemic stroke (1.11, 95% CI 0.74-1.69) haemorrhagic stroke (0.71, 95% CI 0.29-1.74) and unknown stroke (1.44, 95% CI 0.65-3.19).

6.1.5 Cause-specific mortality

Overall, allocation to a coxib was associated with a 58% proportional increase in the risk of any vascular death (144 deaths: RR 1.58, 1.11 to 2.24; $P = 0.01$) (Figure 6.7). There was no significant difference in the incidence of non-vascular mortality (330 deaths; RR 1.00, 0.80 to 1.25; $P = 0.9$) for coxib versus placebo. Although 220 colorectal cancer deaths (RR 0.98; 0.75-1.27, $P = 0.87$) accounted for 84% of all cancer deaths, this was due predominantly to the results of one trial (the VICTOR study). Overall, allocation to a coxib was associated with a 22% proportional increase in overall mortality (RR 1.22, 1.04 to 1.44; $P = 0.01$), predominantly due to the increase in vascular mortality.

6.1.6 Effects by time to first major vascular event

Of the 89 placebo-controlled comparisons in which at least one major vascular event was observed, eight were long term trials with over one year of scheduled treatment (Figure 6.8). Incorporating the tabular data from fifteen trials in which the duration was known to be less than six months, there was no strong evidence of a latent effect in the incidence of major vascular events (trend $\chi^2 = 2.8$; $P = 0.09$).

6.1.7 Subgroup analyses

Even before accounting for multiple testing, there was no strong evidence of heterogeneity by pre-specified baseline categories (age, sex, indication for treatment, prior disease, concomitant drug use, smoking, drinking, BMI, blood pressure, laboratory measures) (Figures 6.9 and 6.10). When the larger trials were considered separately from the other trials for this comparison, there was no strong evidence of heterogeneity (χ^2 for heterogeneity = 7.8; $df = 6$; $P = 0.26$) (Figure 6.11). When larger placebo-controlled trials that stopped early (ie, APPROVe, VICTOR and VIP) were excluded, the rate ratio [RR] estimates of effect for MVEs remained at 1.37 (95% CI 1.02 to 1.78, $P < 0.001$), suggesting no strong evidence of bias by this factor.

6.2 COMPARISONS OF A COXIB VERSUS A TRADITIONAL NSAID

Overall, 1132 first major vascular events occurred in 126 106 person-years for all comparisons of a coxib versus a traditional NSAID. There was no significant difference in the incidence of a first major vascular event between participants allocated to a coxib and those allocated to a traditional NSAID: 614 events during 64 003 person years of exposure to a coxib (0.91%/year) compared with 518 events during 62 103 person years of exposure to a traditional NSAID (0.83%/year) (RR 1.08, 0.96 to 1.22; $P = 0.19$) (Fig 6.12). However, as pre-specified, there was marked heterogeneity ($\chi^2 = 8.5$; $P = 0.004$) between the rate ratios for major vascular events in trials comparing a coxib with a traditional NSAID with antiplatelet activity (in this case, all naproxen: RR 1.49; 1.16 to 1.92; $P = 0.002$) and those comparing a coxib with a traditional NSAID without antiplatelet activity (predominantly diclofenac and ibuprofen: RR 0.98; 0.86 to 1.13; $P = 0.78$). These results would suggest that naproxen at the doses studied was associated with a lower risk of major vascular events compared to coxibs and to traditional NSAIDs without antiplatelet activity.

6.3 COMPARISONS OF A COXIB VERSUS A NSAID WITH ANTIPLATELET ACTIVITY (ALL NAPROXEN)

6.3.1 *Major vascular events*

Overall, 268 first major vascular events occurred among 46 comparisons, 175 during 16 284 person years of exposure to a coxib (1.07%/year) compared with 93 during 13 336 person years of naproxen (0.70%/year) (Figure 6.13). This corresponded to a 49% proportional increase in the incidence of a first major vascular event (RR 1.49, 1.16 to 1.92; $P = 0.002$), reflecting a twofold proportional increase in the risk of MI or CHD death (2.11, 1.44 to 3.09; $P < 0.001$), a non-significant difference in the incidence of stroke (RR 1.14, 0.74 to 1.73; $P = 0.61$), and a non-significant (and imprecise) difference in other vascular deaths (RR 1.50, 0.78 to 2.85; $P = 0.22$). The proportional increase in major vascular events corresponded to an annual absolute excess of about 3 (95% CI 1 to 5) major vascular events per 1000 patients allocated a coxib instead of naproxen.

6.3.2 *Type of coxib and dose response*

In comparisons of a coxib versus naproxen, there was no evidence that the proportional excess incidence of major vascular events varied among the different coxibs (χ^2 for heterogeneity = 6.6, df = 4; P = 0.16). However, as only two coxibs (rofecoxib and lumiracoxib) had recorded appreciable numbers of such outcomes in such trials, the power to identify any real differences that might exist between coxibs was limited. There was, however, no significant difference between these two coxibs in the rate ratio for major vascular events (χ^2 for heterogeneity = 0.09, P = 0.95).

Too few major vascular events were available to reliably assess dose-response in trials comparing naproxen versus celecoxib, etoricoxib or valdecoxib. For lumiracoxib versus naproxen, 90% of major vascular events occurred at a dose of 400 mg daily, with few events at lower or higher daily doses, so dose dependence could not be evaluated reliably (trend χ^2 = 0.6; P = 0.43). For rofecoxib versus naproxen, there was no significant evidence of a trend, albeit with limited power (trend χ^2 = 0.1; P = 0.79).

6.3.3 *Heart failure and other vascular complications*

In comparisons of coxib versus naproxen that supplied IPD, 96 first events of hospitalisation for heart failure occurred in 26 527 person-years, corresponding to a non-significant difference in the overall incidence in heart failure events (RR 1.17, 0.76 to 1.79; P = 0.53) (Figure 6.14). Of these reports, 83 (88%) episodes of heart failure were not associated with reports of other vascular events.

In comparisons of coxib versus naproxen that supplied IPD, 135 other vascular complications (coronary revascularisation, pulmonary embolus, peripheral arterial event, resuscitated cardiac arrest and hospitalisation for unstable angina) occurred in 26 226 person years (Figure 6.14). There was no significant difference in the overall incidence of other vascular complications (RR 1.03, 0.72 to 1.47; P = 0.95).

6.3.4 *Stroke subtypes*

During 25 970 person years follow-up, there were a total of 72 ischaemic strokes, 13 haemorrhagic strokes and 13 strokes of unknown aetiology. Allocation to a coxib versus naproxen had no significant effect on any stroke (RR 1.14, 95% CI 0.74-1.73) and there was no significant heterogeneity ($\chi^2 = 2.11$, $P = 0.35$) among the rate ratios for ischaemic stroke (0.95, 95% CI 0.58 -1.57) haemorrhagic stroke (2.03, 95% CI 0.58 - 7.06) and unknown stroke (1.67, 95% CI 0.46 – 6.00). (Figure 6.15)

6.3.5 *Cause-specific mortality*

Allocation to a coxib compared to allocation to naproxen was associated with a non-significant 53% proportional increase in any vascular death (62 deaths; RR 1.53, 0.89 to 2.62; $P = 0.13$) (Figure 6.16). There were too few deaths to assess the incidence of other cause-specific mortality reliably (8 known non-vascular and 68 unknown deaths in 27 168 person-years follow-up). Overall, allocation to a coxib compared to allocation to naproxen was associated with no significant difference in death by any cause (138 deaths: rate ratio 1.23; 0.86 to 1.75; $P = 0.25$).

6.3.6 *Effects by time to first major vascular event*

Of the 42 coxib versus naproxen comparisons, nine were long term trials with one year or longer of scheduled treatment. Incorporating the tabular data from six trials in which the duration was known to be less than six months, there was no significant evidence of a latent effect for naproxen versus coxib in the incidence of major vascular events (trend $\chi^2 = 2.2$; $P = 0.14$).

6.3.7 *Subgroup analyses*

Even before accounting for multiple testing, there was no strong evidence of heterogeneity by pre-specified baseline categories for coxib versus naproxen comparisons (ie, age/sex, indication, prior disease, concomitant drug use, smoking, drinking, BMI/BP, laboratory measures). Nor was there any evidence of heterogeneity

when the larger coxib versus naproxen trials were considered separately from the other trials (χ^2 for heterogeneity = 2.1; df = 5; P = 0.84).

6.4 COMPARISONS OF A COXIBS VERSUS A NSAID WITHOUT ANTIPLATELET ACTIVITY (PREDOMINANTLY DICLOFENAC AND IBUPROFEN)

6.4.1 *Major vascular events*

Overall, 864 first major vascular events occurred among 43 comparisons, 439 during 51 540 person years of exposure to a coxib (0.85%/year) compared with 425 during 48 767 person years of a traditional NSAID without antiplatelet activity (0.87%/year) (Figure 6.17). There was no significant difference in the incidence of a first major vascular event (RR 0.98, 0.86 to 1.13; P = 0.78), reflecting no significant difference in the incidences of myocardial infarction or CHD death (RR 1.03, 0.85 to 1.28; P = 0.78), any stroke (RR 0.93, 0.73 to 1.19; P = 0.53) or any other vascular death (RR 0.97, 0.72 to 1.29; P = 0.82). Coxib versus diclofenac comparisons (RR 0.96, 95% CI 0.84 to 1.11; P = 0.60) accounted for more than 80% of the outcomes, and there were no overall difference in the incidence of a first major vascular event compared to those versus ibuprofen (RR 0.94, 95% CI 0.61 to 1.46; P = 0.78) or versus any other traditional NSAID (RR 3.00, 0.97 to 9.31; P = 0.06) (χ^2 for heterogeneity = 3.9, df = 2; P = 0.15).

6.4.2 *Type of coxib and dose*

There was no evidence that the proportional excess incidence of major vascular events varied among the different coxibs versus a traditional NSAID without antiplatelet activity (χ^2 for heterogeneity = 6.4, df = 4; P = 0.14). However, as one coxib (etoricoxib) had recorded the vast majority of such outcomes, the power to identify any real differences that might exist between coxibs was limited. For etoricoxib, principally studied at 60mg and 90mg versus diclofenac in the MEDAL programme, there was no evidence of a trend for coxib versus a traditional NSAID without antiplatelet activity (trend χ^2 = 0.7; P = 0.42).

6.4.3 Heart failure & other vascular complications

In coxibs versus traditional NSAIDs without antiplatelet activity comparisons that supplied IPD, 200 first events of hospitalisation for heart failure occurred in 98 610 person-years, corresponding to no significant difference in the overall incidence of heart failure events (rate ratio 1.01, 0.76 to 1.35; $P=0.98$) (Figure 6.18). Of these events reported, 178 (89%) were not associated with other vascular events.

In coxibs versus traditional NSAIDs without antiplatelet activity comparisons that supplied IPD, 334 other vascular complications occurred in 97 744 person-years, with no significant difference in the overall incidence for coxibs versus traditional NSAIDs without antiplatelet activity (rate ratio 0.97, 0.78 to 1.22; $P=0.77$) (Figure 6.18).

6.4.4 Stroke subtypes

During 97 960 person years follow-up, there were a total of 200 ischaemic strokes, 43 haemorrhagic strokes and 35 strokes of unknown aetiology, without any significant difference by stroke subtype between patients allocated a coxib and patients allocated NSAIDs without antiplatelet activity (χ^2 for heterogeneity = 2.05, $p = 0.36$) (Figure 6.19). Allocation to a coxib had no significant effect on any stroke (RR 1.09, 95% CI 0.78-1.52) and there was no significant heterogeneity ($\chi^2 = 0.81$, $P = 0.67$) among the rate ratios for ischaemic stroke (1.11, 95% CI 0.74-1.69) haemorrhagic stroke (0.71, 95% CI 0.29-1.74) and unknown stroke (1.44, 95% CI 0.65-3.19).

6.4.5 Cause-specific mortality

Between patients allocated a coxib and patients allocated traditional NSAIDs without antiplatelet activity in 98 434 person years of follow-up, there were no significant differences in the incidence of any vascular death (282 deaths; RR 0.96, 0.75 to 1.22; $P=0.67$), non-vascular mortality (158 deaths; RR 1.05, 0.76 to 1.45; $P=0.82$), nor of mortality by any cause (488 deaths; RR 1.01, 0.84 to 1.21; $P=0.98$) (Figure 6.20).

6.4.6 *Effects by time to first major vascular event*

Of the 43 coxib versus NSAID without antiplatelet activity comparisons, 7 were long-term trials with one year or more of scheduled treatment. Incorporating the tabular data from four trials in which the duration was known to be less than six months, there was no evidence of any latent effect for traditional NSAIDs without antiplatelet activity versus coxibs in the incidence of major vascular events (trend $\chi^2 = 1.4$; $P=0.24$).

6.4.6 *Subgroup analyses*

Even before accounting for multiple testing, there was no strong evidence of heterogeneity by pre-specified baseline categories (ie, age/sex, indication, prior disease, concomitant drug use, smoking, drinking, BMI/BP, laboratory measures).

Although the MEDAL programme constitutes around 80% of the data for this comparison, there was no strong evidence of heterogeneity when the larger trials of coxib versus NSAID without antiplatelet activity were considered separately from the other trials (χ^2 for heterogeneity= 4.3, df = 6; $P = 0.63$).

6.5 COMPARISONS OF A TRADITIONAL NSAID VERSUS PLACEBO

6.5.1 *Direct estimates of major vascular events*

Overall, 97 first major vascular events occurred during 7070 person-years in 14 placebo-controlled comparisons of a NSAID with antiplatelet activity (naproxen, indobufen or flurbiprofen), corresponding to a non-significant 27% reduction in the risk of a major vascular event (RR 0.73, 95% CI 0.48 to 1.13; $P=0.11$) (Figure 6.21).

For NSAIDs without antiplatelet activity, there were 24 first major vascular events during 1191 person-years in 15 placebo-controlled comparisons, corresponding to a non-significant (and extremely imprecise) relative risk estimate of 0.66 (95% CI 0.26 to 1.69; $P=0.24$) (Figure 6.22).

6.6 COMBINING DIRECT AND INDIRECT ESTIMATES FOR MAJOR VASCULAR EVENTS FOR COXIBS AND TRADITIONAL NSAIDS

Direct estimates of treatment effect (from comparisons of a coxib versus placebo or NSAID versus placebo) were combined with indirect information (from comparisons of a coxib versus placebo and a coxib versus NSAID) in order to provide estimates of comparative effects for the different medications (see Table 6.1). Incorporating indirect evidence as well as direct evidence slightly attenuated the estimated effect for major vascular events for coxib versus placebo from 1.38 to 1.30 (95% CI 1.09 to 1.55), corresponding to a moderate 30% increase in the risk of major vascular events associated with coxibs.

Incorporating indirect evidence was of more value in estimating the effects of traditional NSAIDs due to the paucity of direct evidence for these drugs. Compared with placebo, the summary rate ratio for major vascular events for NSAIDs with antiplatelet activity was attenuated to 0.84 (0.66 to 1.08) from 0.73, corresponding to a small non-significant decrease in the risk of major vascular events associated with these NSAIDs (primarily naproxen). Although this result suggests up to one third reduction in major vascular events cannot be excluded, it is compatible with a neutral cardiovascular phenotype (ie, neither beneficial nor harmful).

Although the direct estimates of effect for a traditional NSAID without antiplatelet activity versus placebo were extremely imprecise, incorporating indirect evidence altered the qualitative effect of this comparison considerably. Compared with placebo, the summary rate ratios for NSAIDs without antiplatelet activity was 1.30 (1.05 to 1.62) from 0.66 using the direct evidence alone. This corresponded to a moderate 30% increase in the risk of major vascular events associated (ie, approximately the same proportional effect as coxibs).

6.7 CONSIDERING VIGOR AS THE HYPOTHESIS-GENERATING STUDY

Overall results for major vascular events for coxibs versus other comparators are shown in Figure 6.23. Since it could be argued that VIGOR generated the hypothesis for major vascular events being tested in the other randomised trials, inclusion of VIGOR in the main analyses may have led to relative risk estimates that are appreciably biased. However, if the VIGOR study was considered separately as a hypothesis-generating study, its exclusion from the primary outcome estimates led to only a small attenuation of the relative risk of a major vascular events for those allocated a coxib compared to those allocated naproxen (rate ratio 1.37, 95% CI 1.04 to 1.82, $P=0.03$), caused by the relative risk of MI or CHD death being reduced from 2.08 to 1.79 (Figure 6.24). Moreover, exclusion of the hypothesis-generating VIGOR study made little overall change on the combined direct and indirect estimates of major vascular events for those allocated coxib or traditional NSAID, as shown in Table 6.1 and Figure 6.25.

6.8 SUMMARISING THE OVERALL RESULTS FOR VASCULAR EVENTS

Overall, allocation to a coxib is associated with a 30-40% increased risk of major vascular events, predominantly mediated by a two-fold increased risk of coronary events (myocardial infarction and coronary heart disease deaths). These analyses indicate that a traditional NSAID with antiplatelet activity (especially diclofenac and ibuprofen) is associated with similar excesses. However, a traditional NSAID with antiplatelet activity (ie, naproxen) is associated with a neutral (neither beneficial nor harmful) effect on major vascular events, predominantly by neutral effects on CHD. Hence, as shown in Table 6.2, although all the drugs tested cause around a two-fold increased risk of hospitalisation for heart failure, if considering effects on major vascular events alone, traditional NSAIDs with persistent antiplatelet activity (ie, naproxen) would appear to be the therapy of choice. However, these vascular results also need to be considered in the context of upper gastrointestinal outcomes associated with these medications, developed further in the next two chapters.

TABLE 6.1 Major vascular effects (MVE): Estimates for comparisons from direct evidence, combining direct and indirect evidence, and excluding the VIGOR study (using regression)

Comparison	Relative risk of major vascular event (95% CI)		
	Direct evidence	Direct + indirect evidence	Direct + indirect (excluding VIGOR)
COXIB vs placebo	1.38 (1.14 – 1.66)	1.30 (1.09 – 1.55)	1.29 (1.08 – 1.54)
Traditional NSAID <u>with</u> antiplatelet activity vs placebo	0.73 (0.48 – 1.13)	0.84 (0.66 – 1.08)	0.87 (0.67 – 1.13)
Traditional NSAID <u>without</u> antiplatelet activity vs placebo	0.66 (0.26 – 1.69)	1.30 (1.05 – 1.62)	1.29 (1.04 – 1.61)

TABLE 6.2 Overall relative and absolute estimates of effects of major vascular events and heart failure events, by type of drug

Type of drug	Effect on outcome and estimated relative risk (absolute risk for average-risk individuals from the CNT Collaboration in brackets)	
	Major vascular events	Heart failure events
COXIB	↑ 1.3- to 1.4-fold (3 per 1000py)	↑ ↑ ~2-fold (4 per 1000py)
Traditional NSAID <u>with</u> antiplatelet activity (eg, naproxen)	↔ (neutral) (no effect)	↑ ↑ ~2-fold (4 per 1000py)
Traditional NSAID <u>without</u> antiplatelet activity (eg, diclofenac)	↑ 1.3- to 1.4-fold (3 per 1000py)	↑ ↑ ~2-fold (4 per 1000py)

Figure 6.1: Effects of COXIBS versus PLACEBO on major vascular events (myocardial infarction, stroke or vascular death)

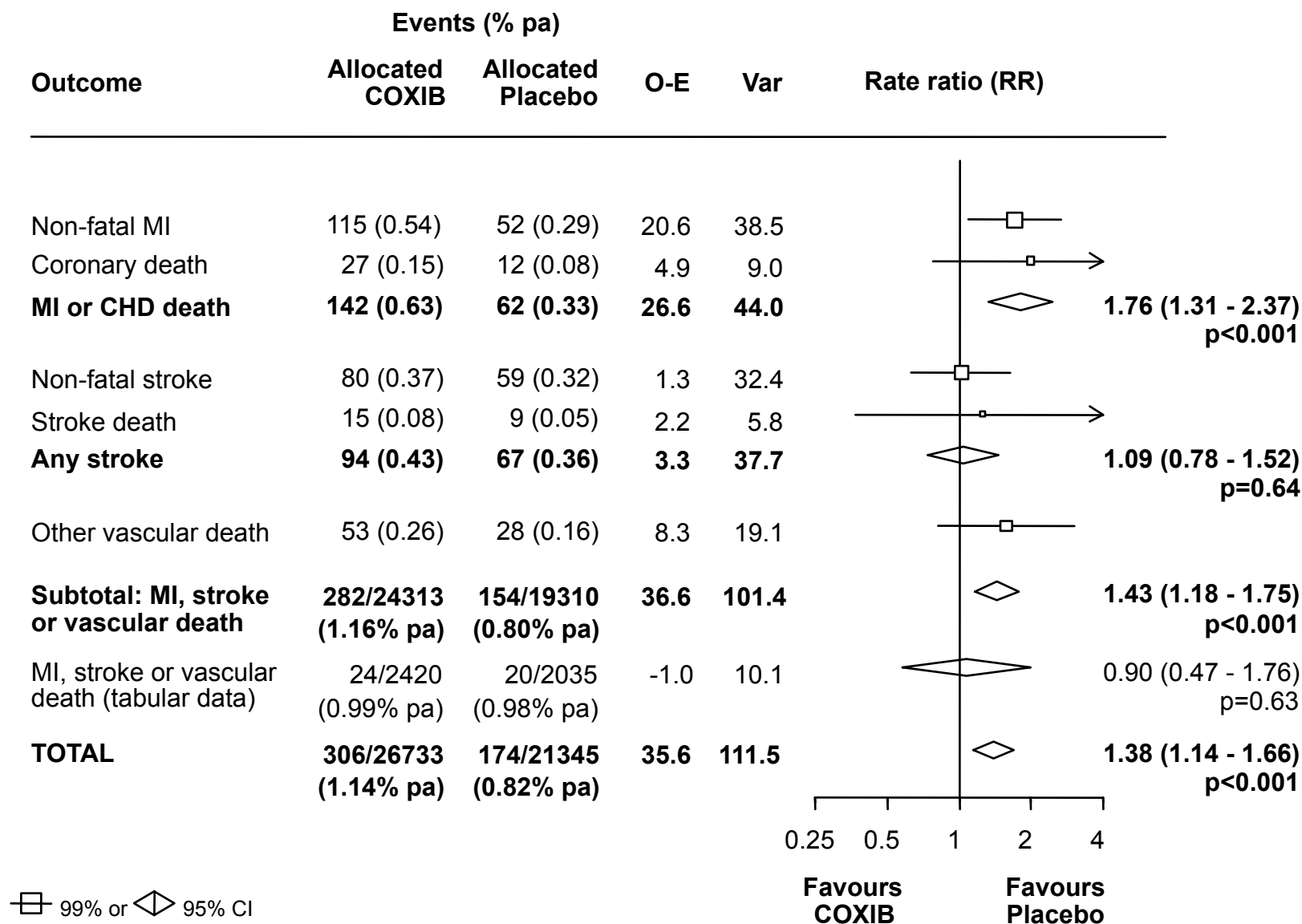
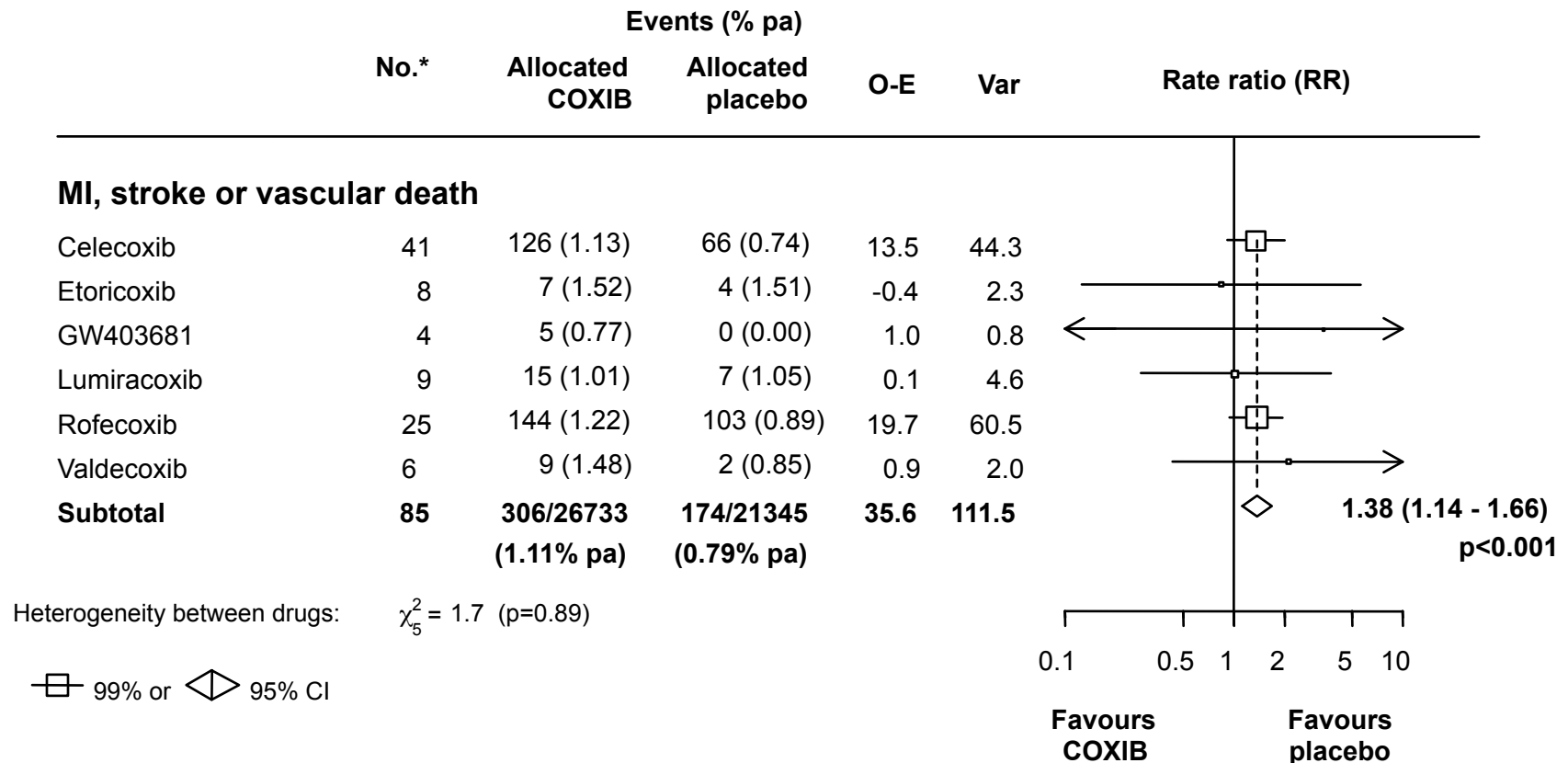


**Figure 6.2: Effects of COXIBS vs PLACEBO
on major vascular events, by type of coxib**



* Number of randomised comparisons that involved at least one event

**Figure 6.3: Effects of CELECOXIB vs PLACEBO
on major vascular events, by dose**

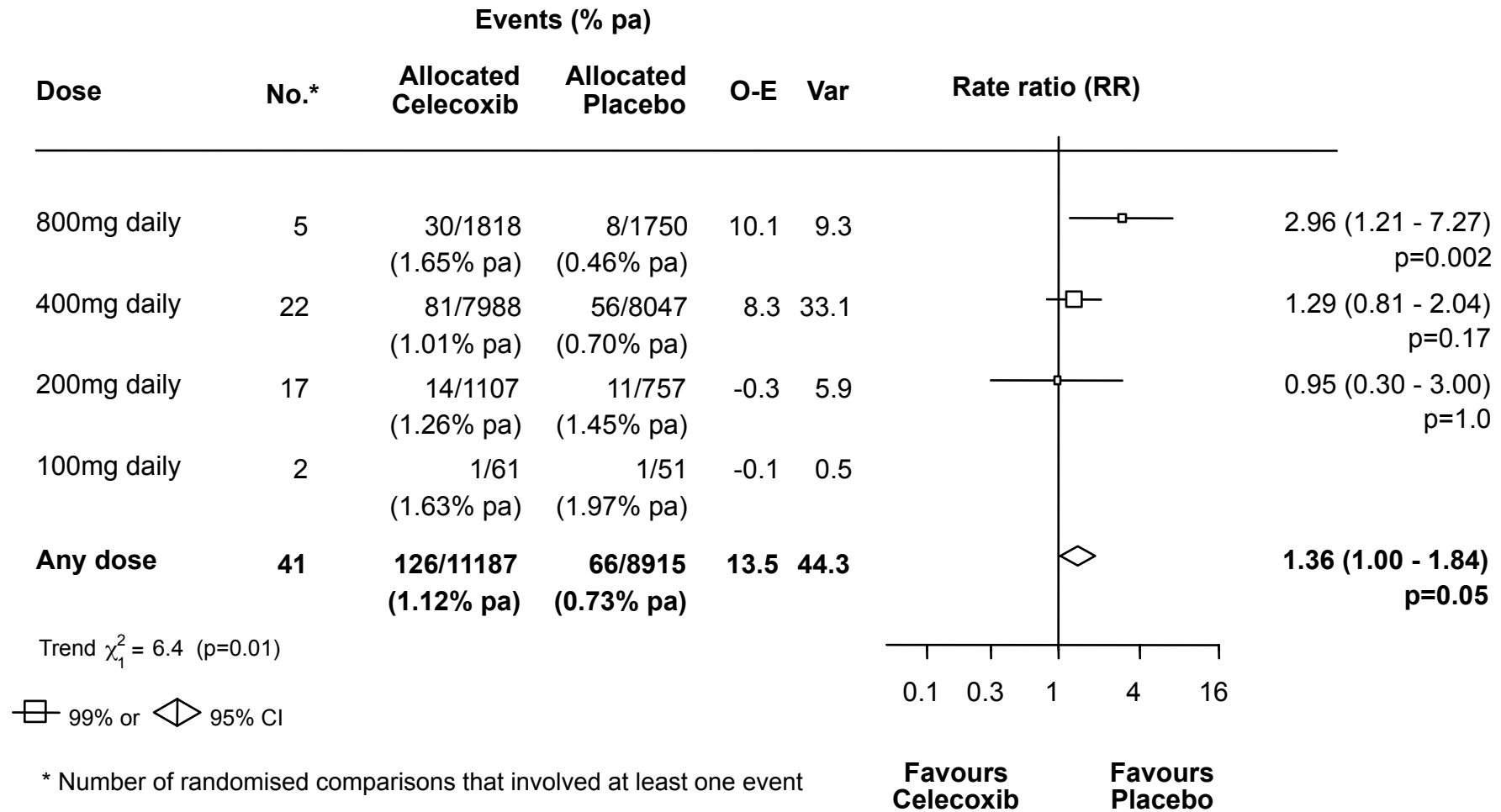


**Figure 6.4: Effects of ROFECOXIB vs PLACEBO
on major vascular events, by dose**

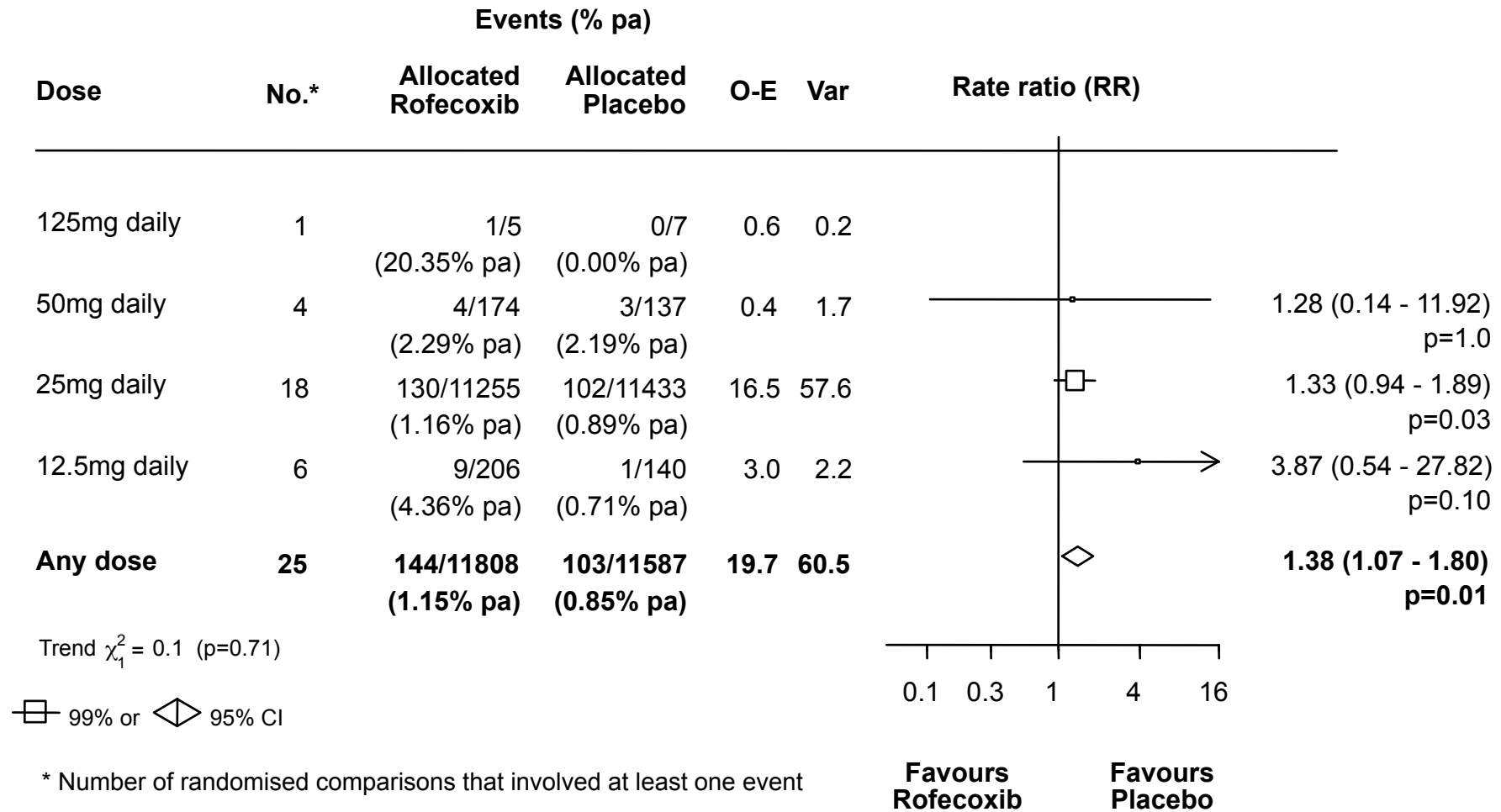


**Figure 6.5: Effects of COXIBS vs PLACEBO
on heart failure and other vascular complications**

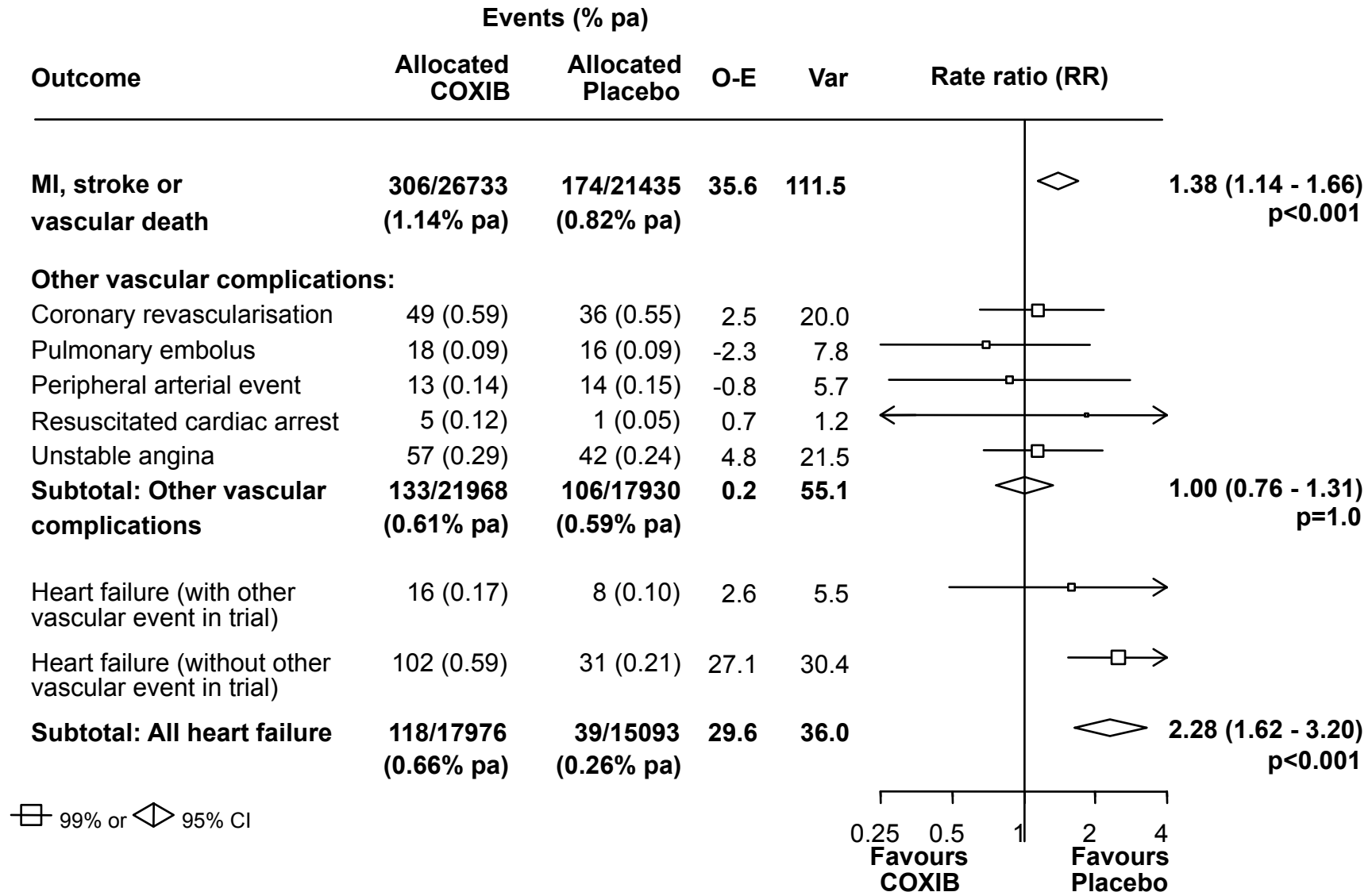


**Figure 6.6: Effects of COXIBS vs PLACEBO
on stroke subtypes (ischaemic, haemorrhagic or unknown cause)**

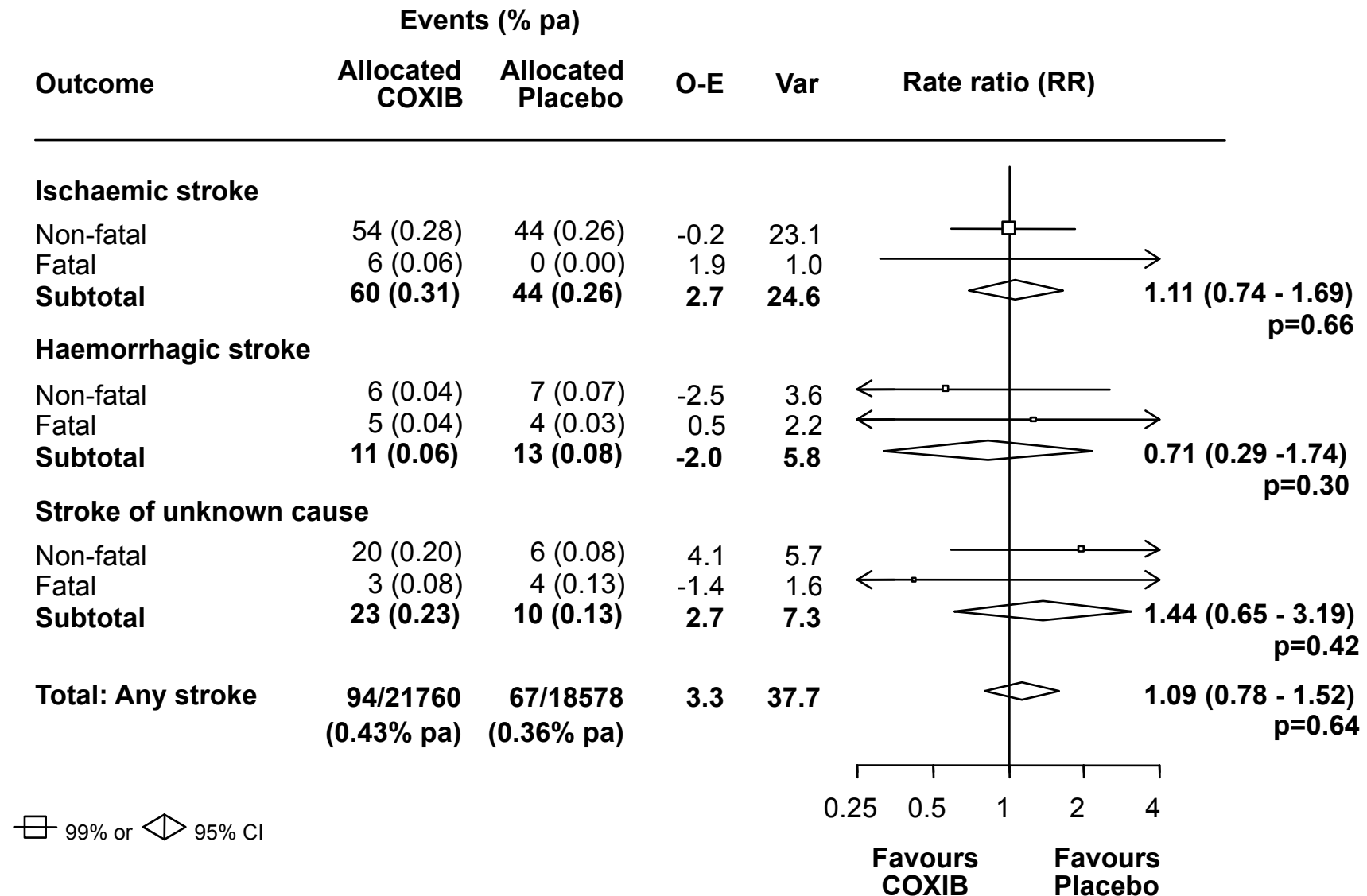


**Figure 6.7: Effects of COXIBS vs PLACEBO
on cause-specific mortality (vascular, non-vascular or unknown cause)**

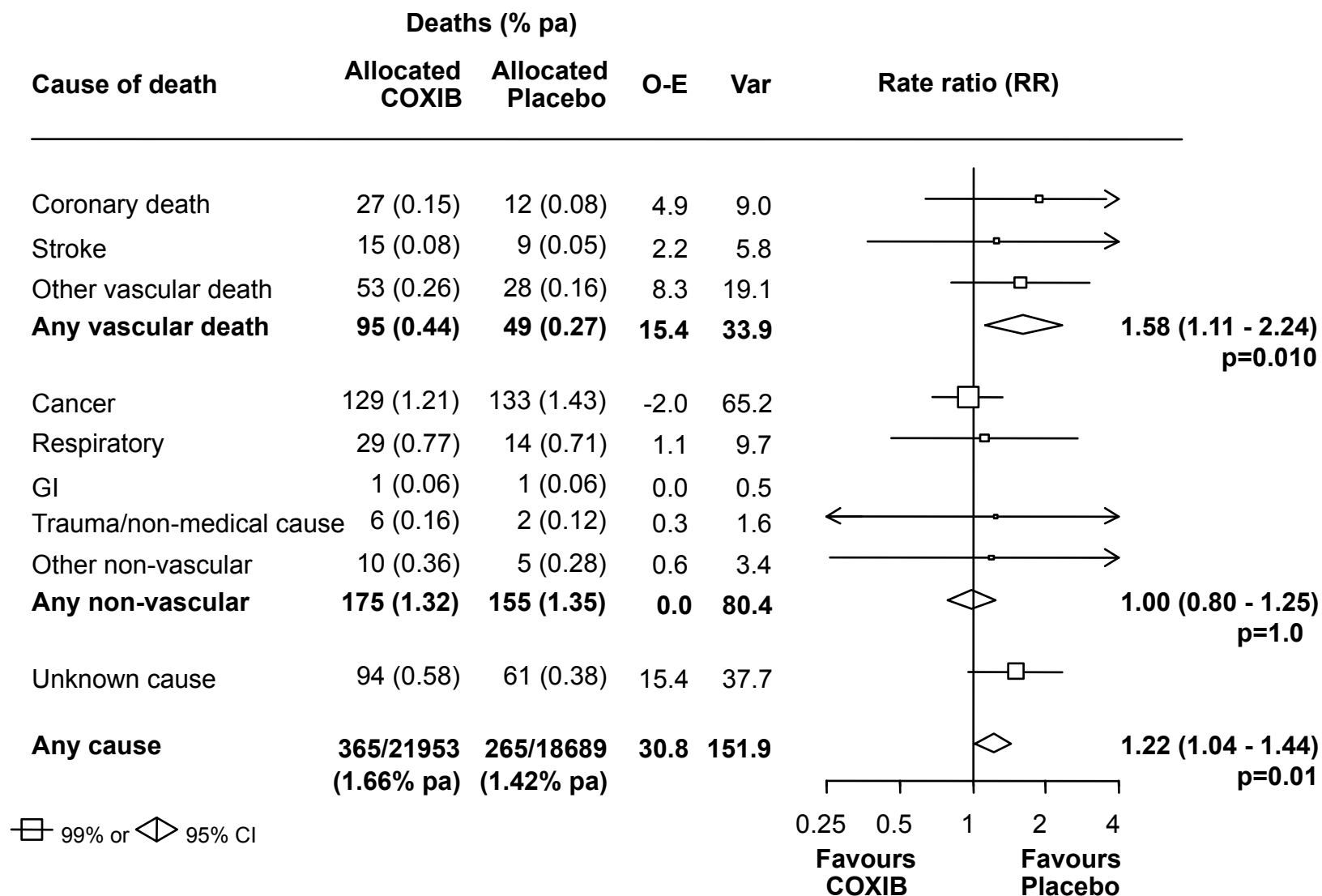
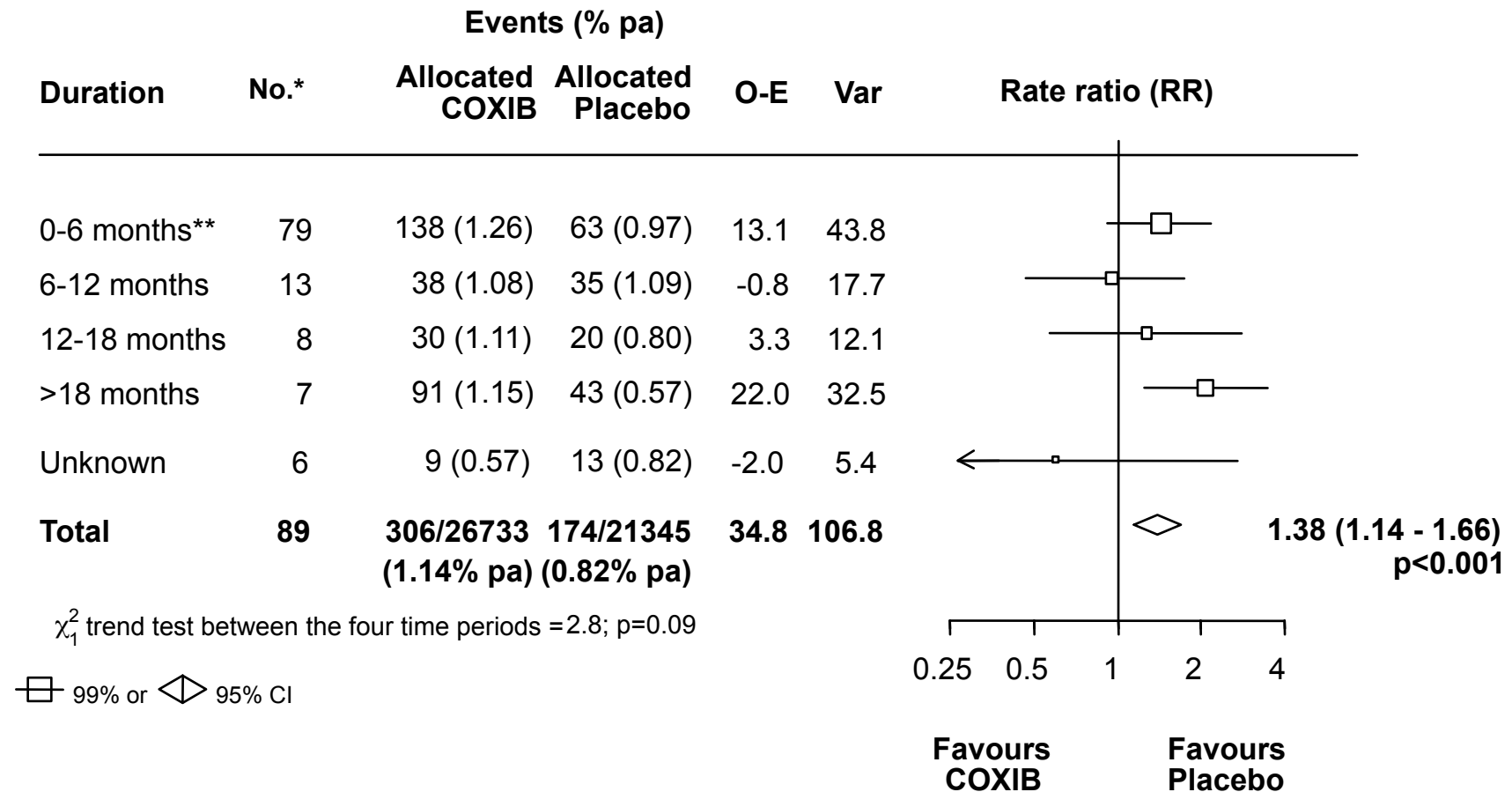


**Figure 6.8: Effects of COXIBS vs PLACEBO
on major vascular events, by time to first event**



- Number of randomised comparisons that involved at least one event
- **Includes tabular data from 15 trials in which the trial duration was known to be <6 months

Figure 6.9: Effects of COXIBS vs PLACEBO on major vascular events, by baseline characteristics

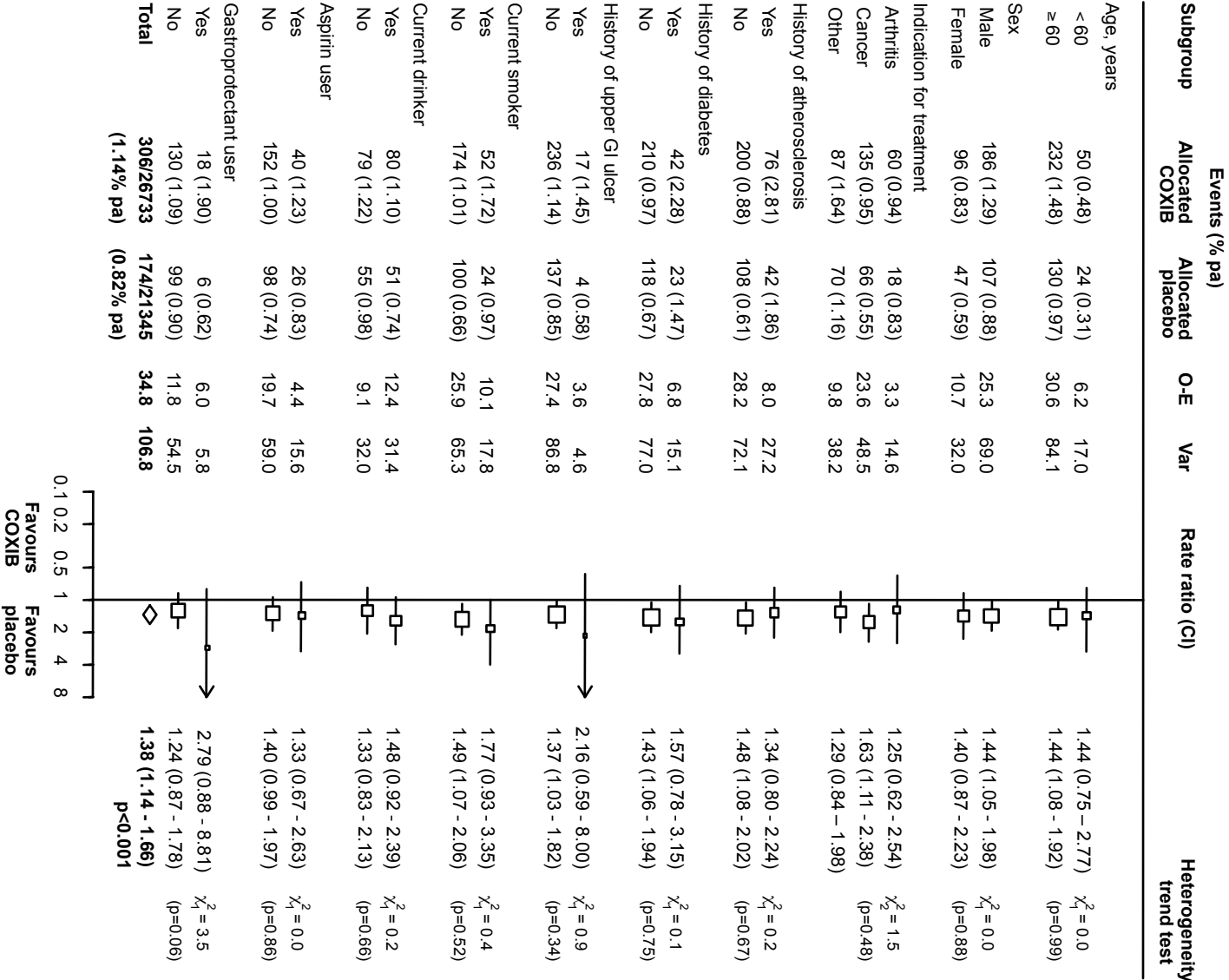


**Figure 6.10: Effects of COXIBS vs PLACEBO
on major vascular events, by baseline physical/laboratory measures**

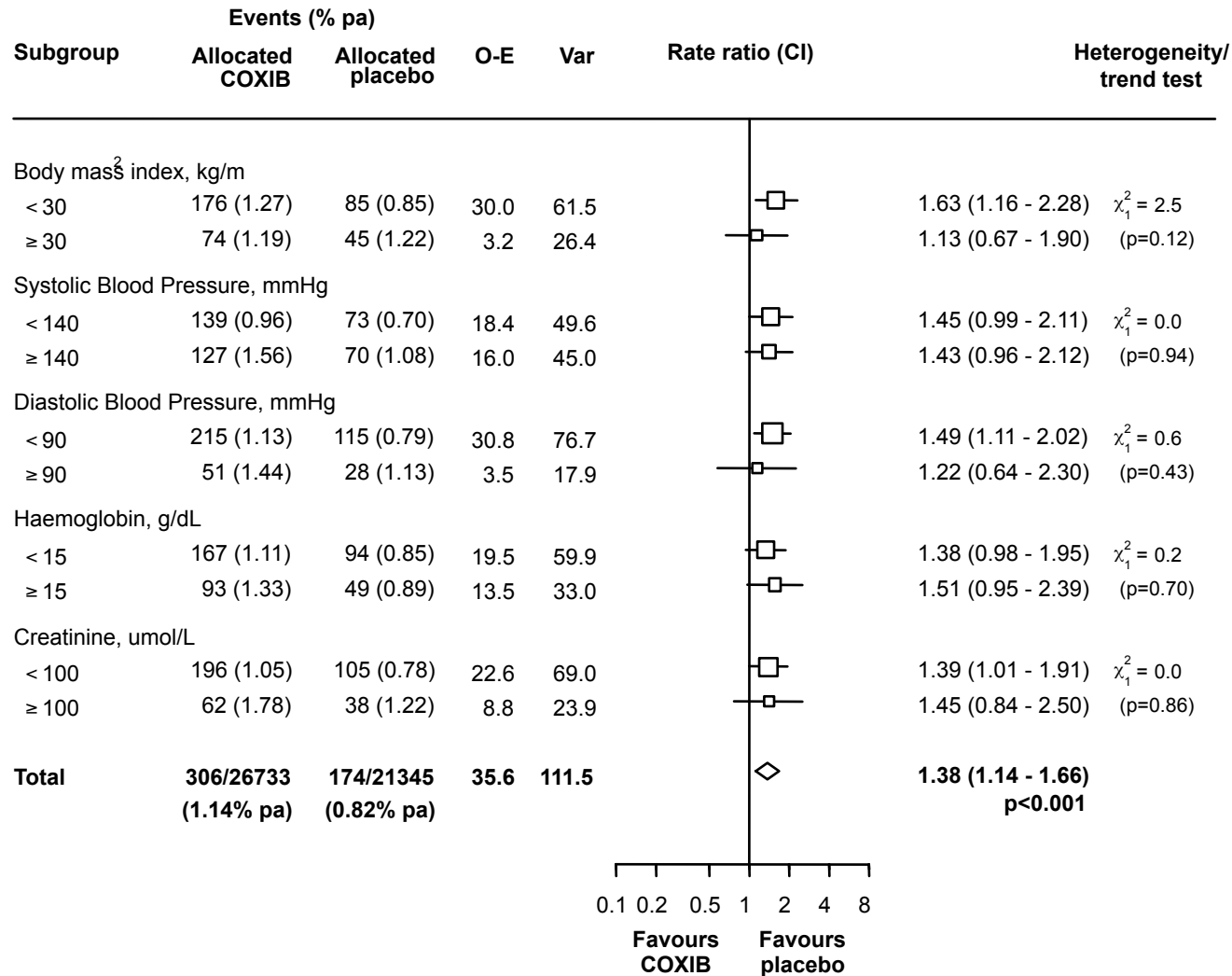


**Figure 6.11: Effects of COXIBS vs PLACEBO
on major vascular events, in selected large-scale trials**

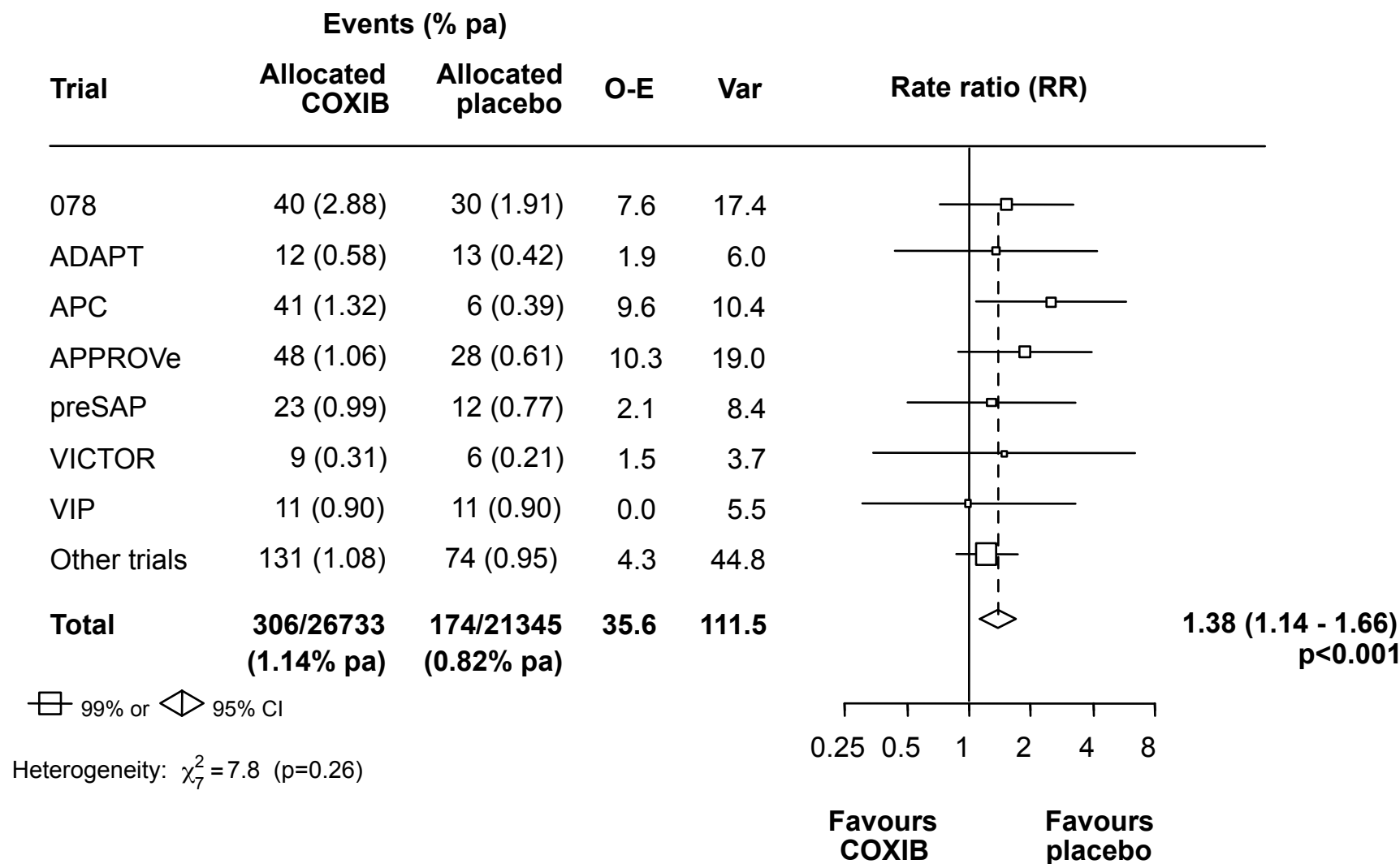
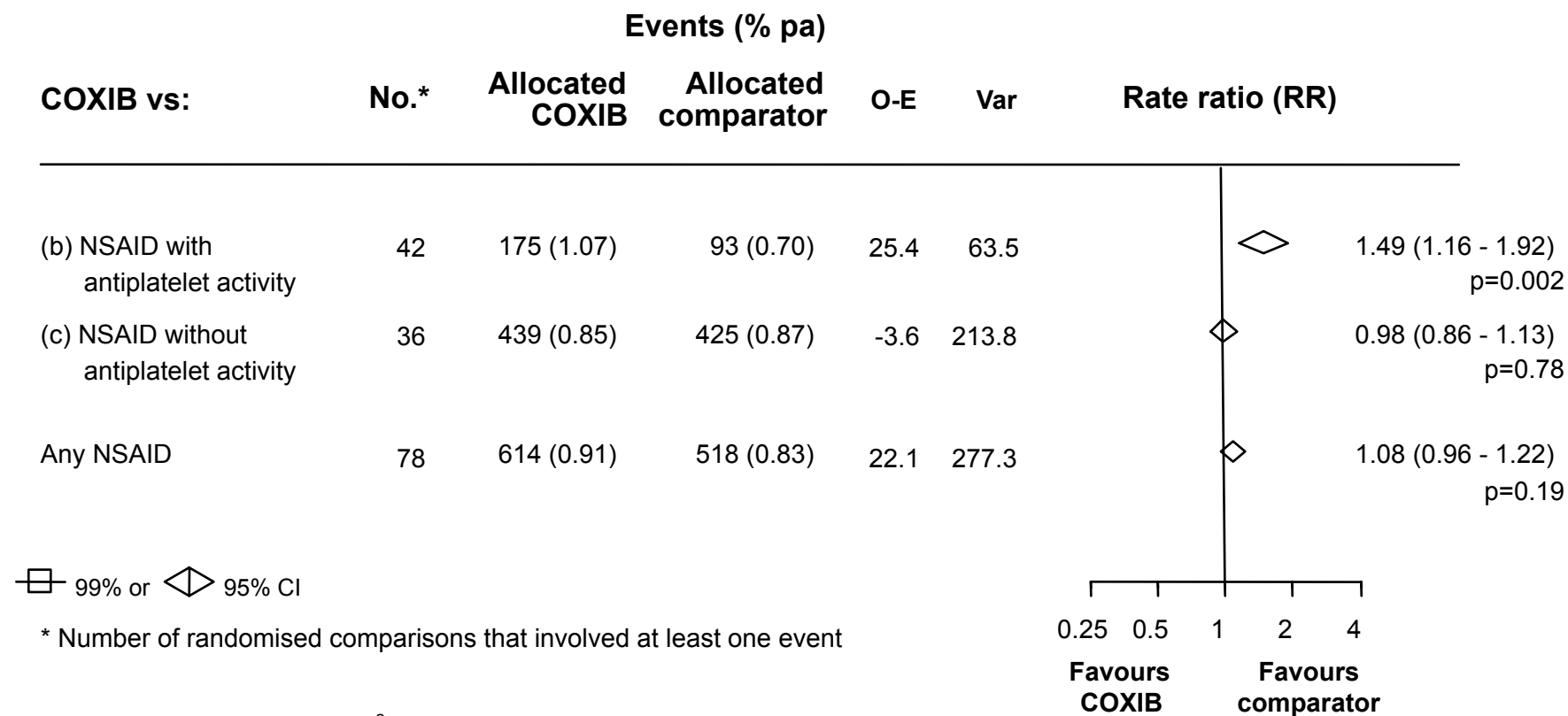


Figure 6.12: Effects of COXIBS vs NSAID on major vascular events, by type of NSAID (with or without antiplatelet activity)



Heterogeneity between (b) and (c): $\chi^2_1 = 8.5$ (p=0.004)

Figure 6.13: Effects of COXIBS vs NSAIDs with antiplatelet activity on major vascular events (myocardial infarction, stroke or vascular death)

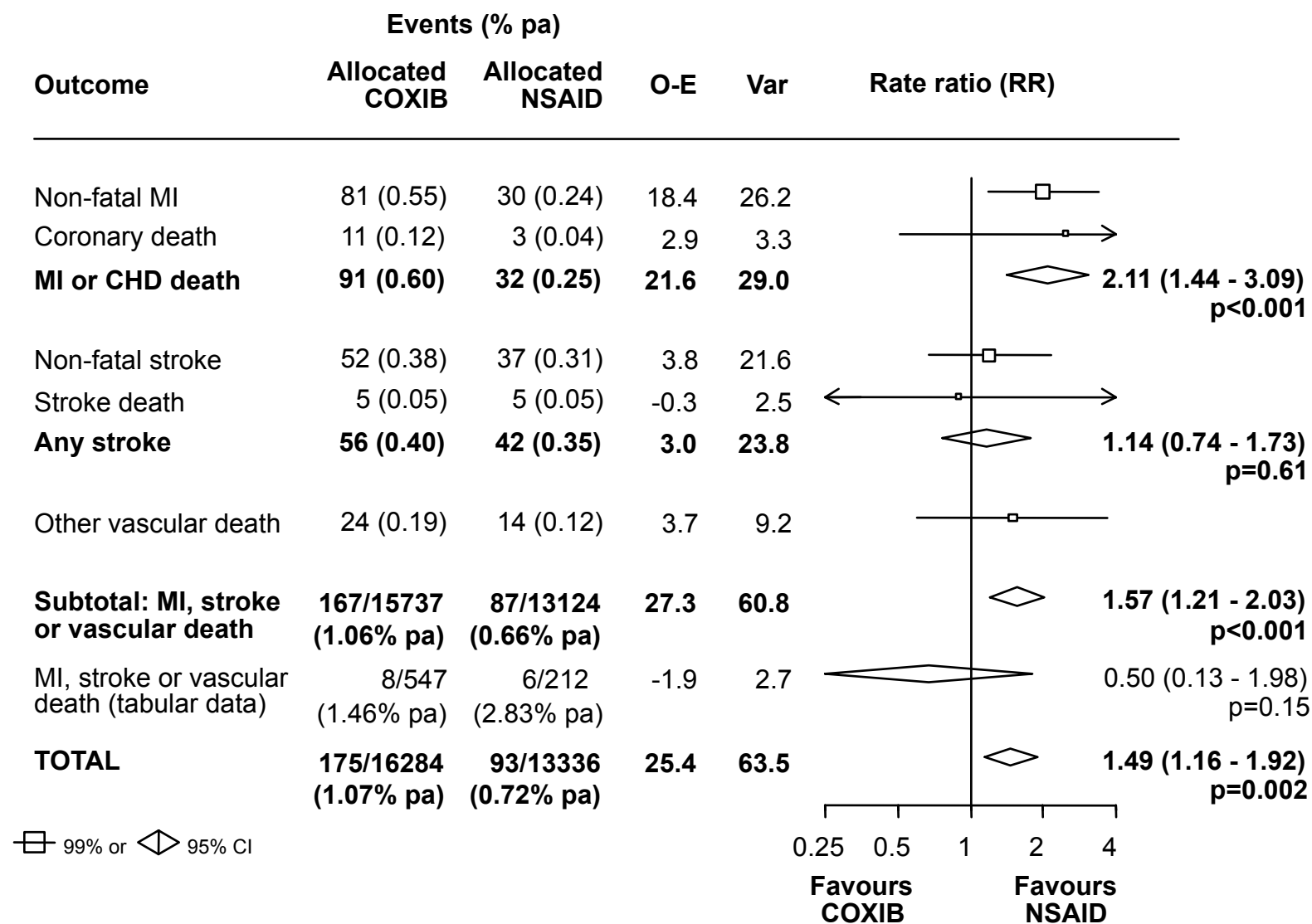


Figure 6.14: Effects of COXIBS vs NSAIDs with antiplatelet activity on heart failure and other vascular complications

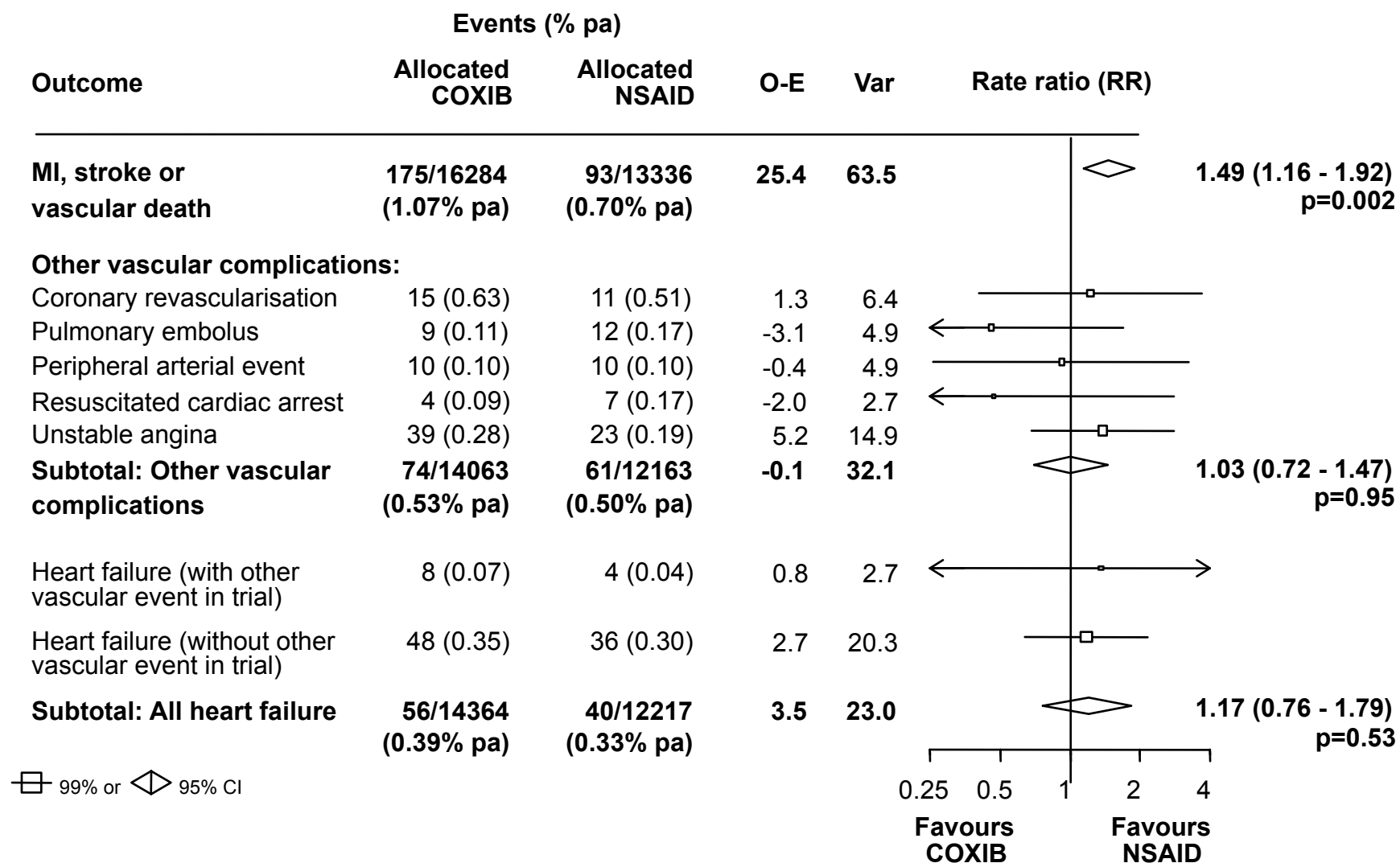


Figure 6.15: Effects of COXIBS vs NSAIDs with antiplatelet activity on stroke subtypes (ischaemic, haemorrhagic or unknown)

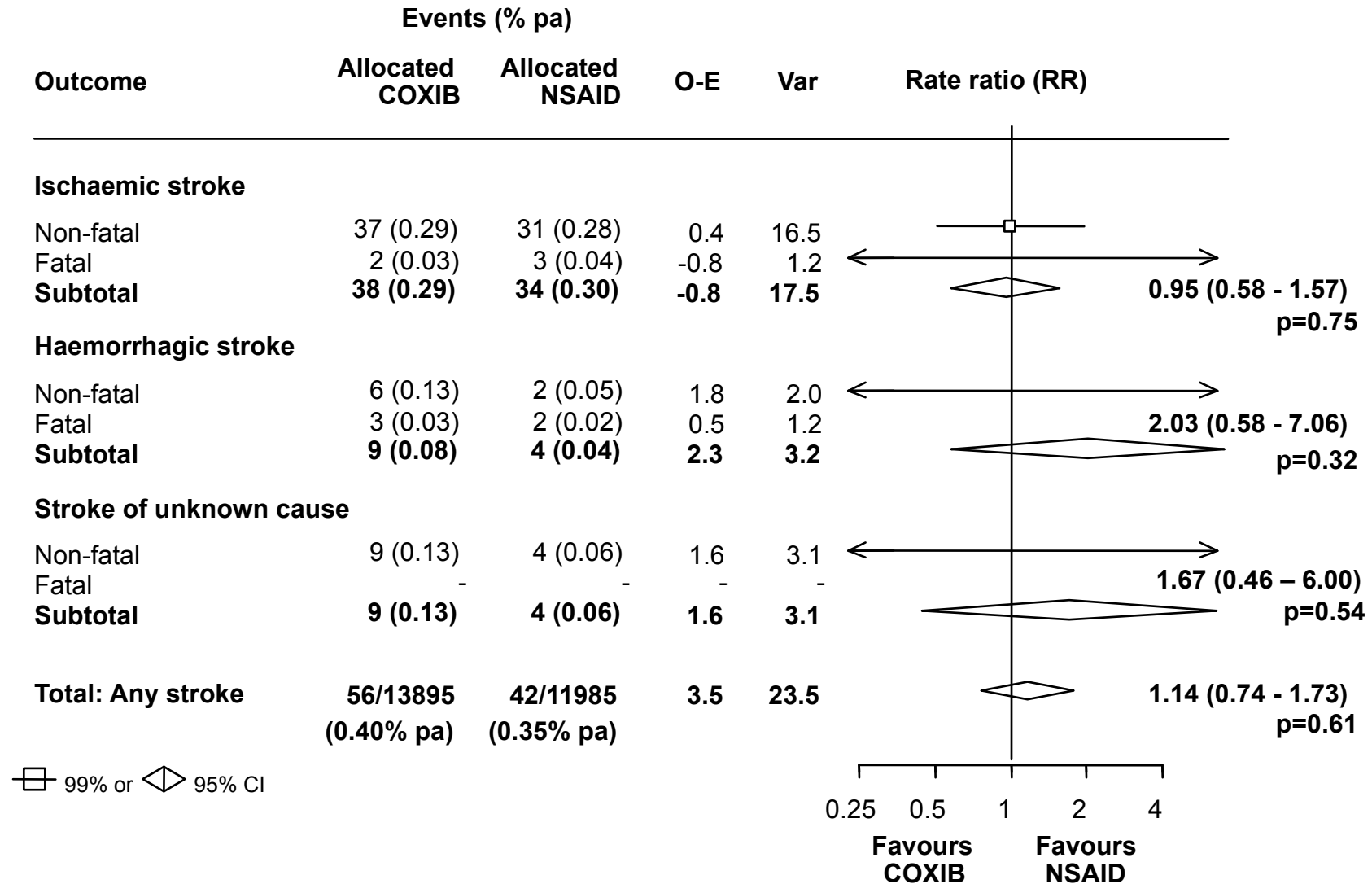


Figure 6.16: Effects of COXIBS vs NSAIDs with antiplatelet activity on cause-specific mortality (vascular, non-vascular or unknown cause)

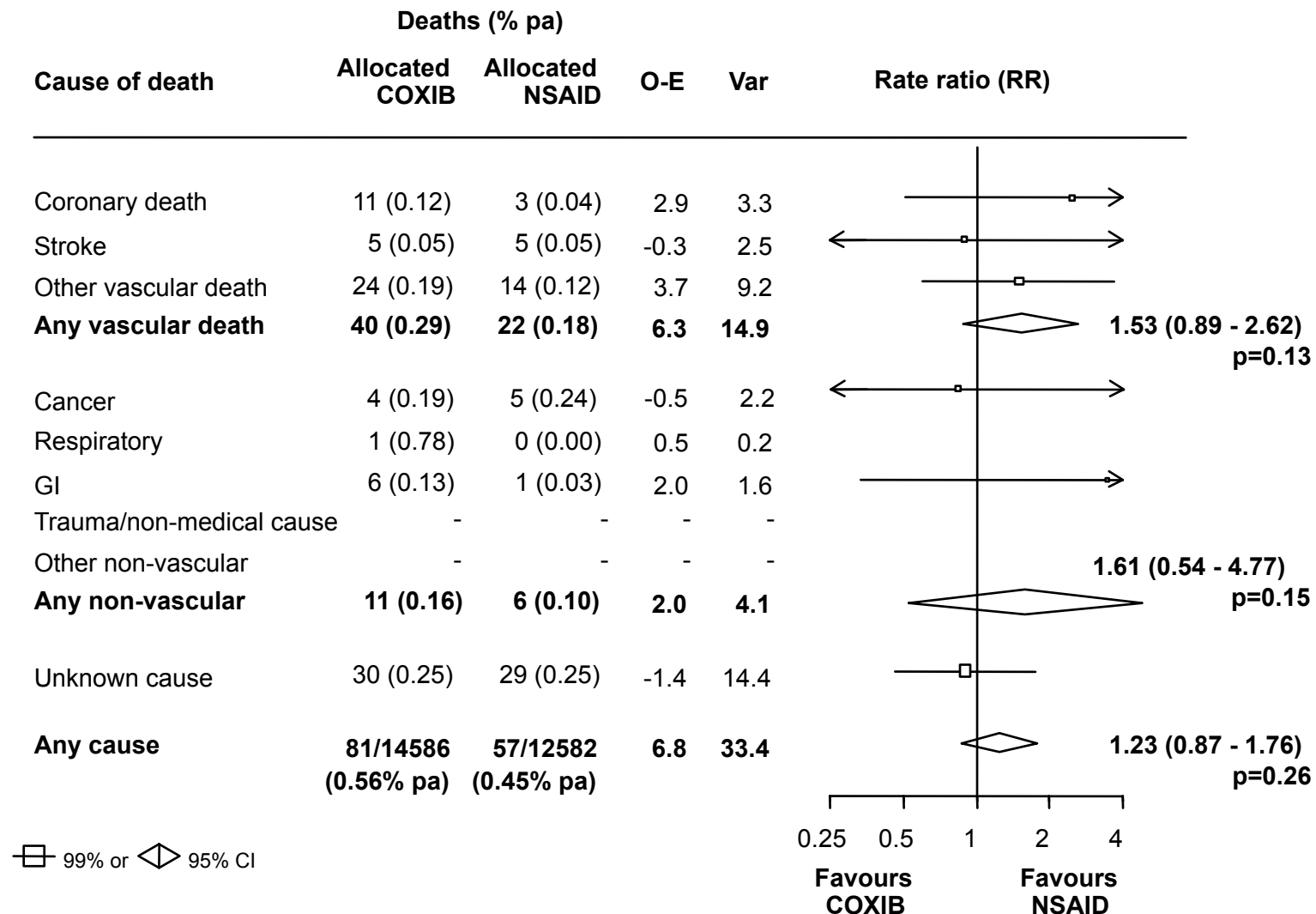


Figure 6.17: Effects of COXIBS vs NSAIDs without antiplatelet activity on major vascular events (myocardial infarction, stroke or vascular death)

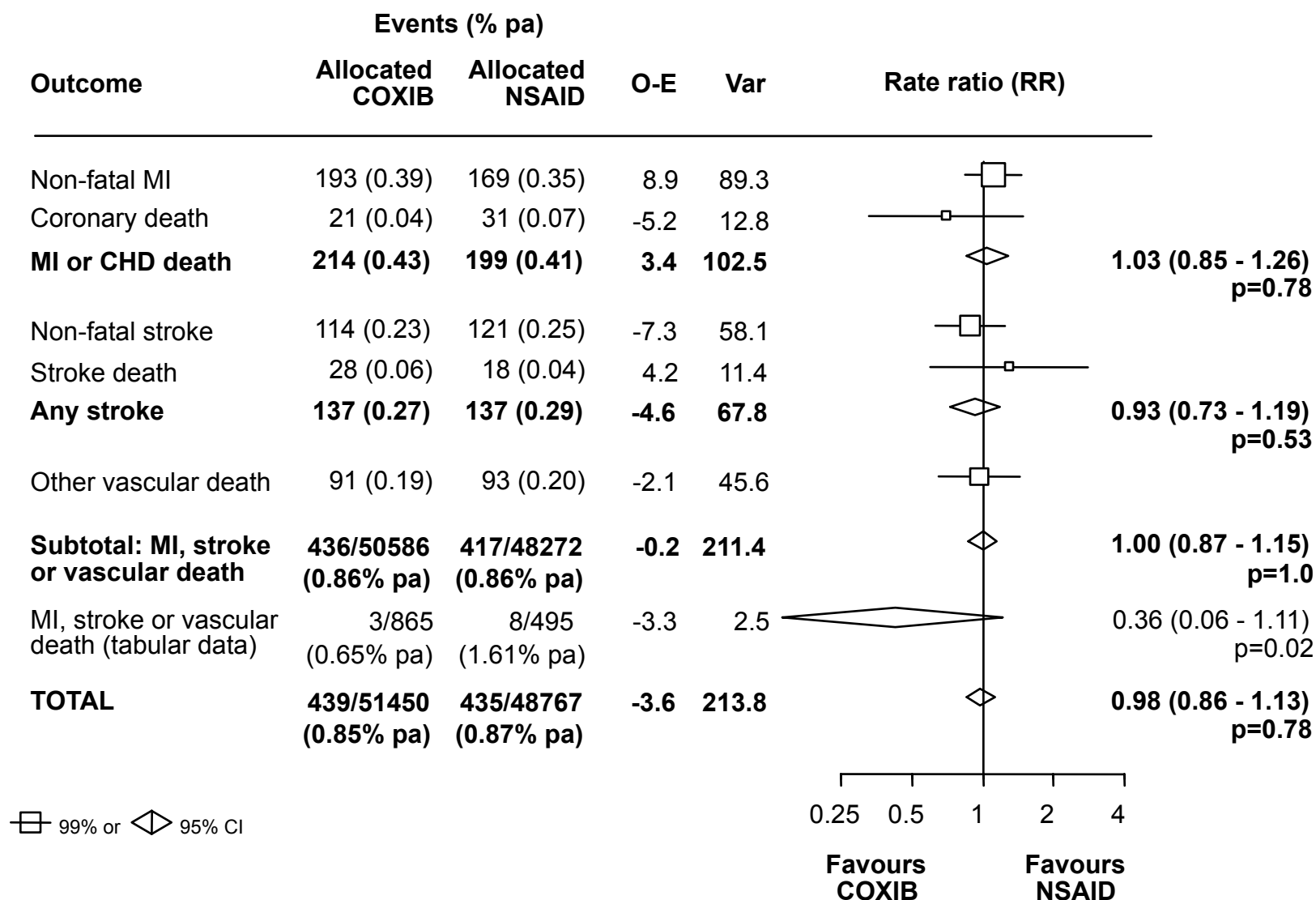


Figure 6.18: Effects of COXIBS vs NSAIDs without antiplatelet activity on heart failure and other vascular complications

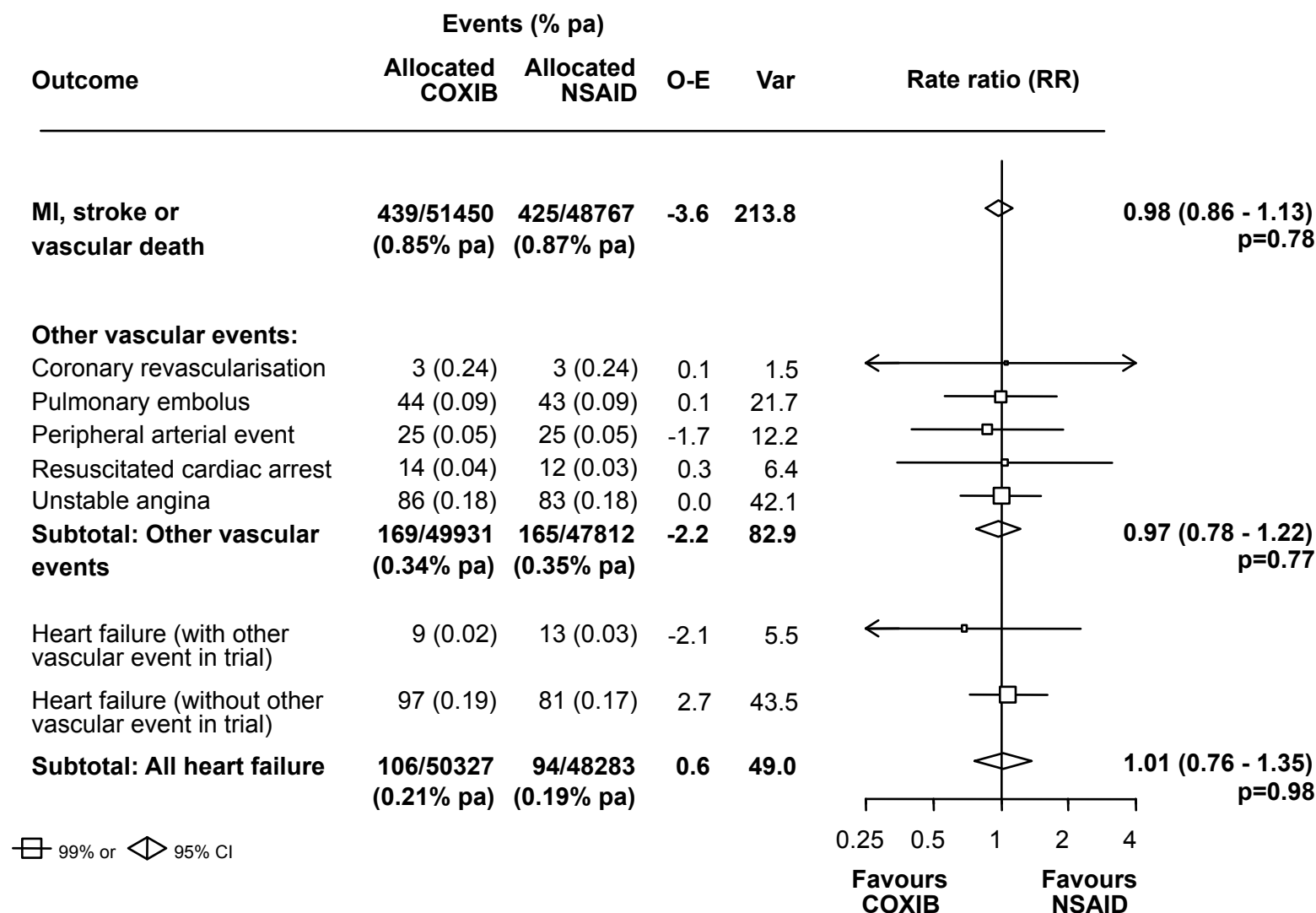


Figure 6.19: Effects of COXIBS vs NSAIDs without antiplatelet activity on stroke subtypes (ischaemic, haemorrhagic or unknown cause)

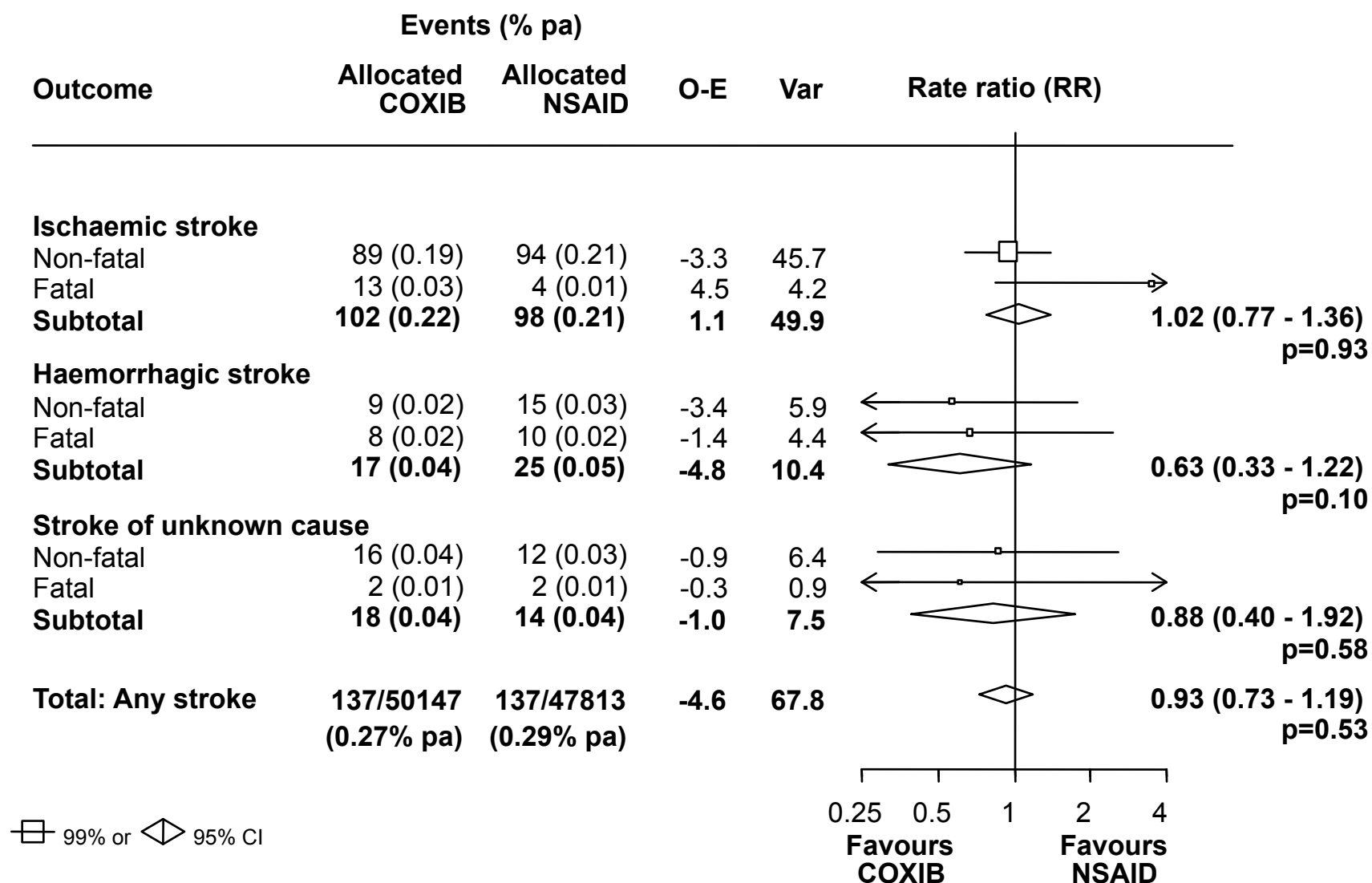


Figure 6.20: Effects of COXIBS vs NSAIDs without antiplatelet activity on cause-specific mortality (vascular, non-vascular or unknown cause)

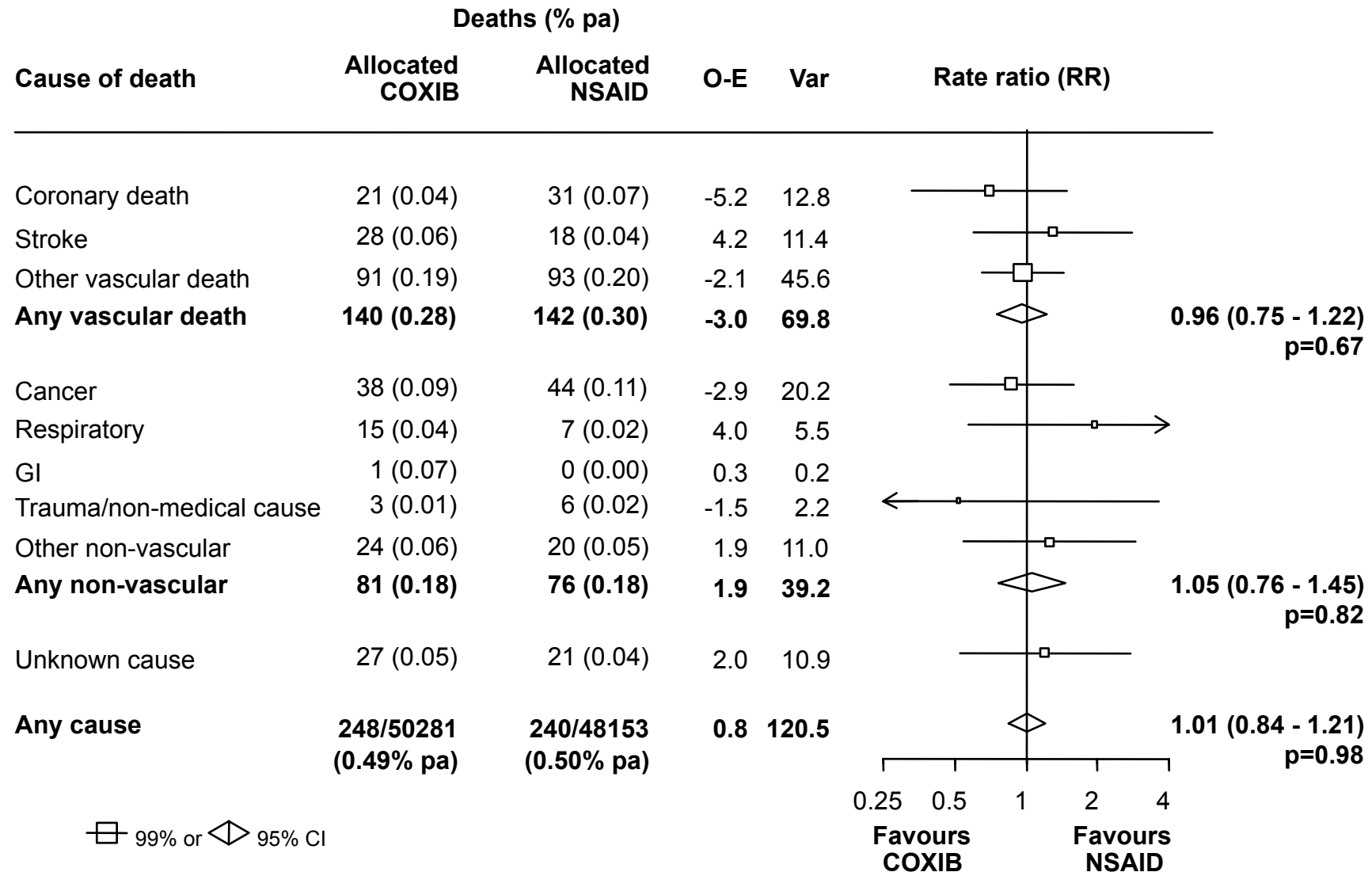


Figure 6.21: Effects of NSAIDs with antiplatelet activity versus PLACEBO on major vascular events (myocardial infarction, stroke or vascular death)

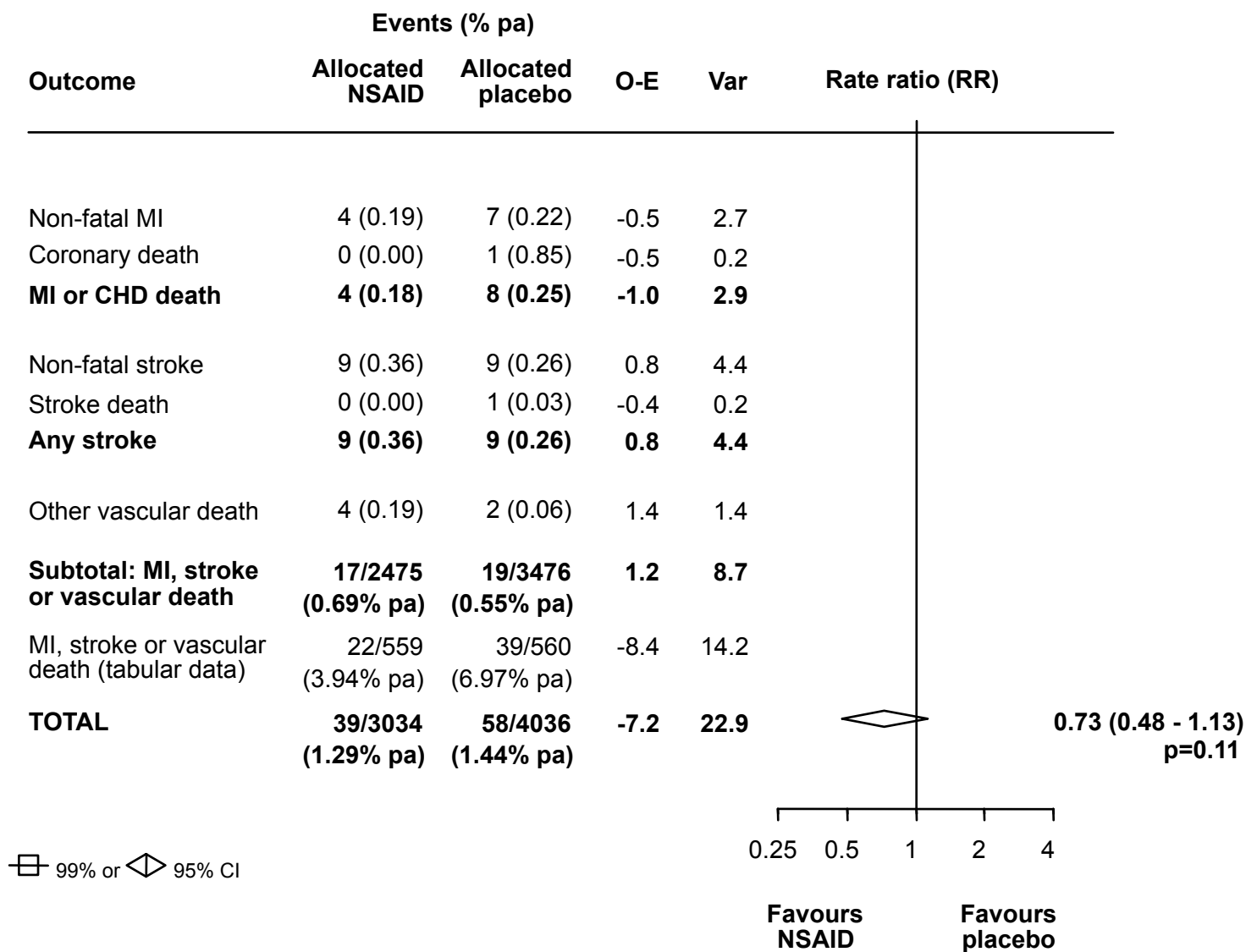


Figure 6.22: Effects of NSAIDs without antiplatelet activity versus PLACEBO on major vascular events (myocardial infarction, stroke or vascular death)

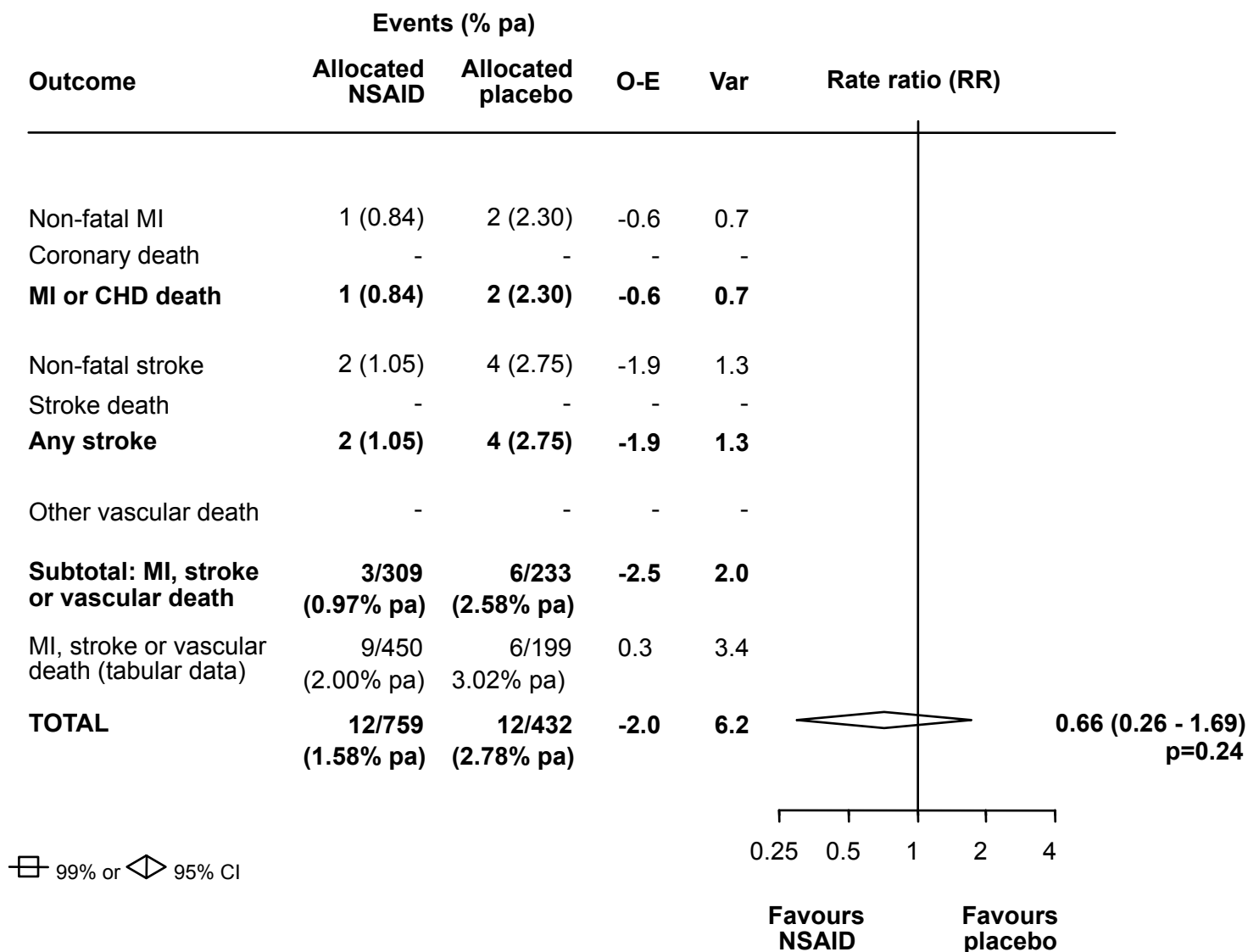


Figure 6.23: Effects of COXIBS on major vascular events (myocardial infarction, stroke or vascular death), by comparator

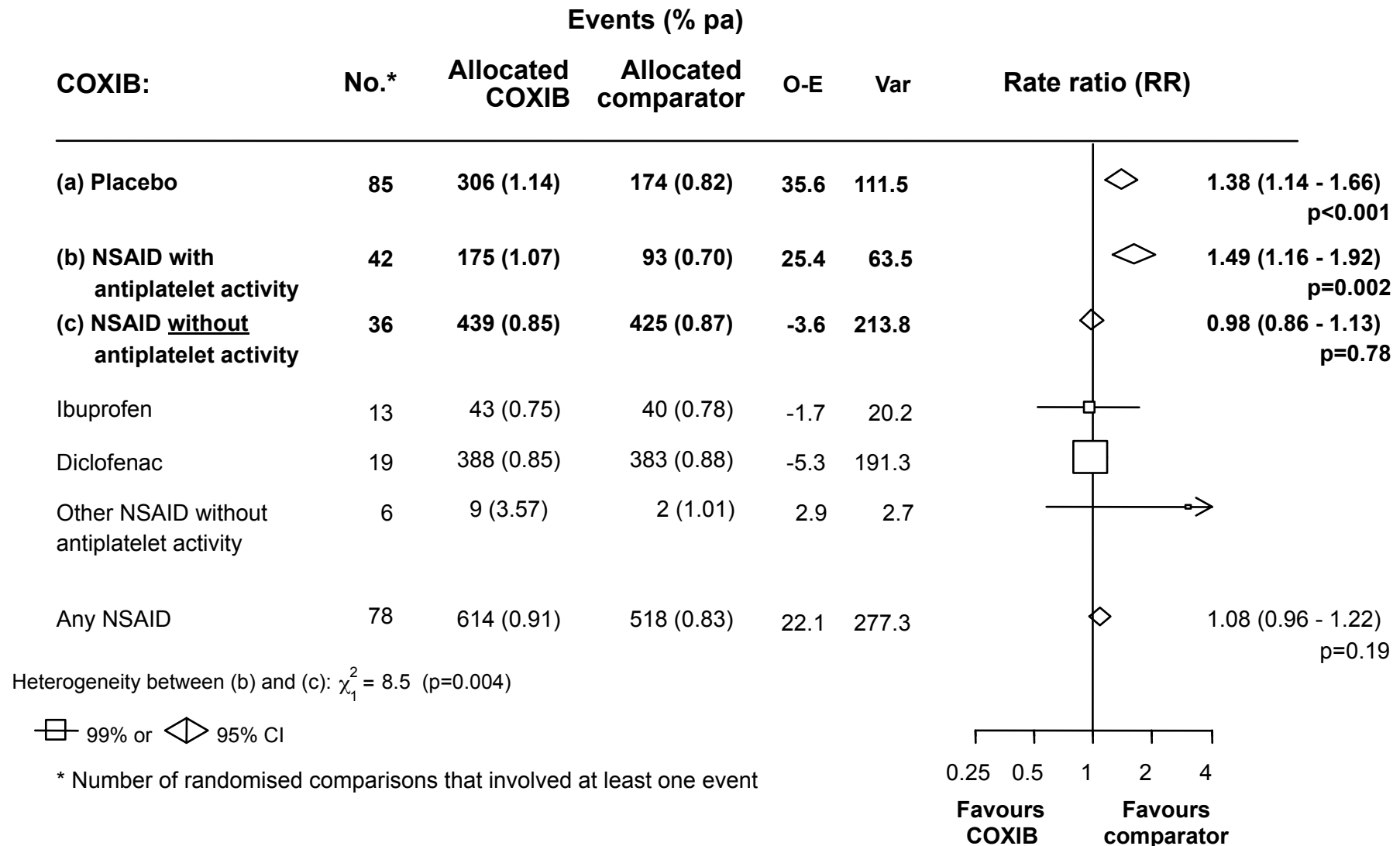


Figure 6.24: Effects of COXIBS vs NSAIDs with antiplatelet effect on major vascular events and myocardial infarctions (excluding VIGOR)

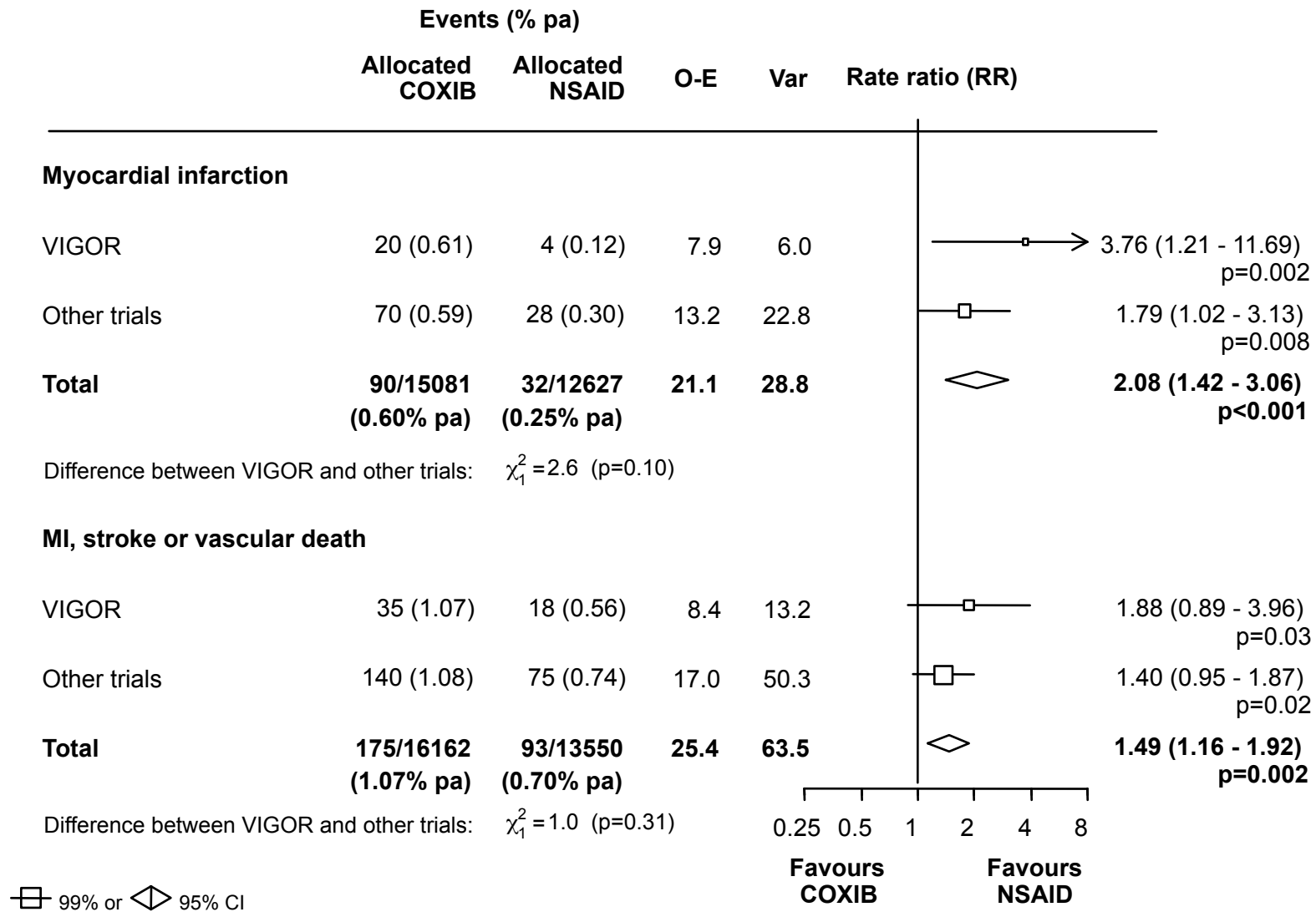
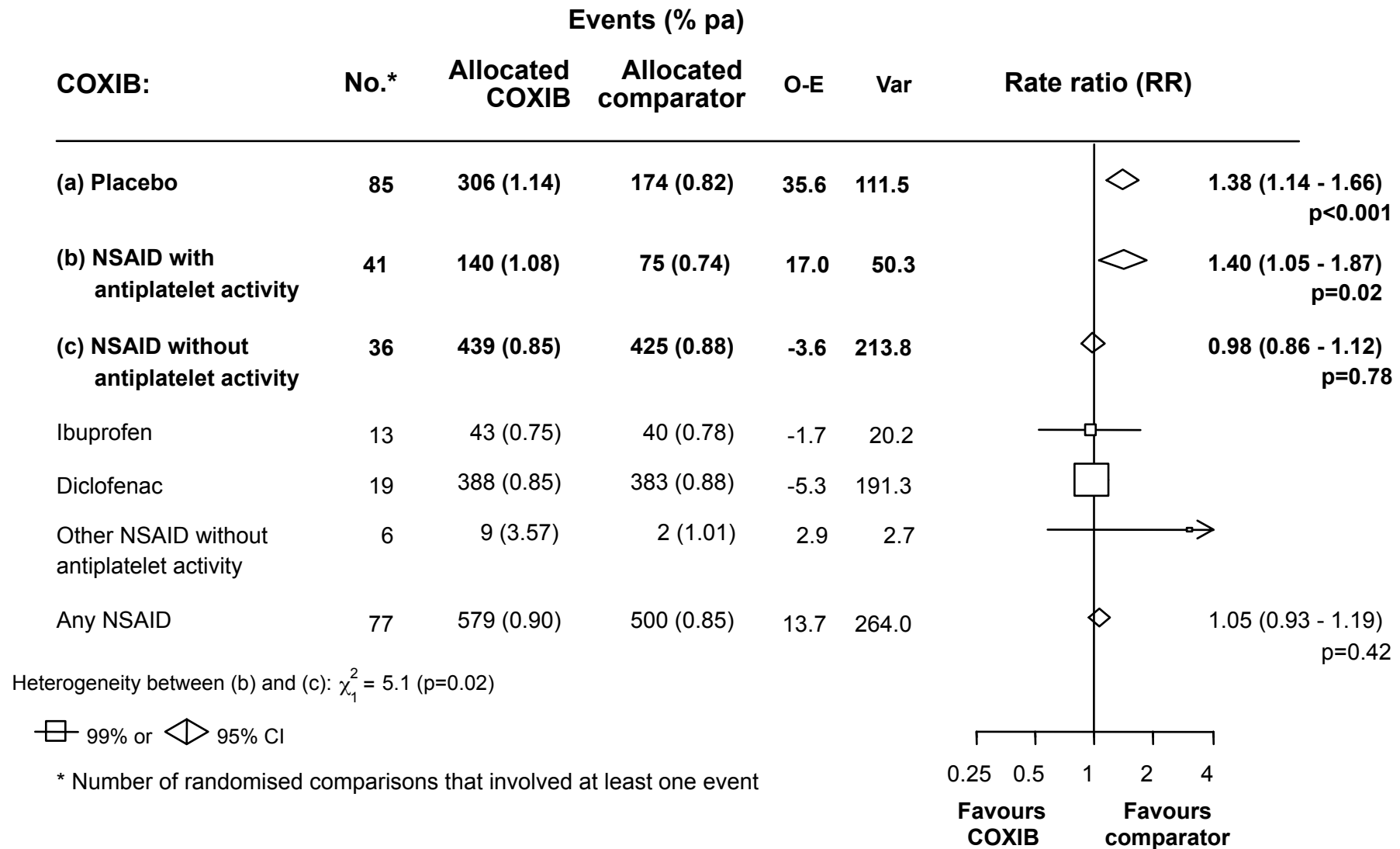


Figure 6.25: Effects of COXIBS on major vascular events, by comparator (excluding hypothesis-generating VIGOR study)



CHAPTER 7: Upper gastrointestinal effects of coxibs and traditional NSAIDs

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Table 7.2 Overall relative and absolute estimates of effects of upper gastrointestinal complications (UGIC) and symptomatic upper gastrointestinal ulcers, by type of drug

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7.1 COMPARISONS OF A COXIB VERSUS PLACEBO

7.1.1 *Upper gastrointestinal complications and symptomatic ulcers*

Overall, 97 first upper gastrointestinal (GI) complications (ie, upper GI bleed, perforation or obstruction) occurred among 30 placebo-controlled comparisons during 33 452 person-years, 68 during 18 133 person-years of exposure to a coxib (0.38%/year) compared with 29 during 15 319 person-years of placebo (0.19%/year) (Figure 7.1). This corresponded to an 81% proportional increase in the incidence of a first upper GI complication (rate ratio [RR] 1.81, 95% confidence interval [CI] 1.17 to 2.81; $P = 0.007$). At least three quarters of the upper GI complications were upper GI bleeds, but there was no strong evidence of different effects for perforation, obstruction or bleeding (χ^2 for heterogeneity = 4.66, $P = 0.10$).

A further 128 first uncomplicated ulcers occurred in 33 749 person years follow-up, 97 during exposure to a coxib (0.53%/year) compared with 31 (0.20%/year) on placebo, corresponding to a two-fold increase in the incidence of a first uncomplicated ulcer (RR 2.00, 1.36 to 2.95; $P < 0.001$). As shown in Figure 7.1, numbers related to two primary and secondary outcomes, and their combination: (i) the primary GI outcome (upper GI complications [bleed, perforation or obstruction]); (ii) the secondary GI outcome (symptomatic upper GI ulcer [uncomplicated ulcers]); and (iii) their combination (any upper GI ulcers). When combining all ulcer events, there was no evidence of heterogeneity between complicated and uncomplicated upper GI outcomes (χ^2 for heterogeneity = 0.26, $P = 0.88$). This provided a rationale of combining all upper GI ulcer events in order to provide increased statistical power to detect effects. This proportional difference corresponded to an excess of 5 (95% CI 3 to 7) people with any upper GI ulcer event or 2 (95% CI 1 to 4) upper GI complications per 1000 allocated to a coxib per year versus placebo.

7.1.2 *Type of coxib and dose response*

There was no evidence that the proportional excess incidence of upper GI complications varied among the different coxibs (χ^2 for heterogeneity = 7.7, df = 5; P = 0.17) (Figure 7.2). However, as only two coxibs (rofecoxib and celecoxib) had recorded appreciable numbers of such outcomes, the power to identify any real differences that might exist between coxibs was limited, even when testing for any upper GI ulcer (χ^2 for heterogeneity = 8.2, df = 5; P = 0.15) (Figure 7.3). (Hence, it is reasonable to look at combining both uncomplicated and complicated upper GI ulcers when exploring subgroup effects, given both previous heterogeneity tests and likely shared pathophysiology). Nonetheless, there was no significant difference between rofecoxib and celecoxib in the rate ratio for upper GI complications (χ^2 for heterogeneity = 4.23, P = 0.12) or any upper GI ulcers (χ^2 for heterogeneity = 5.22, P = 0.07).

Too few upper GI events were available to assess dose-response in placebo-controlled trials of etoricoxib, lumiracoxib, or valdecoxib. For celecoxib and rofecoxib, over 80% of upper GI events occurred during exposure to daily doses of 400mg and 25 mg respectively, with few events at lower or higher daily doses. Therefore, dose dependence could not be evaluated reliably for rofecoxib versus placebo (for upper GI complications χ^2 for trend = 0.1, P = 0.77; for any upper GI events χ^2 for trend = 0.2, P = 0.68) (Figure 7.4) nor for celecoxib (for upper GI complications χ^2 for trend = 0.3, P = 0.58; for any upper GI events χ^2 for trend = 0.1, P = 0.75) (Figure 7.5) respectively.

7.1.3 *Effects by time to first upper gastrointestinal event*

Of the 46 placebo-controlled comparisons that assessed upper GI complications, five were long term trials with over one year of scheduled treatment. There was no strong evidence of a latent effect for exposure to coxibs in the placebo-controlled studies in the incidence of upper GI complications (χ^2 for trend = 3.0, P = 0.08), nor in any upper GI ulcer events (χ^2 for trend = 3.4, P = 0.06) (Figure 7.6).

7.1.4 Subgroup analyses

Even before accounting for multiple testing, there was no strong evidence of heterogeneity by pre-specified baseline categories (ie, age/sex, indication, prior disease, concomitant drug use, smoking, drinking, BMI/BP, laboratory measures) (Figure 7.7 and Figure 7.8). When larger placebo-controlled trials that stopped early (ie, APPROVe, VICTOR and VIP) were excluded, the rate ratio [RR] estimates of effect for UGICs was similar at 1.83 (95% CI 1.05 to 2.93, $P = 0.01$), suggesting no strong evidence of bias by this factor.

7.2 COMPARISONS OF A COXIB VERSUS A TRADITIONAL NSAID

Overall, 533 first upper GI complications occurred in 126 106 person-years of exposure for 68 comparisons of a coxib versus a traditional NSAID. There was a significantly lower incidence of a first upper GI complication between participants allocated to a coxib compared to those allocated to a traditional NSAID: 208 events with a coxib (0.31%/year) versus 325 events with a traditional NSAID (0.53%/year) (RR 0.56, 0.47 to 0.67; $P < 0.001$) (Figure 7.9).

There was marked heterogeneity between the rate ratios for upper GI complications in trials comparing allocation of a coxib with traditional NSAIDs with antiplatelet activity (in this case, all naproxen: RR 0.37; 0.28 to 0.49; $P < 0.001$) and those allocated a coxib with a traditional NSAID without antiplatelet activity (predominantly diclofenac and ibuprofen: RR 0.75; 0.60 to 0.95; $P = 0.01$) (χ^2 for heterogeneity = 15.6, $df = 1$; $P < 0.001$) (Figure 7.9). Similar evidence for heterogeneity was found for any upper GI ulcers (χ^2 for heterogeneity = 6.0, $df = 1$; $P = 0.01$).

7.3 COMPARISONS OF A COXIB VERSUS A TRADITIONAL NSAID WITH ANTIPLATELET ACTIVITY (ALL NAPROXEN)

7.3.1 *Upper gastrointestinal complications and symptomatic ulcers*

Overall, 225 first upper GI complications occurred among 38 comparisons during 29 024 person years, 68 during 15 901 person years of exposure to a coxib (0.43%/year) compared with 157 during 13 123 person years of traditional NSAID with antiplatelet activity, all of which were naproxen for this comparison (1.20%/year) (Figure 7.10). This corresponded to a 63% proportional decrease for exposure to coxibs compared with naproxen in the incidence of a first upper GI complication (RR 0.37, 0.28 to 0.49; $P < 0.001$). More than half of the upper GI complications were bleeds, with 40% being of unspecified subtype, although there was no significant heterogeneity among the rate ratios for each of the subtypes of upper GI complications ($\chi^2 = 2.45$; $P = 0.29$).

418 first uncomplicated ulcers occurred, 140 during exposure to a coxib (0.90%/year) compared with 278 with naproxen (2.12%/year), corresponding to a 56% proportional decrease in the incidence of a first uncomplicated ulcer for exposure to coxibs compared with naproxen (RR 0.44, 0.36 to 0.54; $P < 0.001$) (Figure 7.10). In the trials of a coxib versus naproxen there was no evidence of heterogeneity in the rate ratios for upper GI complications and uncomplicated ulcers (χ^2 for heterogeneity = 1.0; $P = 0.61$). Overall, these proportional differences corresponded to an annual decrease of 18 (15 to 20) people with any upper GI ulcer events or a decrease of 8 (6 to 10) upper GI complications per 1000 allocated to a coxib versus naproxen.

7.3.2 *Type and dose of coxib*

There was no evidence that the proportional excess incidence of upper GI complications varied among the different coxibs at the doses studied compared to naproxen (χ^2 for heterogeneity = 2.4, $df = 4$; $P = 0.66$) (Figure 7.11). However, as only two coxibs (rofecoxib and lumiracoxib) had recorded appreciable numbers of such outcomes compared to naproxen, the power to identify any real differences that

might exist between coxibs was limited, even when testing for any upper GI ulcer (χ^2 for heterogeneity = 1.1, df = 4; P = 0.89) (Figure 7.12). Nonetheless, there was no significant difference between these two coxibs in the rate ratio for upper GI complications (χ^2 for heterogeneity = 0.01, P = 0.99) or any upper GI ulcers (χ^2 for heterogeneity = 0.17, P = 0.92).

Compared to naproxen, variations in the effects on upper GI outcomes of coxibs by dose could not be evaluated reliably, due to limited power to detect any differences. For participants allocated lumiracoxib, 90% of any upper GI ulcers occurred at a dose of 400 mg daily (χ^2 for trend = 1.7, P = 0.19) and for participants allocated rofecoxib, 90% of any upper GI ulcers occurred at a dose of 50 mg daily, (χ^2 for trend = 2.9, P = 0.09).

7.3.3 *Effects by time to first upper gastrointestinal event*

Of the 38 coxib versus naproxen comparisons, ten were long term trials with one year or longer of scheduled treatment and events after this point. There was no evidence of a latent effect for exposure to a coxib versus exposure to naproxen in the incidence of any upper GI complication (χ^2 for trend = 1.9; P = 0.17). In the incidence of any upper GI ulcers, there was, however, some evidence of a diminishing effect over time for exposure to a coxib versus exposure to naproxen (ie, regressing towards null) (χ^2 for trend = 8.0; P = 0.005).

7.3.4 *Subgroup analyses*

There was weak evidence of heterogeneity for an increased effect on any upper GI ulcers of a coxib versus naproxen according to baseline aspirin use (χ^2 for heterogeneity = 5.9, P = 0.01) and baseline *Helicobacter pylori* serology (χ^2 for heterogeneity = 4.2, P = 0.04; although the data for this measure were missing for two thirds of participants). However, when accounting for multiple testing, the evidence for any heterogeneity for aspirin (adjusted p = 0.2) and H. pylori (adjusted p = 0.8) was much weaker. Even before accounting for multiple tests, there was no other evidence

of heterogeneity by other pre-specified baseline categories (ie, age/sex, indication, prior disease, other concomitant drug use, smoking, drinking, BMI/BP, other laboratory measures).

7.4 COXIBS VERSUS A TRADITIONAL NSAID WITHOUT ANTIPLATELET ACTIVITY (PREDOMINANTLY DICLOFENAC AND IBUPROFEN)

7.4.1 *Upper gastrointestinal complications and symptomatic ulcers*

Overall, 309 upper GI complications occurred among 31 comparisons, 141 during 51 193 person years of exposure to a coxib (0.28%/year) compared with 168 during 48 666 person years of a NSAID without antiplatelet activity (0.35%/year), corresponding to a 25% proportional decrease in the incidence of a first upper GI complication (RR 0.75, 0.60 to 0.95; $P = 0.01$) (Figure 7.13). At least two thirds of the upper GI complications were bleeds, with 20% being of unspecified type, although there was no strong evidence of different effects for perforation, obstruction or bleeding (χ^2 for heterogeneity = 4.67, $P = 0.10$).

An additional 620 uncomplicated ulcers occurred, 226 during exposure to a coxib (0.45%/year) compared with 394 with a NSAID without antiplatelet activity (0.82%/year), corresponding to a 51% proportional decrease in the incidence of a first uncomplicated ulcer (RR 0.49, 0.41 to 0.58; $P < 0.001$) (Figure 7.13). There was strong evidence of a difference between upper GI complications and uncomplicated ulcers (albeit coxibs reduced both outcomes versus a NSAID without antiplatelet activity) (χ^2 for heterogeneity = 11.1, $P = 0.004$). Overall, these proportional differences corresponded to an absolute annual excess of 4 (95% CI 2 to 6) people with any upper GI event or 1 (95% CI 0 to 2) upper GI complications per 1000 allocated to a NSAID without antiplatelet activity per year instead of a coxib.

Comparisons of a coxib versus diclofenac (RR 0.94, 95% CI 0.73 to 1.22; $P = 0.66$), versus ibuprofen (RR 0.45, 95% CI 0.28 to 0.71; $P = 0.0006$) or versus any other NSAID

(RR 1.40, 95% CI 0.94 to 4.94; $P = 0.53$) yielded different rate ratios for upper GI complications (χ^2 for heterogeneity = 8.57, $df = 2$; $P = 0.014$). There was also a significant difference when considering ibuprofen and diclofenac separately for upper gastrointestinal complications (χ^2 for heterogeneity = 7.65; $P = 0.022$).

7.4.2 Type and dose of coxib

There was weak evidence that the proportional excess incidence of upper GI complications varied among the different coxibs versus NSAIDs without antiplatelet activity (χ^2 for heterogeneity = 10.7, $df = 4$; $P = 0.03$) (Figure 7.14). However, as one coxib (etoricoxib) had recorded the vast majority of such outcomes, the power to identify any real differences that might exist between coxibs was limited, even when testing for any upper GI ulcer (χ^2 for heterogeneity = 13.5, $df = 4$; $P = 0.01$) (Figure 7.15).

For etoricoxib, principally studied at 60mg and 90mg versus diclofenac in the MEDAL programme, there was weak evidence of a trend for increased effect with higher doses for upper GI complications (χ^2 for trend = 3.7, $P = 0.05$), which was slightly stronger when assessing any upper GI events (χ^2 for trend = 6.6, $P = 0.01$). There were comparable trends for celecoxib for upper GI complications (χ^2 for trend = 4.3, $P = 0.04$) and any upper GI events (χ^2 for trend = 4.9, $P = 0.03$).

7.4.3 Effects by time to first upper gastrointestinal events

Of the 31 coxib versus NSAID without antiplatelet activity comparisons, seven were long term trials with one year or more of scheduled treatment. There was no evidence of any latent effect for those allocated NSAIDs without antiplatelet activity versus those allocated coxibs in the incidence of any upper GI complications (χ^2 for trend = 1.4, $P = 0.24$) or any upper GI events (χ^2 for trend = 2.6, $P = 0.11$).

7.4.4 Subgroup analyses

There was strong evidence for heterogeneity by baseline aspirin use, with those taking aspirin having little apparent difference in any upper GI ulcer events when allocated NSAIDs without antiplatelet activity or allocated coxibs (χ^2 for heterogeneity = 11.9, $P < 0.001$). After adjusting for multiple testing, this was still some evidence of an effect ($P = 0.001 \times 20$: adjusted $P = 0.02$). This effect was, however, substantially reduced for upper GI complications even before assessing for multiple testing, (χ^2 for heterogeneity = 4.0; $P = 0.05$; amended $P = 1.00$). There was no other strong evidence of heterogeneity by pre-specified baseline categories (ie, age/sex, indication, prior disease, concomitant drug use, smoking, drinking, BMI/BP, laboratory measures).

7.5 COMPARISONS OF A TRADITIONAL NSAID VERSUS PLACEBO

7.5.1 Upper gastrointestinal complications and symptomatic ulcers

Overall, 46 first upper GI complications occurred among 7 280 person-years in 17 placebo-controlled comparisons versus NSAIDs with antiplatelet activity, corresponding to a 3.3-fold increase in the incidence of a first upper GI complication (rate ratio 3.27, 1.73 to 6.19; $P < 0.001$) (Figure 7.16). In addition, 39 first uncomplicated ulcers also occurred among 4 152 person-years, corresponding to an overall 2.9-fold increase in the incidence of any first upper GI event (rate ratio 2.87, 1.80 to 4.58; $P < 0.001$). There was no evidence of heterogeneity between complicated and uncomplicated events (χ^2 for heterogeneity = 0.64, $P = 0.73$).

For traditional NSAIDs without antiplatelet activity, 28 first upper GI complications occurred among 6 082 person-years in 21 placebo-controlled comparisons, corresponding to a non-significant (and imprecise) 1.6-fold increase in the incidence of any first upper GI complication (rate ratio 1.57, 0.67 to 3.70; $P = 0.35$) (Figure 7.17). 32 first uncomplicated ulcers also occurred among 734 person years, corresponding to a 2.5-fold increase in the incidence of any first upper GI event (rate ratio 2.52, 1.42 to 4.45; $P = 0.001$). There was no evidence of heterogeneity between complicated and uncomplicated events (χ^2 for heterogeneity = 1.76, $P = 0.41$).

7.6 COMBINING DIRECT AND INDIRECT ESTIMATES FOR UPPER GASTROINTESTINAL COMPLICATIONS

Direct estimates of treatment effect (from comparisons of a coxib versus placebo or NSAID versus placebo) were combined with indirect information (from comparisons of a coxib versus placebo and a coxib versus NSAID) in order to provide estimates of the comparative upper GI effects for the different medications (see Table 7.1). Incorporating indirect evidence as well as direct evidence slightly attenuated the estimated effect for upper GI complications for coxib versus placebo from 1.81 to 1.59 (1.16 to 2.17), corresponding to a 60% increase in the risk of upper GI complications associated with coxibs.

Incorporating indirect evidence as well as direct evidence also attenuated the upper GI effects of traditional NSAIDs. Although the direct estimates of effect for a traditional NSAID without antiplatelet effect versus placebo were extremely imprecise, incorporating indirect evidence altered the precision of this comparison considerably. Compared with placebo, the summary rate ratios for NSAIDs without antiplatelet activity was 1.98 (1.39 to 2.84), corresponding to a two-fold increase in the risk of upper GI complications.

Direct estimates for traditional NSAIDs with antiplatelet effects estimated around a three-fold risk versus placebo of upper GI complications for these therapies. Incorporating indirect evidence attenuated this to suggest that these traditional NSAIDs could actually have higher risks. Compared with placebo, the summary rate ratio for upper GI complications for a traditional NSAID with antiplatelet activity was 4.06 (2.85 to 5.78). This corresponds to a four-fold increase in the risk of upper GI complications associated with these drugs (primarily naproxen), not excluding risks between three- to six-fold.

7.7 SUMMARISING THE OVERALL RESULTS FOR UPPER GASTROINTESTINAL COMPLICATIONS

Allocation to a coxib is associated with a 60-80% increased risk in upper GI complications. Allocation to a traditional NSAID without antiplatelet activity (eg, diclofenac) is associated with around a two-fold increased risk in these events. However, allocation to traditional NSAIDs with antiplatelet activity (ie, naproxen) is associated with around a four-fold increased risk in upper GI complications. As shown in Table 7.2, all the drugs tested also cause corresponding proportional increases in symptomatic ulcers, but when considering upper GI complications, a traditional NSAID with persistent antiplatelet activity (ie, naproxen) is associated with the highest relative hazard. Hence, although NSAIDs with antiplatelet activity, such as naproxen, are associated with the lowest relative risk for major vascular events, they are associated with the highest risk of upper GI complications.

TABLE 7.1 Upper gastrointestinal complications (UGIC): Estimates for comparisons from direct evidence, and combining direct and indirect evidence

COMPARISONS	Relative risk of upper GI complications (95% CI)	
	Direct evidence	Direct + indirect Evidence
COXIB vs placebo	1.81 (1.17 – 2.81)	1.59 (1.16 – 2.17)
Traditional NSAID <u>without</u> antiplatelet activity vs placebo	1.84 (0.81 – 4.15)	1.98 (1.39 – 2.84)
Traditional NSAID <u>with</u> antiplatelet activity vs placebo	3.27 (1.73 – 6.19)	4.06 (2.85 – 5.78)

TABLE 7.2 Overall relative and absolute estimates of effects of upper gastrointestinal complications (UGIC) and symptomatic upper GI ulcers, by type of drug

Type of drug	Effect on outcome versus control and estimated relative risk (absolute risk for average-risk individuals from the CNT Collaboration in brackets)	
	Upper GI Complication	Symptomatic upper GI ulcer
COXIB	↑ ~1.6-fold (2 per 1000py)	↑ ↑ ~2-fold (3 per 1000py)
Traditional NSAID <u>without</u> antiplatelet activity (ie, naproxen)	↑ ↑ ~2-fold (3 per 1000py)	↑ ↑ ↑ ~3-fold (7 per 1000py)
Traditional NSAID <u>with</u> antiplatelet activity (eg, diclofenac)	↑ ↑ ↑ ↑ ~4-fold (8 per 1000 py)	↑ ↑ ↑ ↑ ~4-fold (15 per 1000py)

Figure 7.1: Effects of COXIBS vs PLACEBO on upper gastrointestinal complications (bleed, perforation or obstruction) and symptomatic ulcers

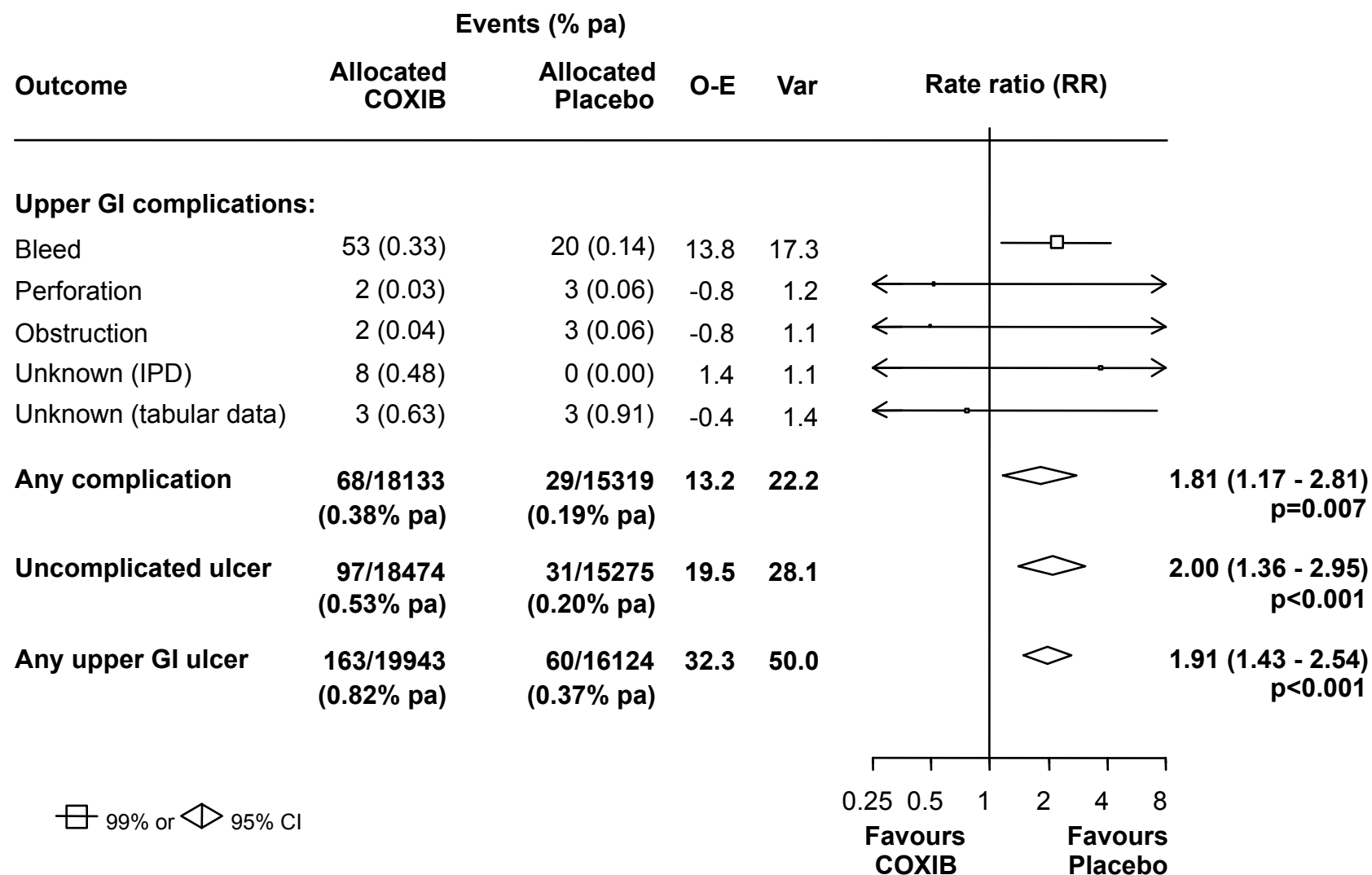


**Figure 7.2: Effects of COXIBS vs PLACEBO
on upper gastrointestinal complications, by type of coxib**

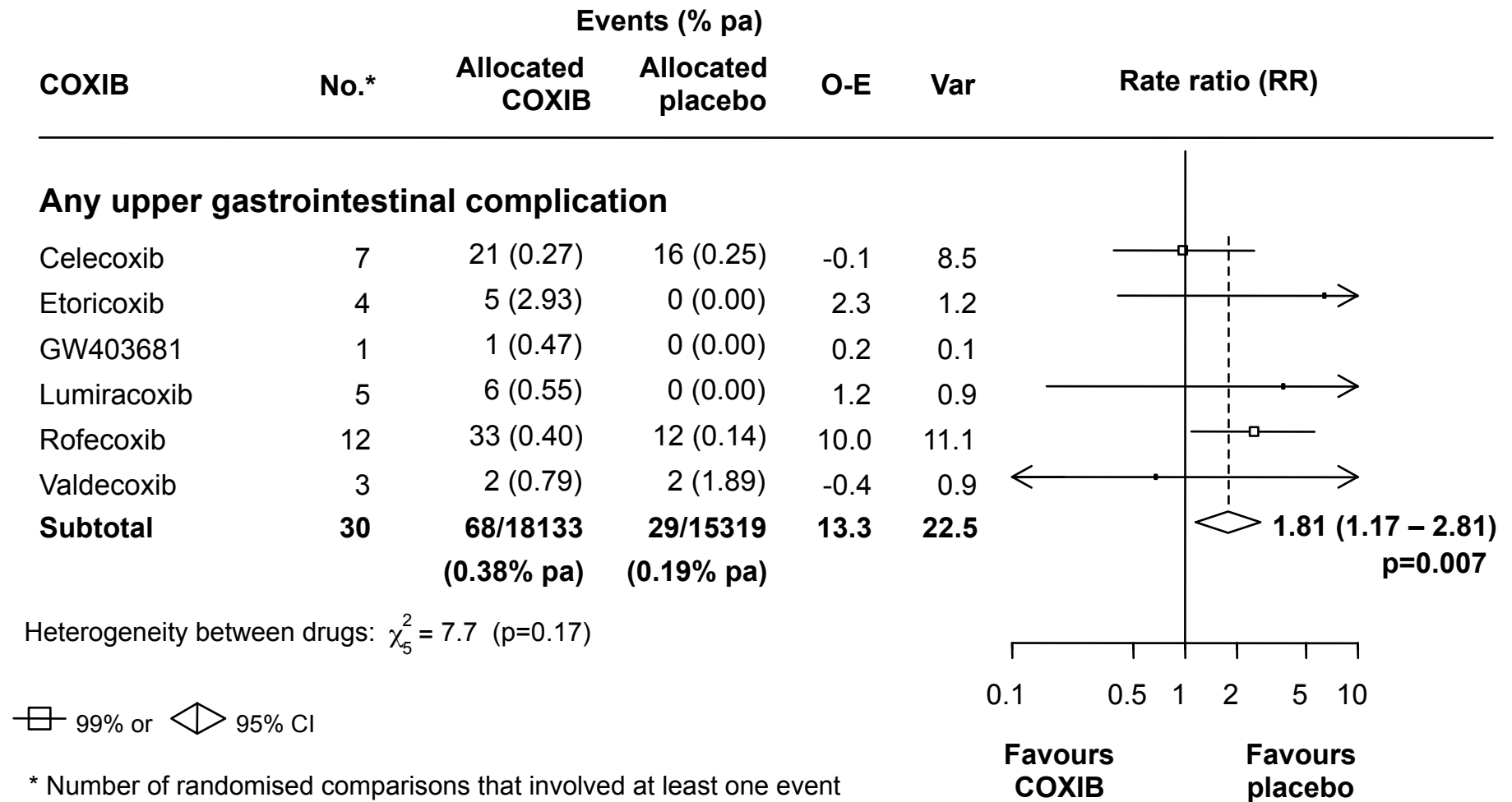
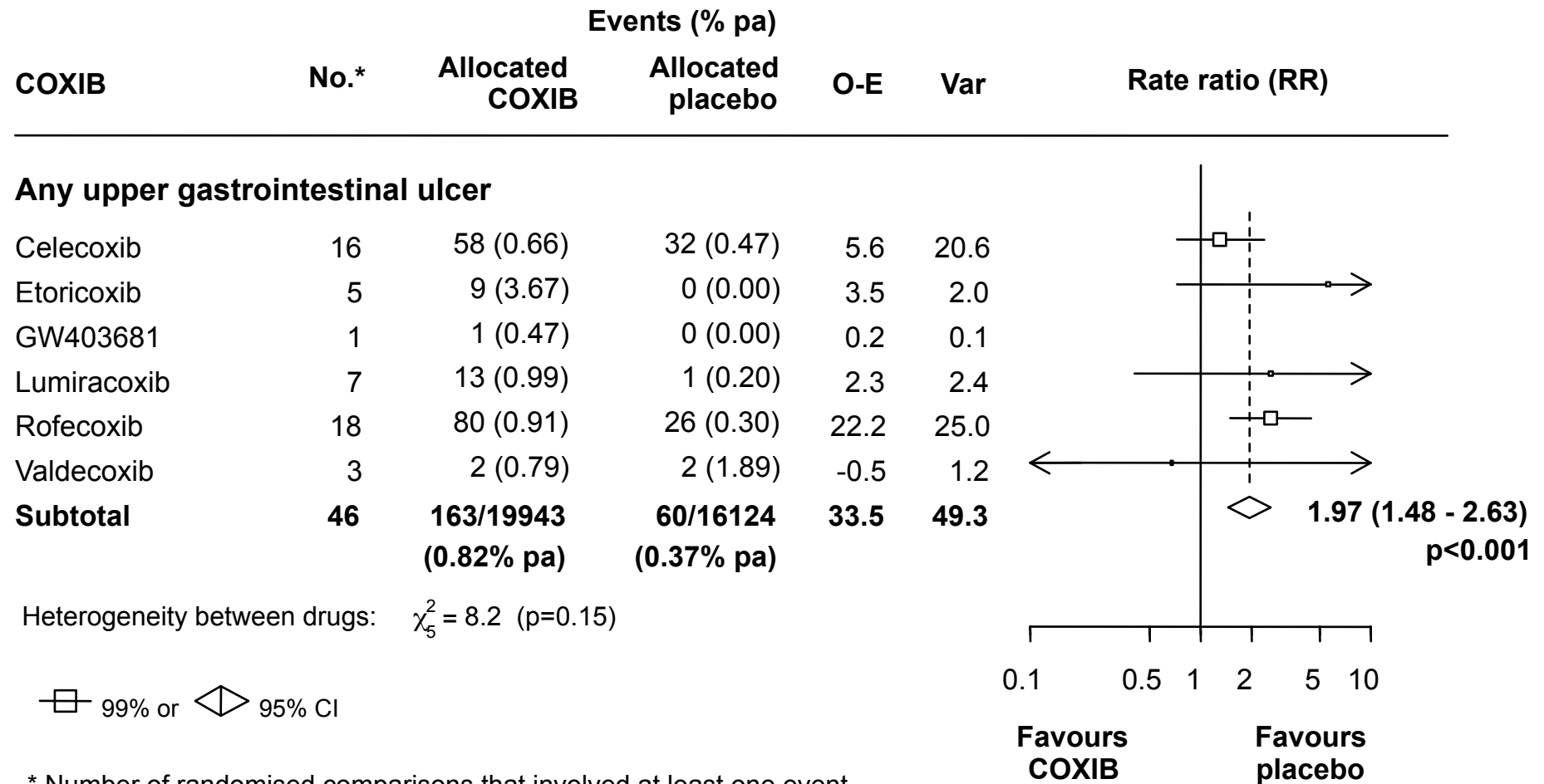
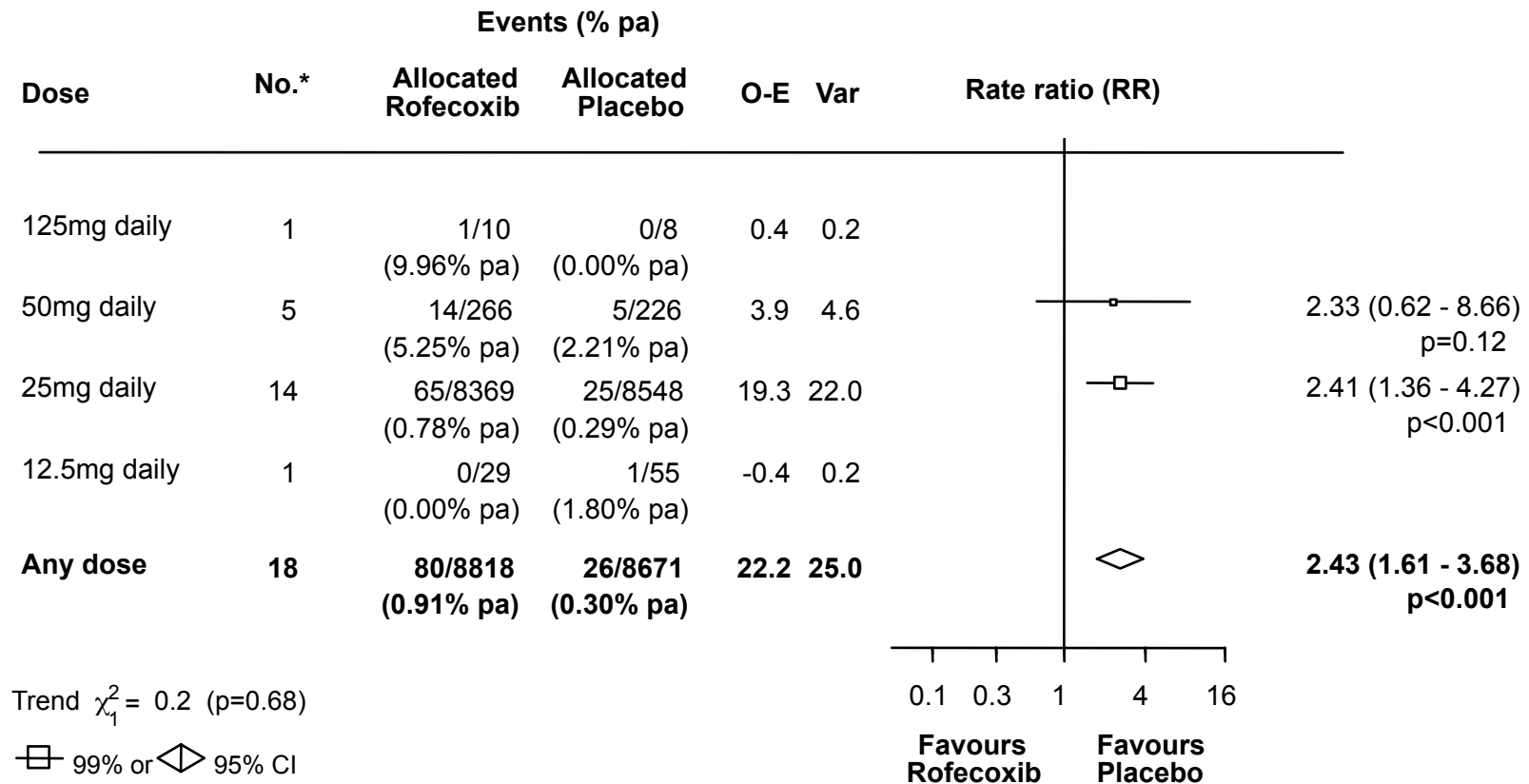


**Figure 7.3: Effects of COXIBS vs PLACEBO
on any upper gastrointestinal ulcers, by type of coxib**



* Number of randomised comparisons that involved at least one event

**Figure 7.4: Effects of ROFECOXIB vs PLACEBO
on any upper gastrointestinal ulcers, by dose**



* Number of randomised comparisons that involved at least one event

**Figure 7.5: Effects of CELECOXIB vs PLACEBO
on any upper gastrointestinal ulcers, by dose**

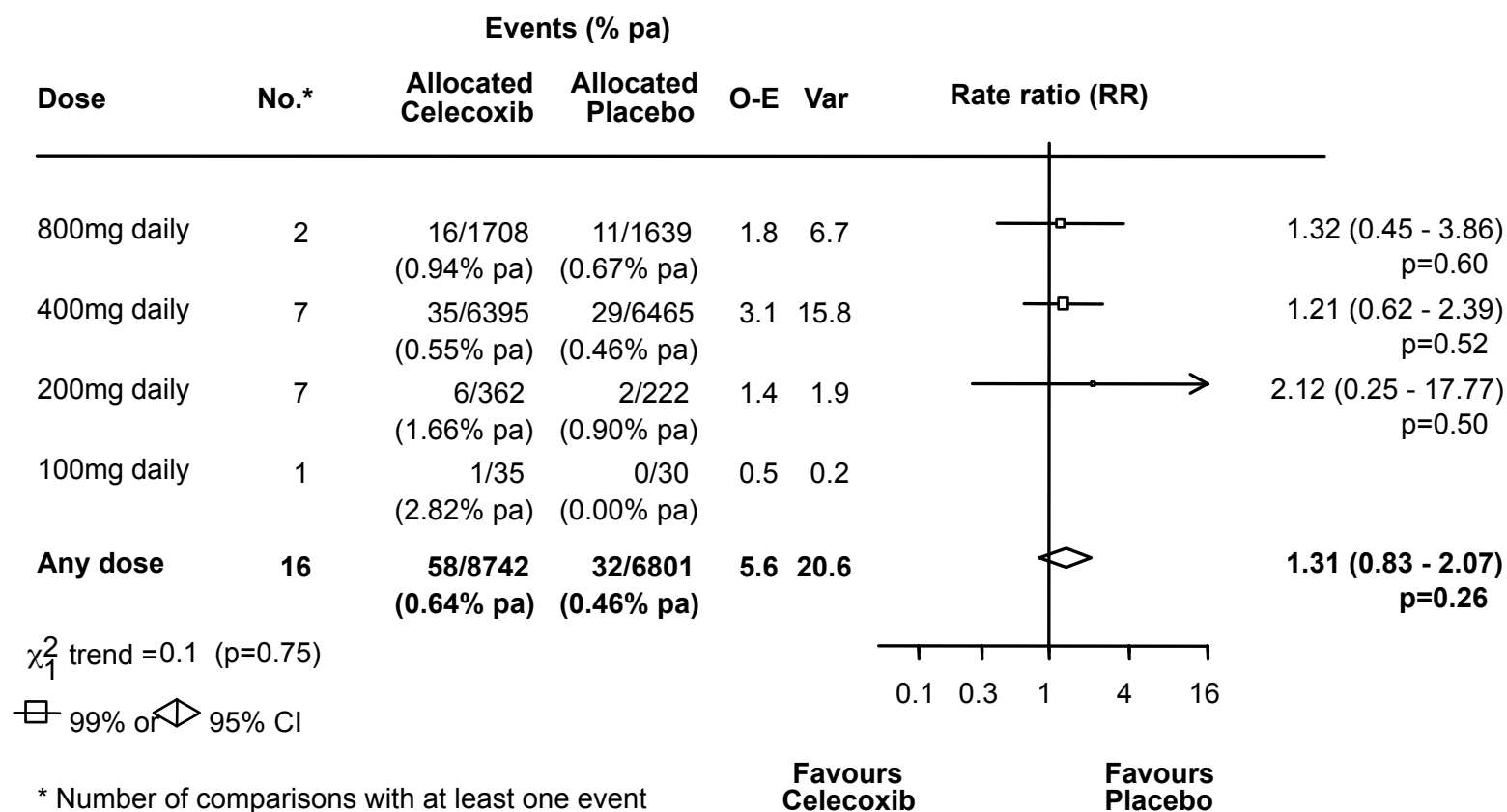
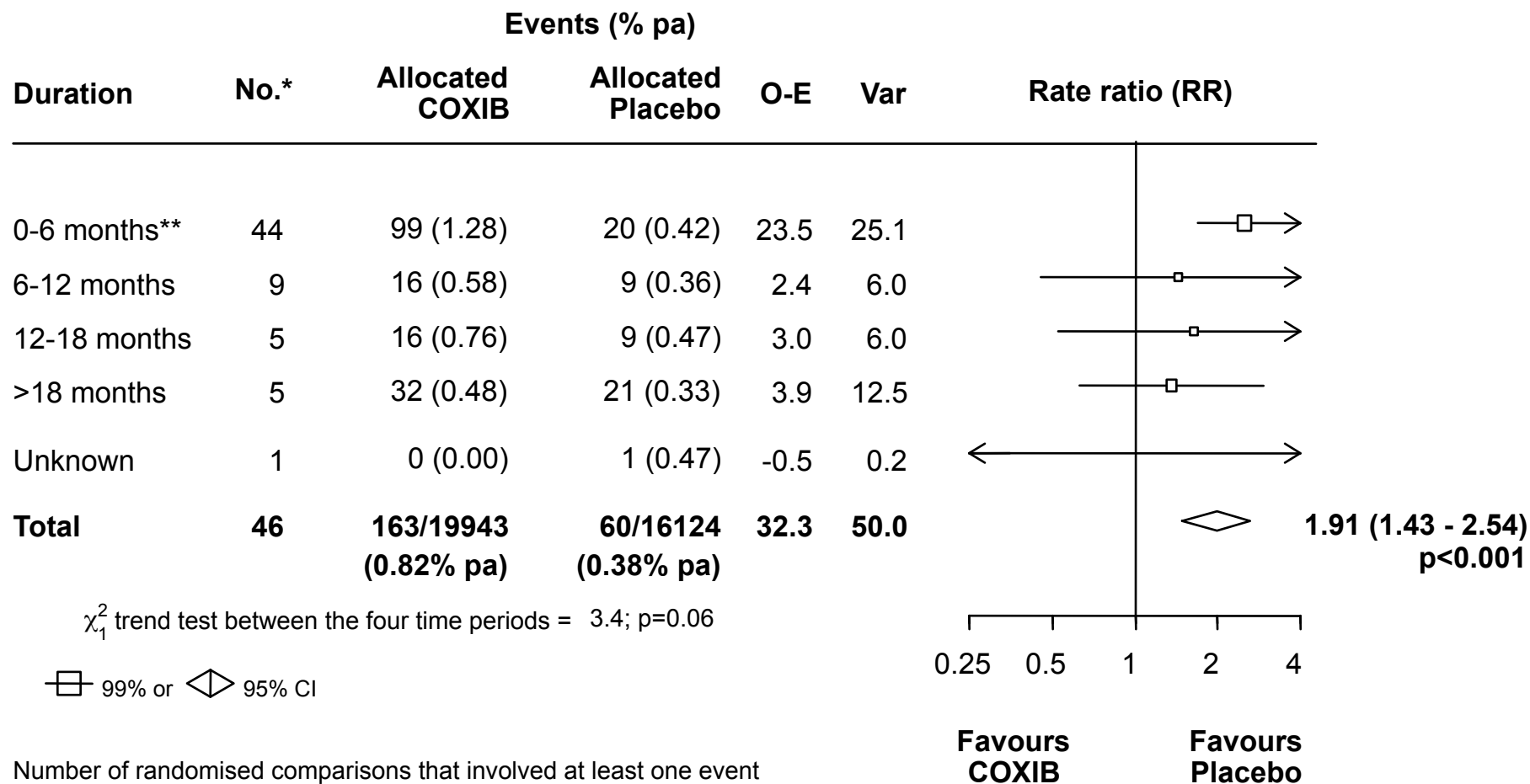


**Figure 7.6: Effects of COXIBS vs PLACEBO
on any upper gastrointestinal ulcers, by time to first event**



**Includes tabular data from 4 trials in which the trial duration was known to be <6 months

Figure 7.7: Effects of COXIBS vs PLACEBO on any upper gastrointestinal ulcers, by baseline characteristics

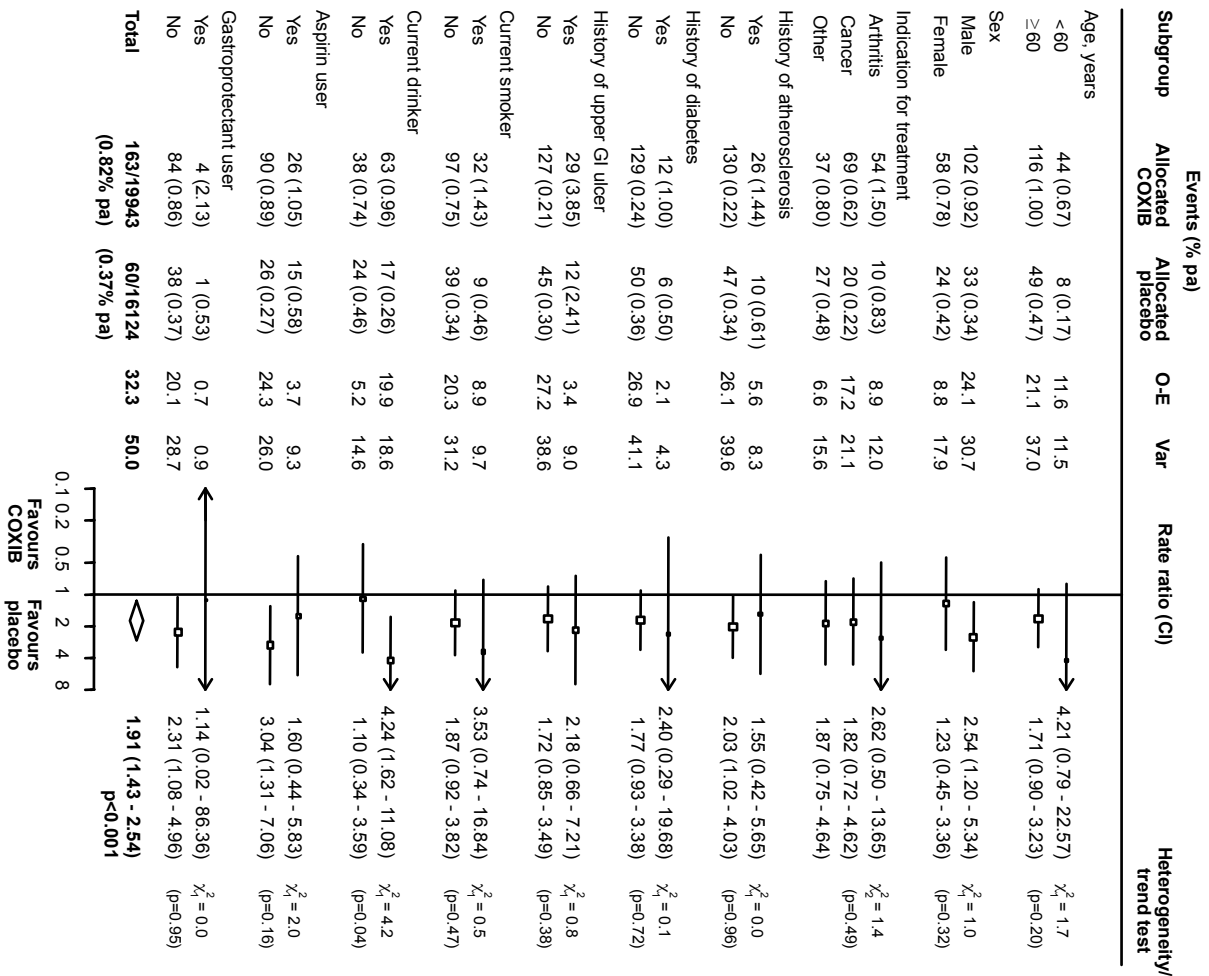


Figure 7.8: Effects of COXIBS vs PLACEBO on any upper gastrointestinal ulcers, by baseline physical/laboratory measures

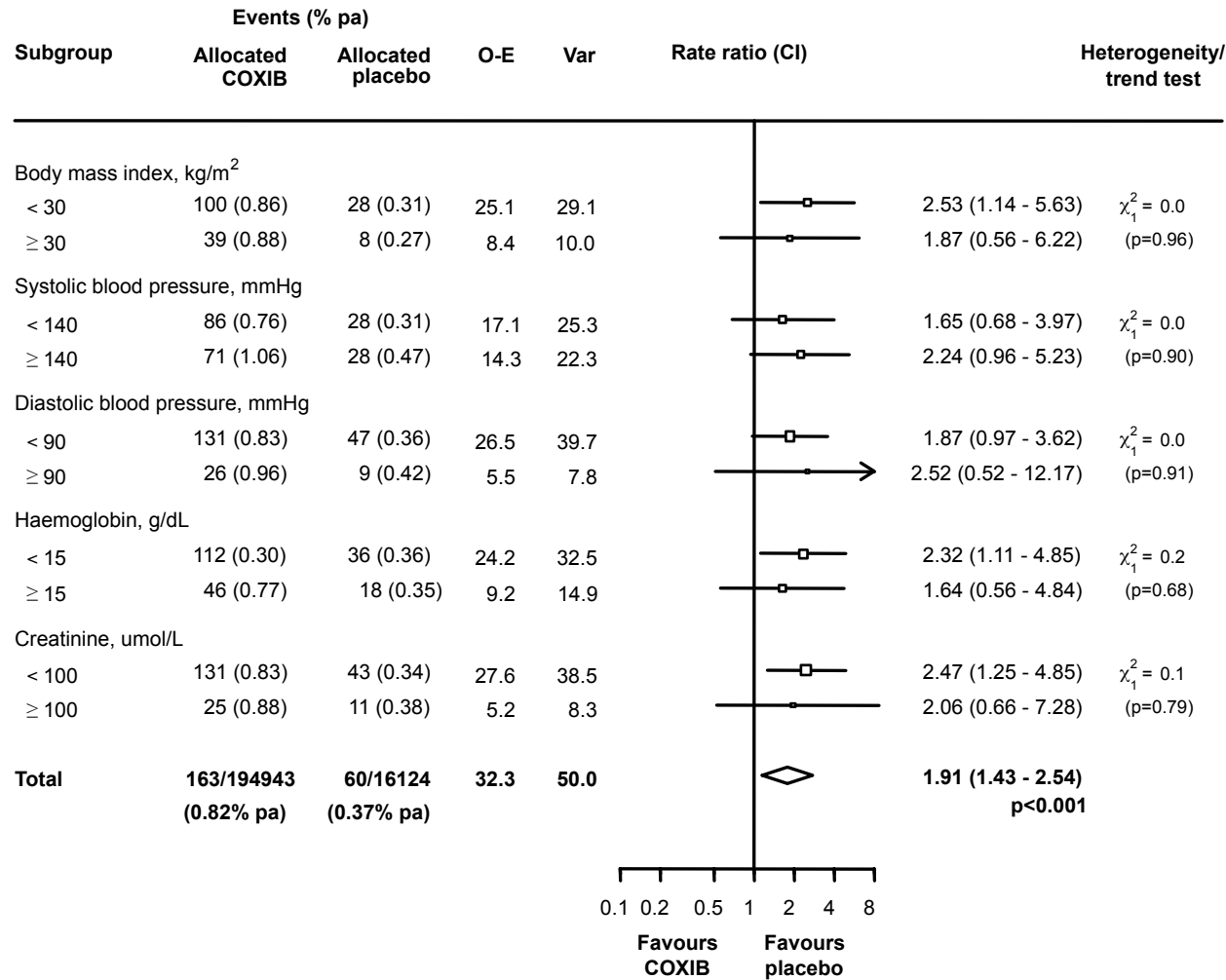
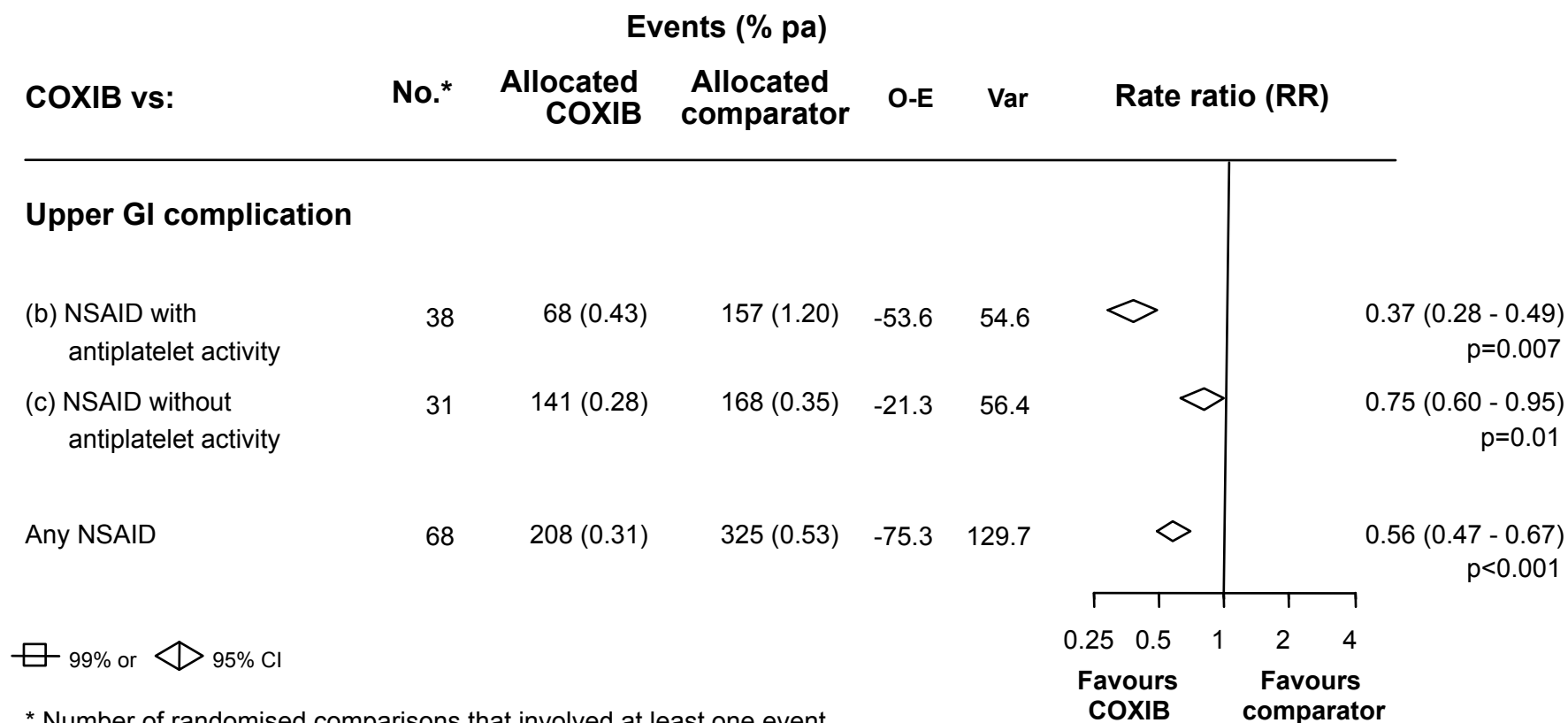


Figure 7.9: Effects of COXIBS vs NSAID on upper gastrointestinal complications, by type of NSAID (with or without antiplatelet activity)



* Number of randomised comparisons that involved at least one event

Heterogeneity between (b) and (c): $\chi^2_1 = 15.6$ (p<0.001)

Figure 7.10: Effects of COXIBS vs NSAIDs with antiplatelet activity on upper gastrointestinal complications and symptomatic ulcers

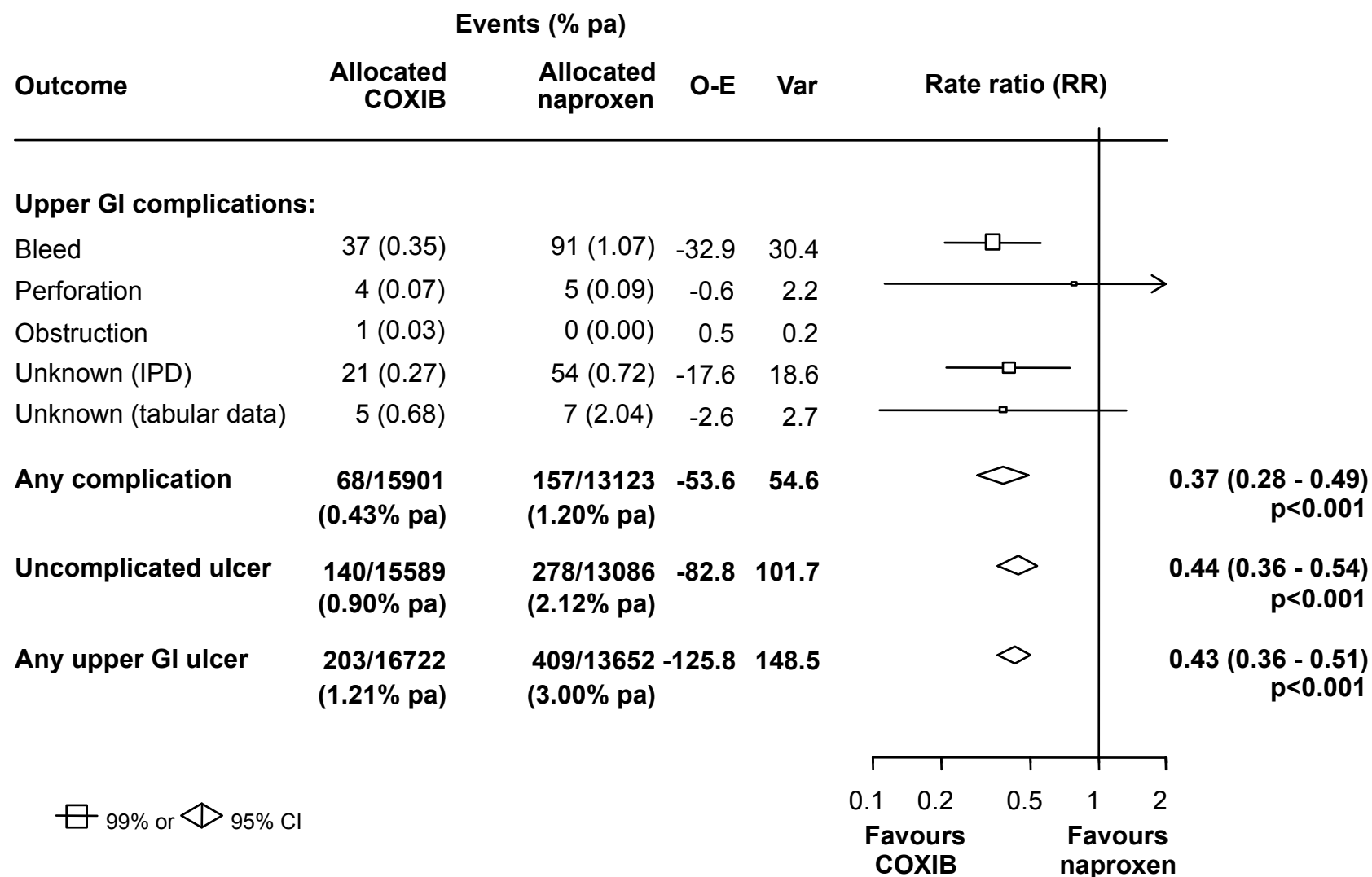


Figure 7.11: Effects of COXIBS vs NSAIDs with antiplatelet activity on upper gastrointestinal complications, by type of coxib

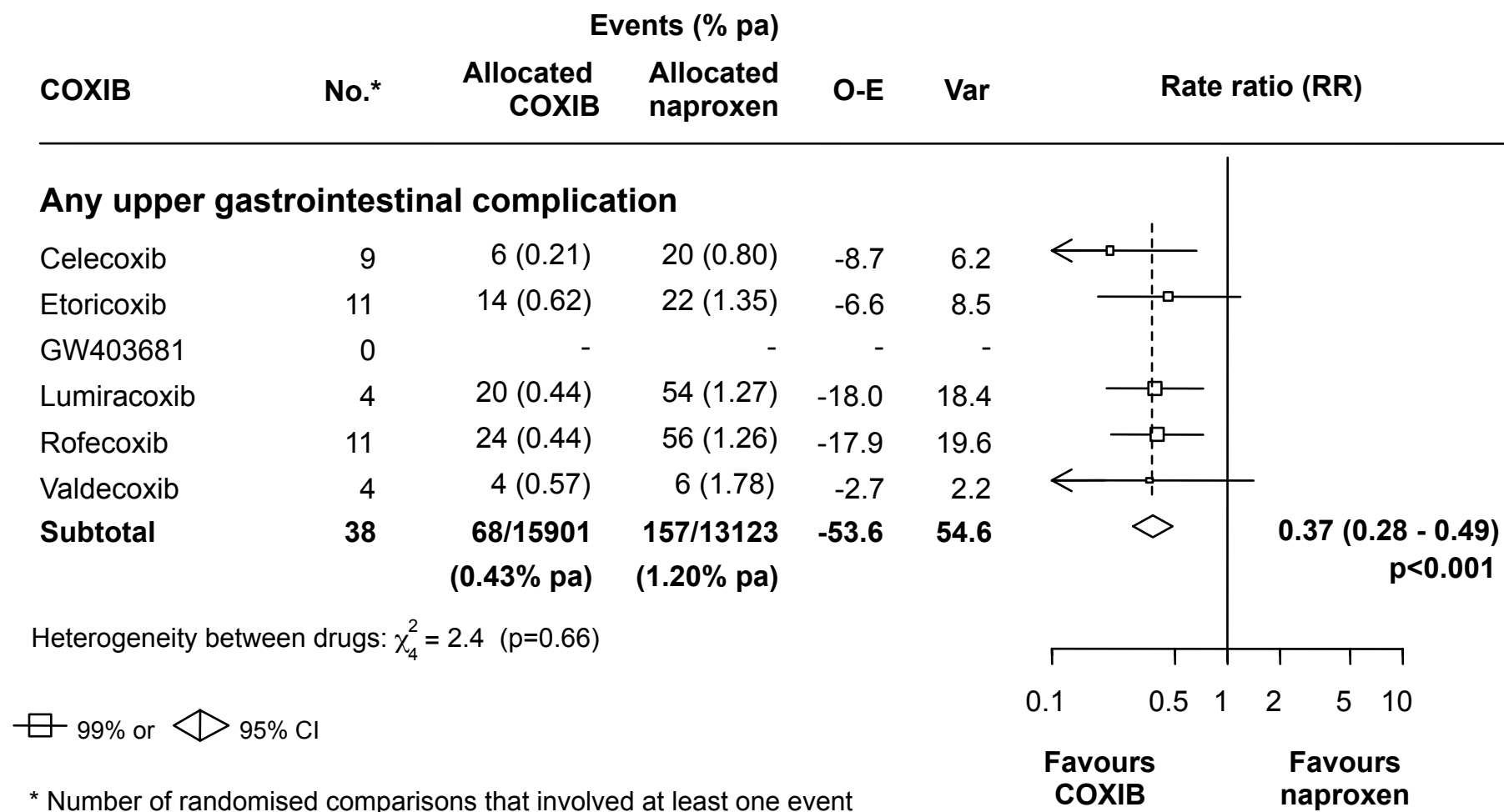


Figure 7.12: Effects of COXIBS vs NSAIDs with antiplatelet activity on any upper gastrointestinal ulcers, by type of coxib

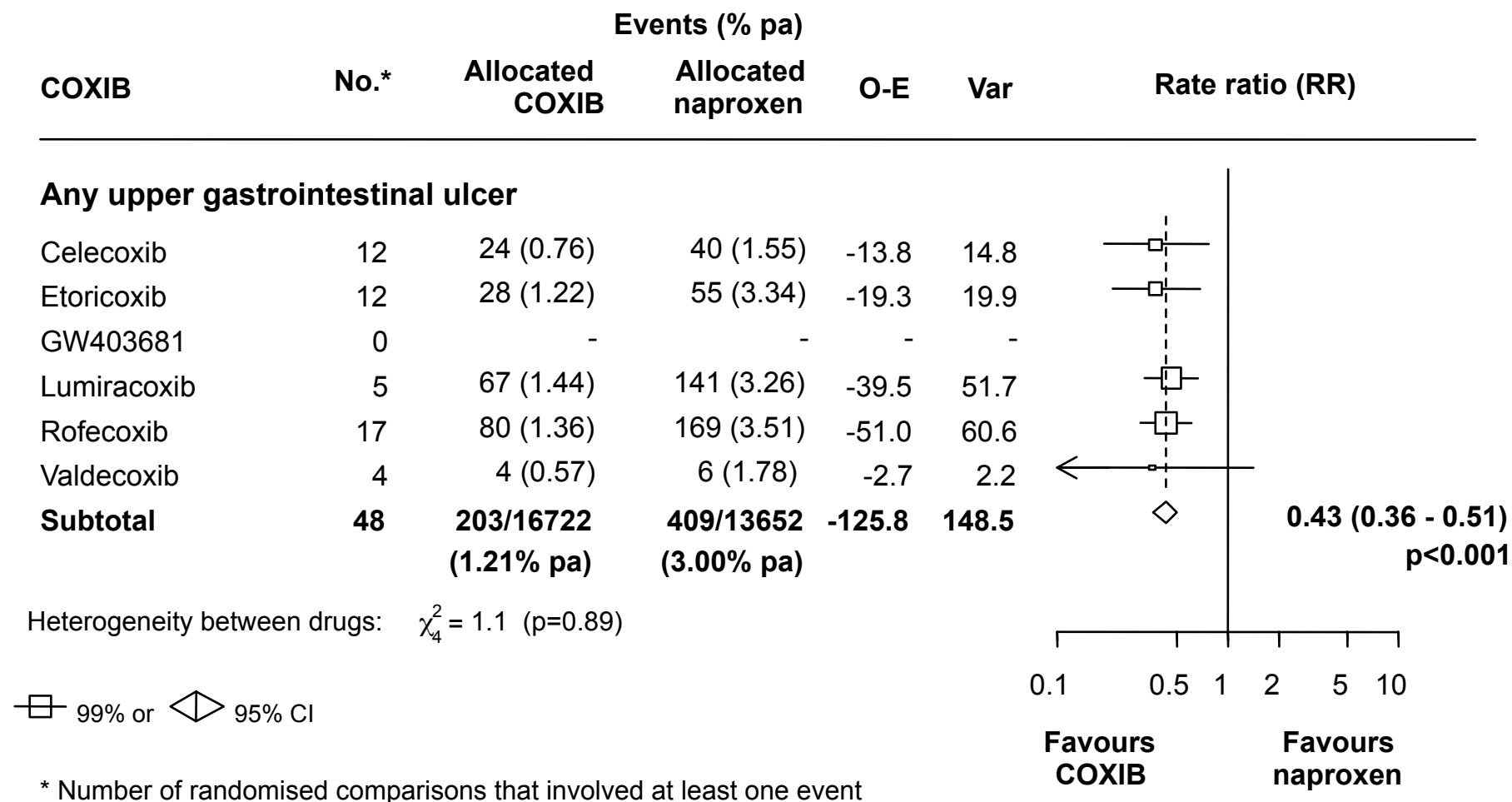


Figure 7.13: Effects of COXIBS vs NSAIDs without antiplatelet activity on upper gastrointestinal complications and symptomatic ulcers

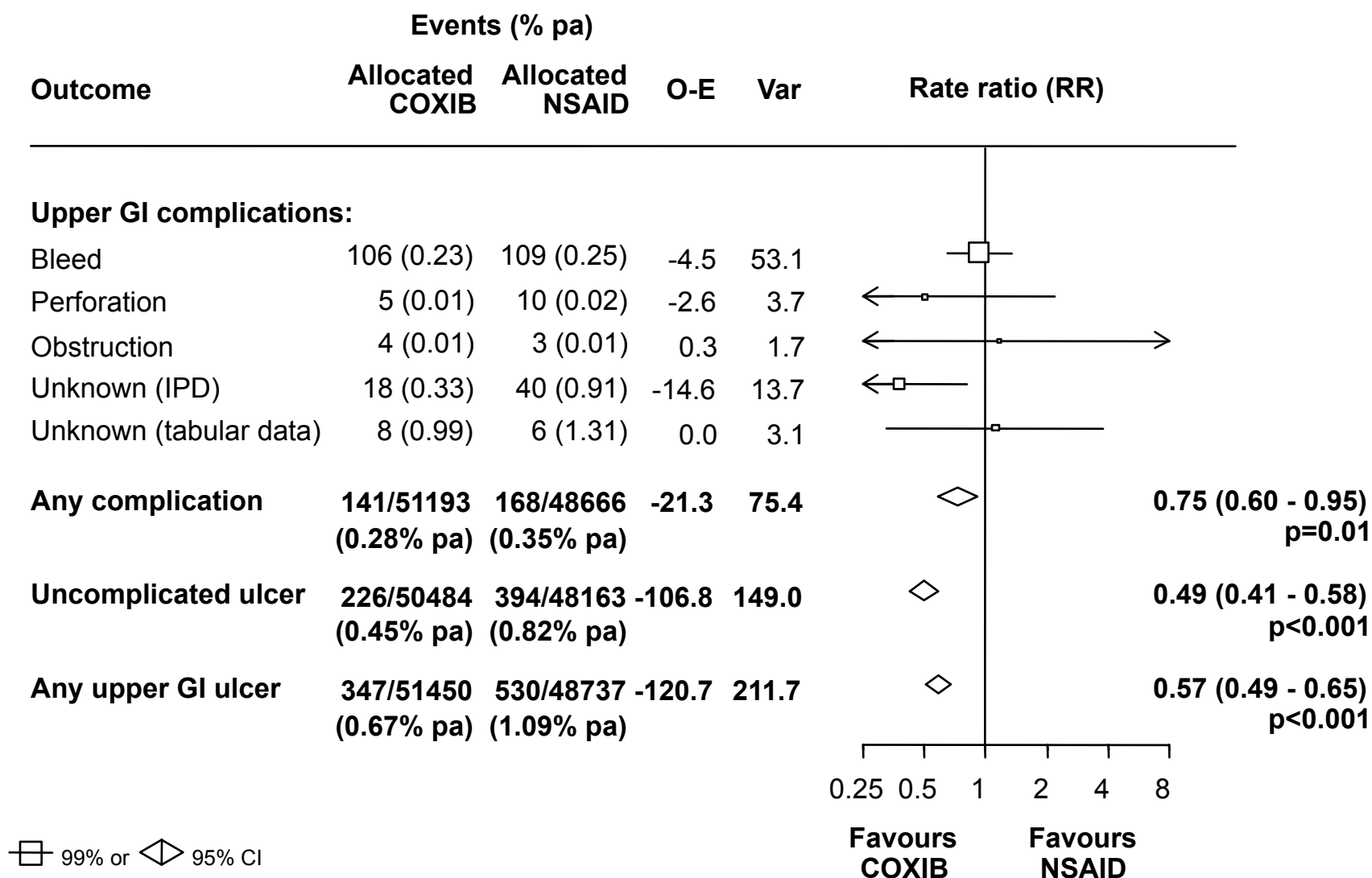
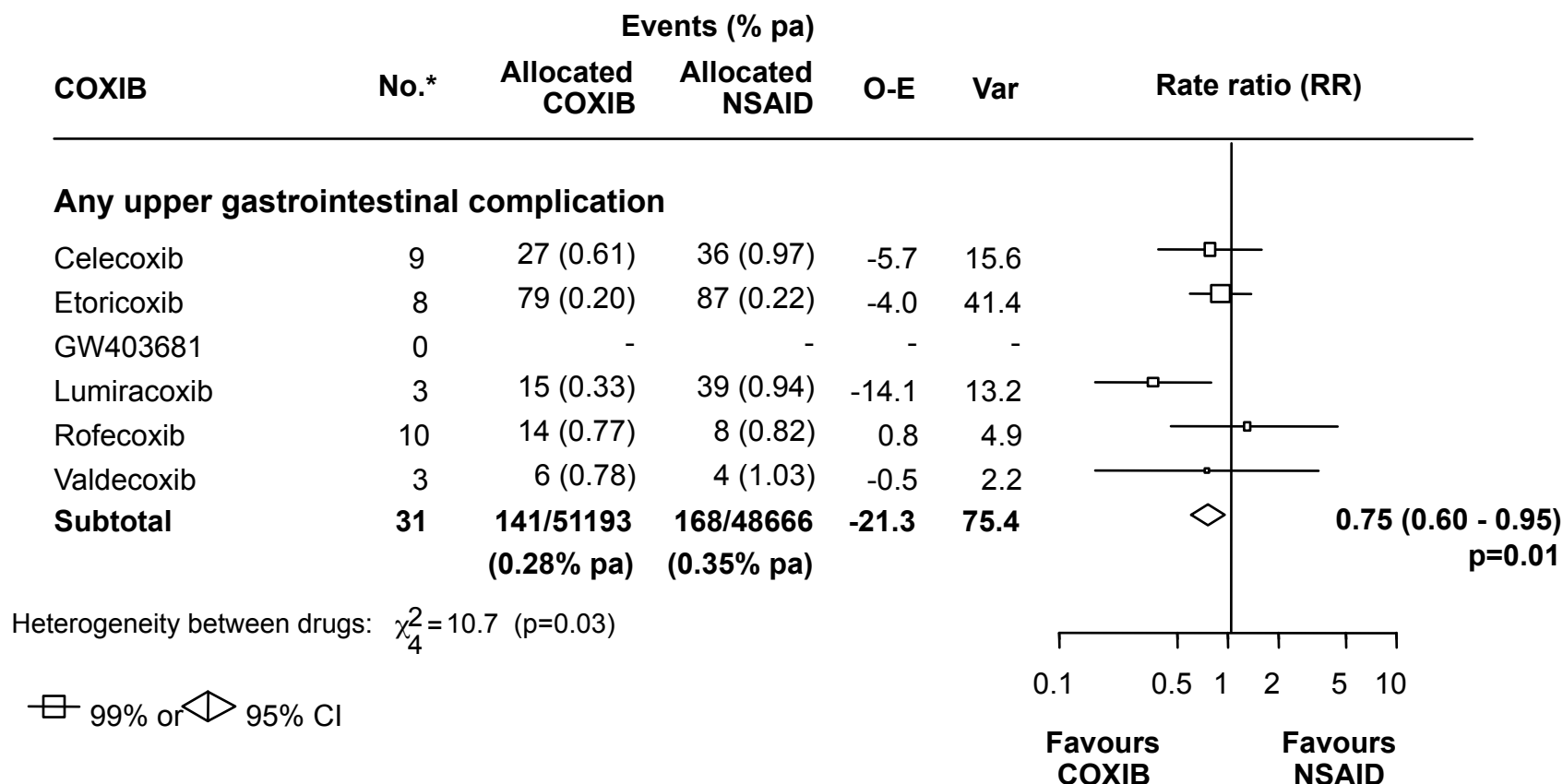


Figure 7.14: Effects of COXIBS vs NSAIDs without antiplatelet activity on upper gastrointestinal complications, by type of coxib



* Number of randomised comparisons that involved at least one event

Figure 7.15: Effects of COXIBS vs NSAIDs without antiplatelet activity on any upper gastrointestinal ulcers, by type of coxib

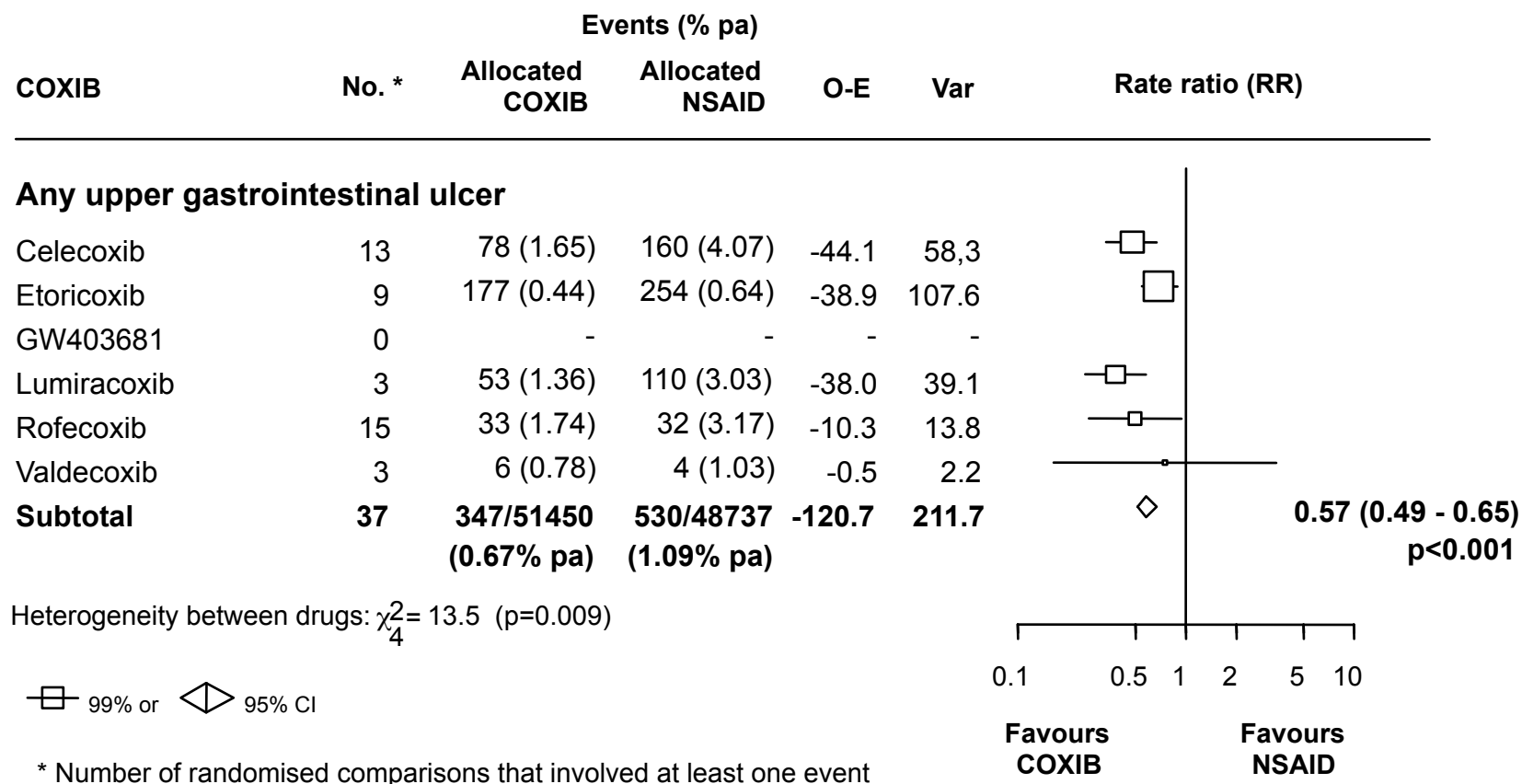


Figure 7.16: Effects of NSAIDs with antiplatelet activity vs PLACEBO on upper gastrointestinal complications and symptomatic ulcers

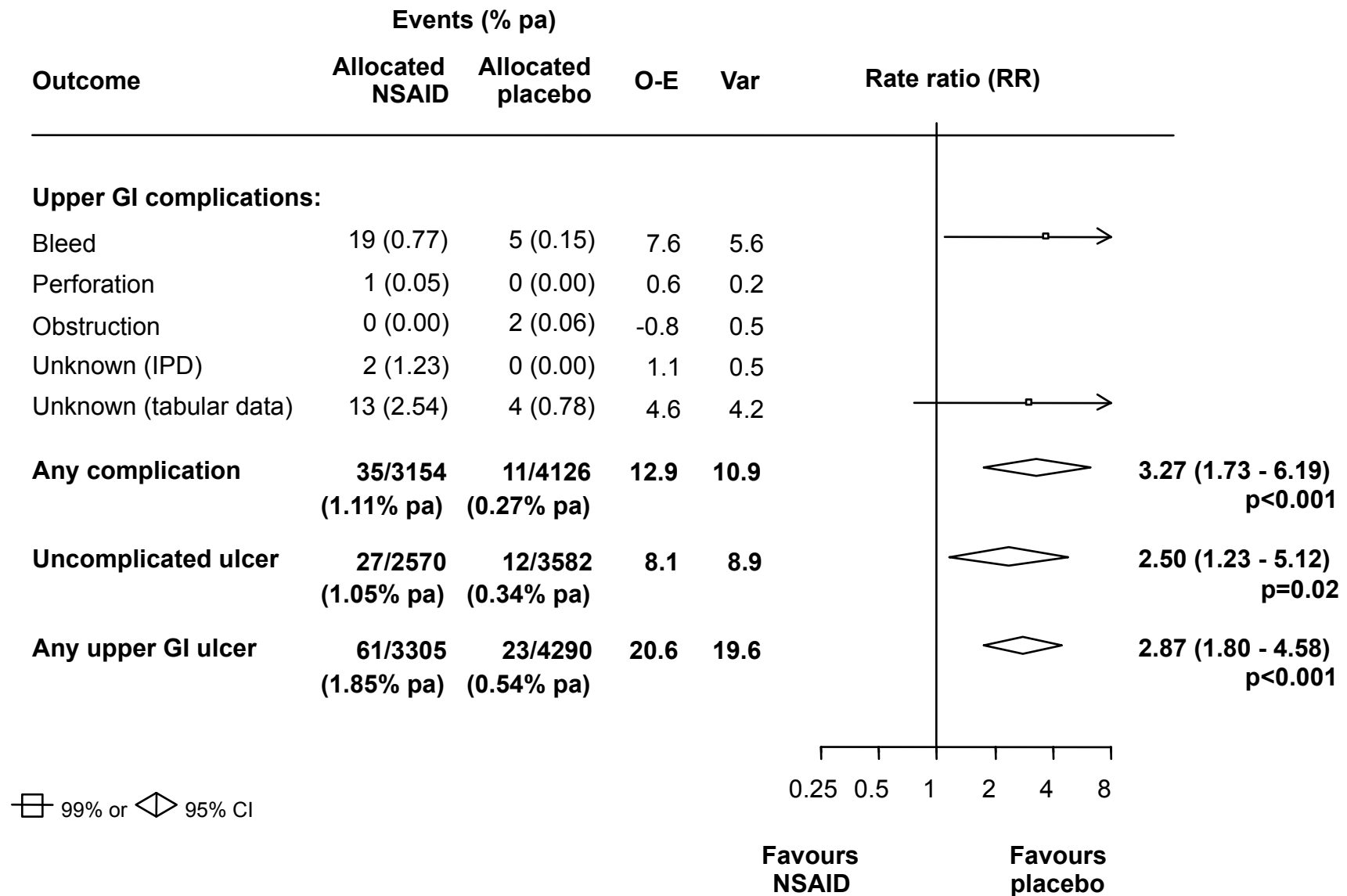


Figure 7.17: Effects of NSAIDs without antiplatelet activity vs PLACEBO on upper gastrointestinal complications and symptomatic ulcers

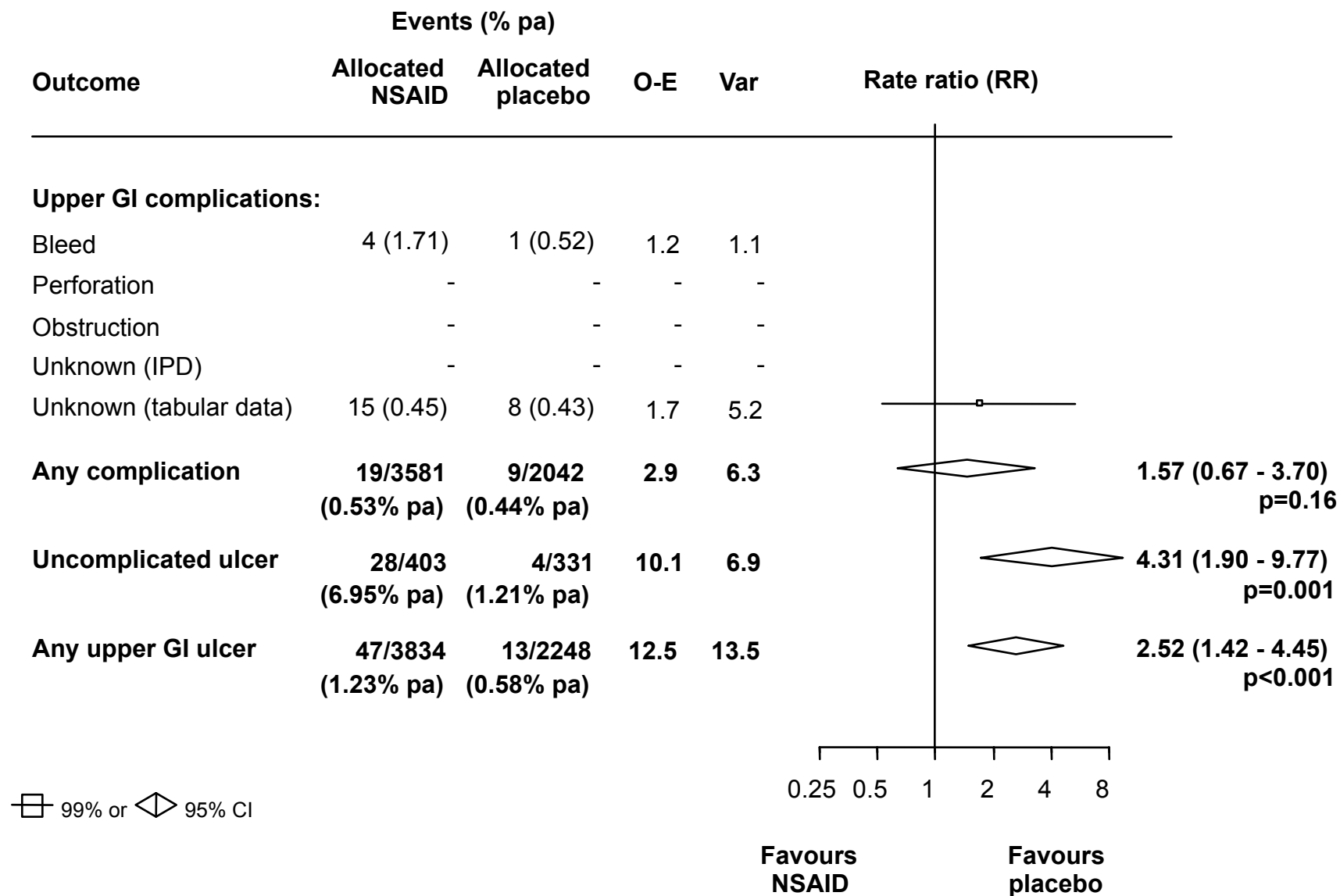
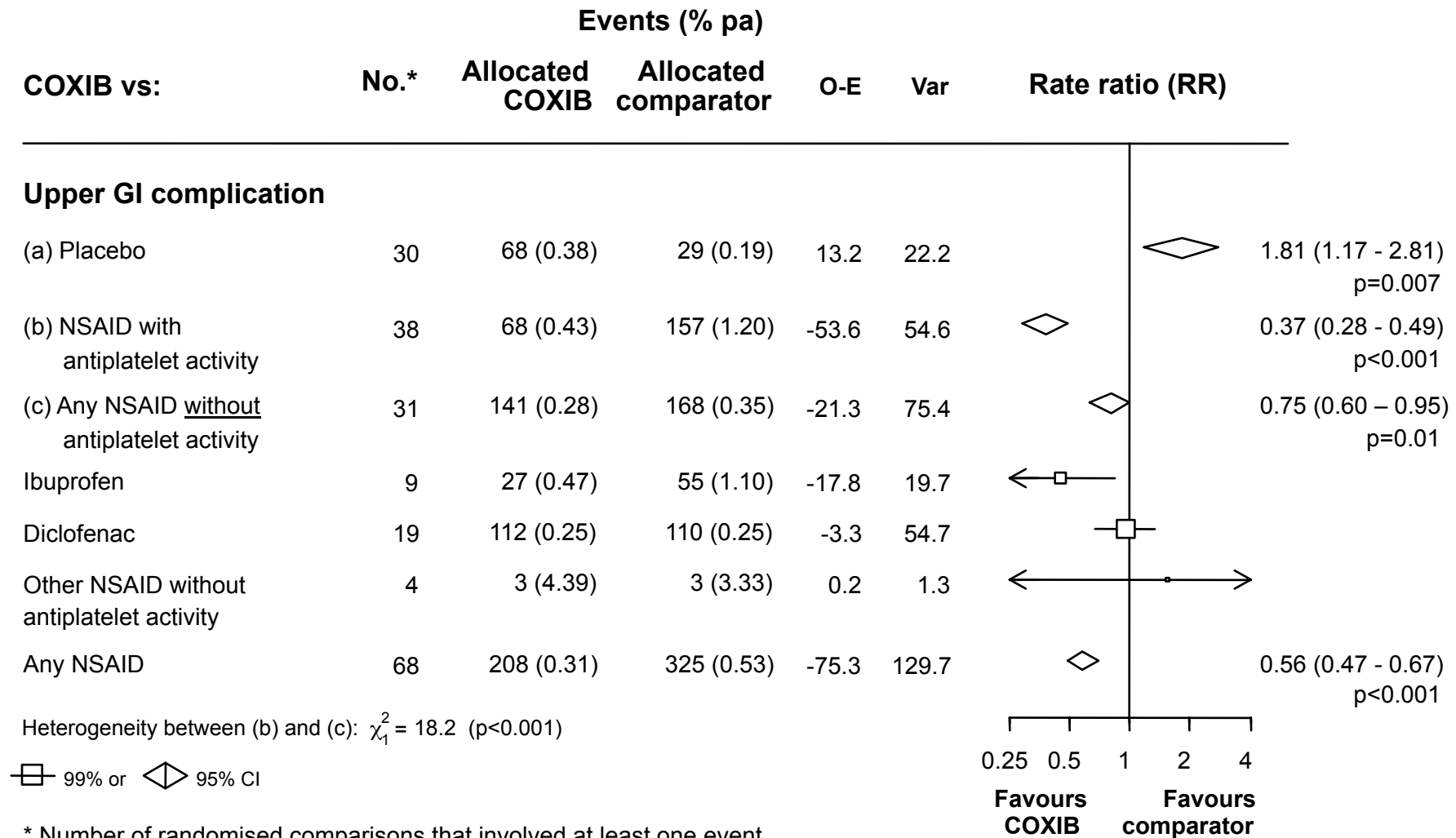


Figure 7.18: Effects of COXIBS on upper gastrointestinal complications, by type of comparator



CHAPTER 8: Evaluating risks and hypothetical effects of coxibs and traditional NSAIDs

8.1 Assessing risk

8.1.1 Methods to assess risk

8.2 Risk factor model development

8.3 Do the proportional effects of coxibs and traditional NSAIDs depend on baseline predicted absolute risks?

8.3.1 Coxib versus placebo

8.3.2 Coxib versus traditional NSAIDs with antiplatelet effect

8.3.3 Coxib versus traditional NSAIDs without antiplatelet effect

8.4 Hypothetical calculations of absolute effects of coxibs and traditional NSAIDs

8.5 Summary

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Table 8.2 Risk factors for major vascular events and any upper gastrointestinal ulcers in participants in trials of coxibs and traditional NSAIDs

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Figure 8.2 Effects of COXIBS versus NSAIDs with antiplatelet activity, by baseline 5-year risk on major vascular events and any upper gastrointestinal ulcers

Figure 8.3 Effects of COXIB versus NSAIDs without antiplatelet activity, by baseline 5-year risk on major vascular events and any upper gastrointestinal ulcers

Figure 8.4 Predicted absolute effects per 1000 of COXIBS and traditional NSAIDS at different baseline risks of major vascular events and upper GI complications (in primary and secondary prevention)

8.1 Assessing risk

Table 8.1 summarises the key results from the previous two chapters regarding the relative risks for the primary outcomes (major vascular events and upper GI complications) associated with each of the different classes of therapeutic agents (ie, a coxib, a traditional NSAID with antiplatelet activity [eg, naproxen] or a traditional NSAID without antiplatelet activity [eg, diclofenac]). However, the decision about which medication to give a particular patient is likely to be influenced by the absolute excess risks of each of the primary outcomes in that patient. We attempted to model the risks of each primary outcome by: (i) estimating the baseline risks of each primary outcome in the absence of treatment; and (ii) estimating the proportional effects of each treatment regimen on the risks of each outcome. Knowledge of the proportional risks of each treatment regimen can then predict the absolute effects of major vascular events and upper GI complications for each regimen in different patients, classified by absolute risk categories.

8.1.1 *Methods to assess risk factors*

In order to identify risk factors for each of the primary outcomes among participants for whom individual data were available in the randomised trials, Poisson regression was used, as has previously been carried out in overviews of cholesterol-lowering and antithrombotic trials. (Baigent et al. 2009; Cholesterol Treatment Trialists' (CTT) Collaboration 2005) Specifically, the natural logarithm of the event rate was modelled as a function of key baseline participant characteristics collected as part of our individual participant data proforma which would affect prognosis (variables including

age [per decade], male sex, current cigarette smoking, previous diagnosis of diabetes mellitus, prior atherosclerotic disease, prior upper GI ulcer, mean arterial blood pressure [per 20 mmHg higher], body mass index [per 5 kg/m² higher], and serum creatinine concentrations [per 50% higher]). There were too few events to stratify by individual trial so the year of randomisation (which was a highly significant predictor of decreasing event rates with increasing calendar year) was also fitted into the model.

The model was developed first using the entire set of participants for whom complete data were available on all the risk factors of interest, and then again after making certain assumptions about missing data in order to increase the number of participants (ie, all were assumed to be non-smokers, non-diabetics, or no baseline history of vascular disease or ulcers).

Similar to the low power of multiple subgroup analyses, the low power of heterogeneity tests mean that individual trend test results for interaction need to be interpreted cautiously. Because the rate ratios for upper GI complications and for symptomatic ulcers are very similar and have a shared pathophysiology, combining these outcomes (as any upper GI ulcer), as was done for the results in Chapter 7, increases the number of events available for analysis. Hence, we used the expanded ulcer outcome of any upper GI ulcers in order to enhance the limited statistical power for tests of interaction.

8.2 Risk factor model development

Complete information on all pre-specified baseline characteristics was available for 83,383 randomised participants (Appendix Table 11). In this subset, results showed that the major baseline predictors for major vascular events associated with about a two-fold increased risk were: being a current smoker (rate ratio [RR] 2.37, 95% confidence interval 2.05 to 2.74), prior atherosclerotic disease (RR 2.07, 1.83 to 2.34) older age (per decade: RR 1.79, 1.68 to 1.90). (Table 8.2) Male sex (RR 1.40, 1.25 to 1.58), diabetes mellitus (RR 1.44, 1.23 to 1.67), and those with higher mean blood pressure (per 20mg mmHg: RR 1.41, 1.28 to 1.55) were each associated with about a

50% increase in major vascular events. (Table 8.2) Other risk factors were of little clinical relevance (or statistical significance) in these multivariate analyses.

We used the expanded ulcer outcome of any upper GI ulcers (combining symptomatic upper GI ulcers with the primary outcome of upper GI complications) in order to enhance power for assessing trends. In this same subset of participants, the risk of any upper GI ulcers was associated particularly with a four-fold increased risk in those participants with a history of prior upper GI ulcer (RR 3.96, 3.22 to 4.88). (Table 8.2) For any upper GI ulcers, older age (per decade) was associated with about a 75% increased risk (RR 1.77, 1.61 to 1.94), and prior atherosclerotic disease a 33% increased risk (RR 1.32, 1.06 to 1.66). (Table 8.2) Other risk factors were of little clinical relevance or statistical significance in these multivariate analyses.

The estimates for major vascular events and any upper GI ulcers did not vary substantially if assumptions were made on the missing data in order to increase the number of participants available for analysis (Appendix Table 11). For example, the results were similar if those individuals with missing data on smoking status were assumed to have baseline disease (a total of 165 285 participants). The results were also similar if age- and sex-specific median blood pressure and serum creatinine were imputed to allow analysis of almost all participants (a total of 192 035 participants).

8.3 Do the proportional effects of coxibs and traditional NSAIDs depend on baseline predicted absolute risks?

The risk factors derived from the model for major vascular events and upper GI complications were used to classify patients into three categories of baseline predicted risks. These were divided for both major vascular events and any upper GI ulcers (again, used to increase statistical power) separately into: low (predicted 5-year risk of events <5%), medium (predicted 5-year risk 5-10%) and high (predicted 5-year risk >10%).

8.3.1 *Coxib versus placebo*

In the trials that tested coxib versus placebo, the relative risk of a major vascular event was similar irrespective of baseline absolute risk of a major vascular event (χ^2 trend = 0.2, $P = 0.62$) (Figure 8.1). Likewise, the relative risk of any upper GI ulcer was similar irrespective of baseline absolute risk of any upper GI ulcer (χ^2 trend = 0.5, $P = 0.50$).

8.3.2 *Coxib versus traditional NSAIDs with antiplatelet effect*

In the trials that tested coxib versus traditional NSAIDs with antiplatelet effect, the relative risk of a major vascular event was similar irrespective of baseline absolute risk of a major vascular event (χ^2 trend = 0.5, $P = 0.46$) (Figure 8.2). Likewise, the relative risk of any upper GI ulcer was similar irrespective of baseline absolute risk of any upper GI ulcer (χ^2 trend = 0.9, $P = 0.34$).

8.3.3 *Coxib versus traditional NSAIDs without antiplatelet effect*

In the trials that tested coxib versus traditional NSAIDs without antiplatelet effect, the relative risk of a major vascular event was similar irrespective of baseline absolute risk of a major vascular event (χ^2 trend = 2.9, $P = 0.18$) (Figure 8.3). Likewise, the relative risk of any upper GI ulcer was similar irrespective of baseline absolute risk of any upper GI ulcer (χ^2 trend = 0.0, $P = 0.89$).

8.4 Hypothetical calculations of absolute effects of coxibs and traditional NSAIDs

These proportional effects of coxibs, traditional NSAIDs with antiplatelet activity (naproxen), or traditional NSAIDs without antiplatelet activity (diclofenac, ibuprofen or other tNSAIDs) appeared similar at different levels of risk of major vascular events and upper GI ulcers (<5%, 5-10%, >10% over 5 years). Given the evidence that the proportional effects were dependent on baseline risk (either linearly, assessed through a test for trend, or not, as assessed by tests for heterogeneity), homogeneity of proportional effects for each regimen is a reasonable assumption when estimating absolute excess risks.

The absolute excess risk of each treatment regimen will therefore depend ultimately on the participants' baseline absolute risk at the point at which coxib or traditional NSAID therapy is initiated, rather than any other participant baseline characteristic. Under this assumption, in order to illustrate the absolute effects of allocation to coxib or traditional NSAID regimens at particular levels of vascular or upper gastrointestinal risks, the right-hand panels of Figure 8.4 show the predicted absolute risks (per 1000/year) of major vascular events and upper GI complications. This is based on constant relative risks for major vascular events and upper GI complications for coxibs, traditional NSAIDs with antiplatelet activity (naproxen), or traditional NSAIDs without antiplatelet activity (diclofenac, ibuprofen or other tNSAIDs), based on each of the predicted levels of absolute risk in the absence of treatment.

We estimated the absolute excess risks of the primary outcomes in both those with no prior disease (primary prevention) and the equivalent of those with prior disease (secondary prevention). For the primary prevention category for MVEs (those with no history of atherosclerotic disease): among these the predicted risk was 0.5% per annum, whilst in the secondary prevention category it was 2% per annum (left panel of Figure 8.4). Corresponding risks of upper gastrointestinal complications were 0.2% per annum (primary prevention), and 0.7% per annum (secondary prevention) (right panel of Figure 8.4). The total length of each bar represents the aggregate vascular and upper gastrointestinal risk for use of coxibs, traditional NSAIDs with antiplatelet activity (naproxen), or traditional NSAIDs without antiplatelet activity (principally diclofenac and ibuprofen), with fatal events represented by dark shading, and standard errors presented in bars.

Several important messages emerge: First, among 1000 patients with a predicted annual risk of a major vascular event equivalent to secondary prevention, a coxib, high-dose diclofenac or ibuprofen regimen would cause 7 patients to experience a major vascular event, with 2 being fatal events, after treatment for a year. For a primary prevention group, such regimens would cause about 2 major vascular events per 1000 patients per year. For this same primary prevention group, naproxen was estimated to have a neutral effect on major vascular events (null effect), although a moderate effect in either direction cannot be ruled out. Although naproxen was

estimated to have a potential protective effect in the secondary prevention group of 1 major vascular event per 1000 person-years, this need to be interpreted cautiously because the confidence intervals also include moderate effects in either direction.

Among 1000 patients with predicted annual risk of an upper GI complication equivalent to secondary prevention, diclofenac and ibuprofen would cause about 9 complications, higher than the 6 caused by a coxib (although very few would be fatal events) if given for a year. For a primary prevention group of upper gastrointestinal complications, the risks between a coxib, diclofenac and ibuprofen are similar (around one event per 1000 per year). Although these analyses suggest that naproxen may not be associated with an increase in the risk of major vascular events, it does, however, cause the most upper GI complications (3 in primary prevention and 22 in secondary prevention equivalents, albeit almost all are non-fatal events).

8.5 Summary

Using data on individual participants allows risk factors that are important predictors of major vascular events and upper GI complications to be identified and for predictive models to be developed. When using this method to separate participants into different groups according to their baseline risk, the relative risk estimates do not show any strong evidence of heterogeneity, suggesting that absolute baseline risks are the key determinant of the primary outcomes.

Applying these principles to each of the risk categories, NSAIDs without antiplatelet activity (eg, diclofenac) are associated with a similar incidence of major vascular events compared to coxibs, but they are associated with increased risk of upper GI complications. Whilst NSAIDs with antiplatelet activity (eg, naproxen) are associated with a lower incidence of major vascular events compared to coxibs, they cause a higher incidence of upper GI complications. Therefore, apart from very low absolute risk groups in whom the absolute effects between the regimens is correspondingly low, the choice of optimal therapy comes down to a traditional NSAID with antiplatelet activity, such as naproxen, or a coxib.

Therapeutic decision-making requires an understanding of the severity of these outcomes (eg, major vascular events, which includes fatal outcomes, versus upper gastrointestinal complications). Whether the underlying vascular and upper gastrointestinal risks can be reduced before commencing NSAID treatment (eg, with vascular therapies or gastroprotectants respectively), relevant pharmacological interactions (eg, aspirin may interact with naproxen/ibuprofen) and patient/physician attitudes to these risks are also relevant. Discussing these considerations and adapting the results of this thesis to clinical practice is considered in the final chapter.

TABLE 8.1 Major vascular events (MVE) and upper gastrointestinal (GI) complications: Estimates for comparisons combining direct and indirect evidence (using regression)

Comparison	Relative risks for outcomes (95% confidence intervals)	
	Major vascular events	Upper GI complications
COX-2 inhibitor vs placebo	1.29 (1.08 – 1.54)	1.59 (1.16 – 2.17)
Traditional NSAID <u>with</u> antiplatelet activity vs placebo	0.87 (0.67 – 1.13)	4.06 (2.85 – 5.78)
Traditional NSAID <u>without</u> antiplatelet activity vs placebo	1.29 (1.04 – 1.61)	1.98 (1.39 – 2.84)

TABLE 8.2 Risk factors for major vascular events and any upper gastrointestinal ulcers in participants in the coxib and traditional NSAID trials that supplied individual participant data.

Risk factors	Rate ratios for outcomes (95% confidence intervals)	
	Major Vascular Events	Any Upper GI Ulcers
Age, per decade	1.79 (1.68, 1.90)	1.77 (1.61, 1.94)
Male sex	1.40 (1.25, 1.58)	1.08 (0.89, 1.30)
Prior atherosclerotic disease	2.07 (1.83, 2.34)	1.32 (1.06, 1.66)
Prior upper GI ulcer	1.28 (1.06, 1.55)	3.96 (3.22, 4.88)
Diabetes mellitus	1.44 (1.23, 1.67)	1.18 (0.89, 1.56)
Current smoker	2.37 (2.05, 2.74)	1.09 (0.80, 1.47)
Mean blood pressure (per 20 mmHg)	1.41 (1.28, 1.55)	1.17 (1.00, 1.36)
Body mass index (per 5 kg/m ²)	1.04 (0.99, 1.10)	0.95 (0.87, 1.03)
Creatinine (per 50% higher)	1.19 (1.07, 1.32)	0.88 (0.75, 1.03)

Figure 8.1: Effects of COXIBS vs PLACEBO, by baseline 5-year risk on major vascular events and any upper gastrointestinal ulcers

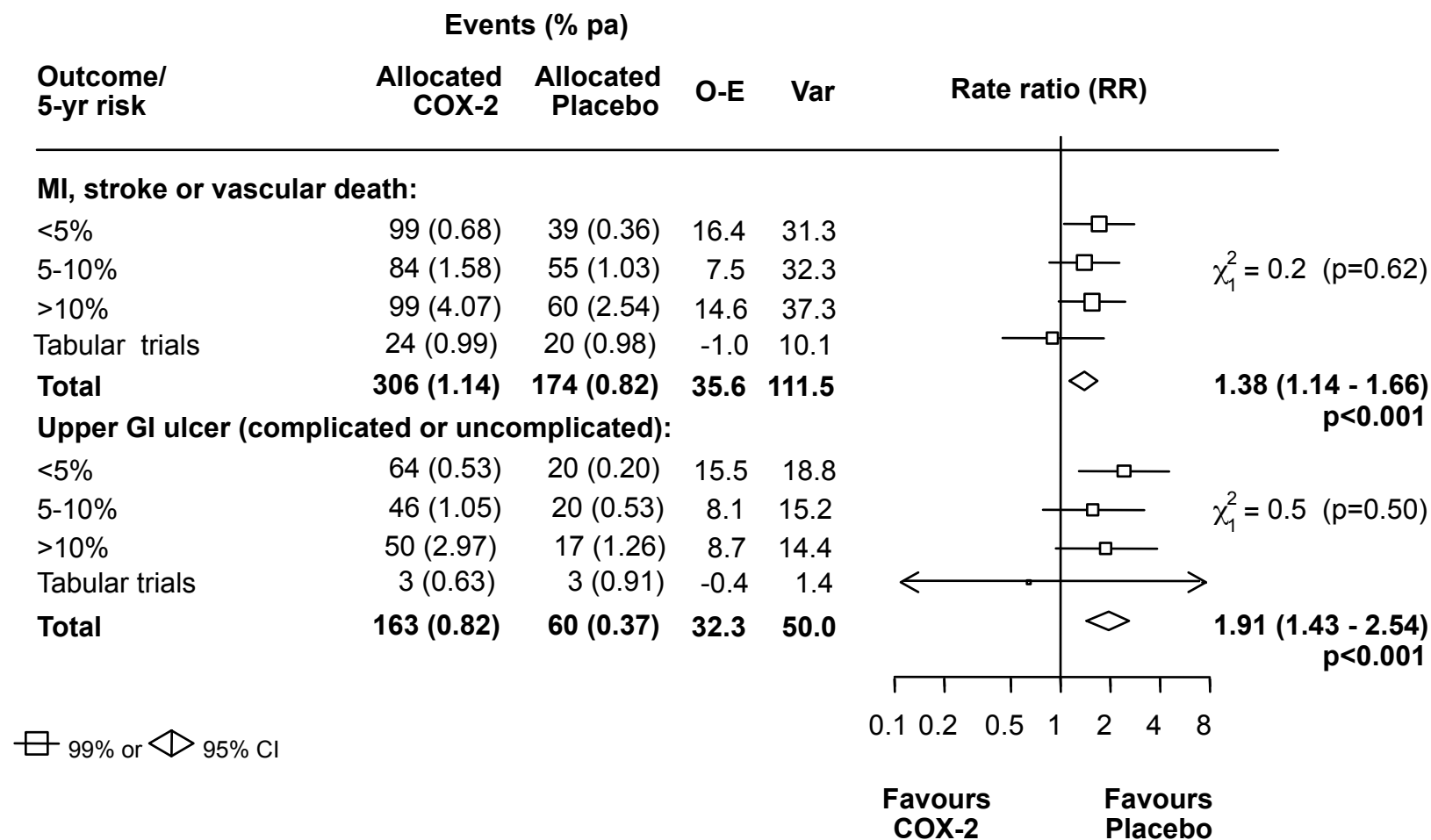


Figure 8.2: Effects of COXIBS vs NSAIDs with antiplatelet activity, by baseline 5-year risk on major vascular events and any upper gastrointestinal ulcers

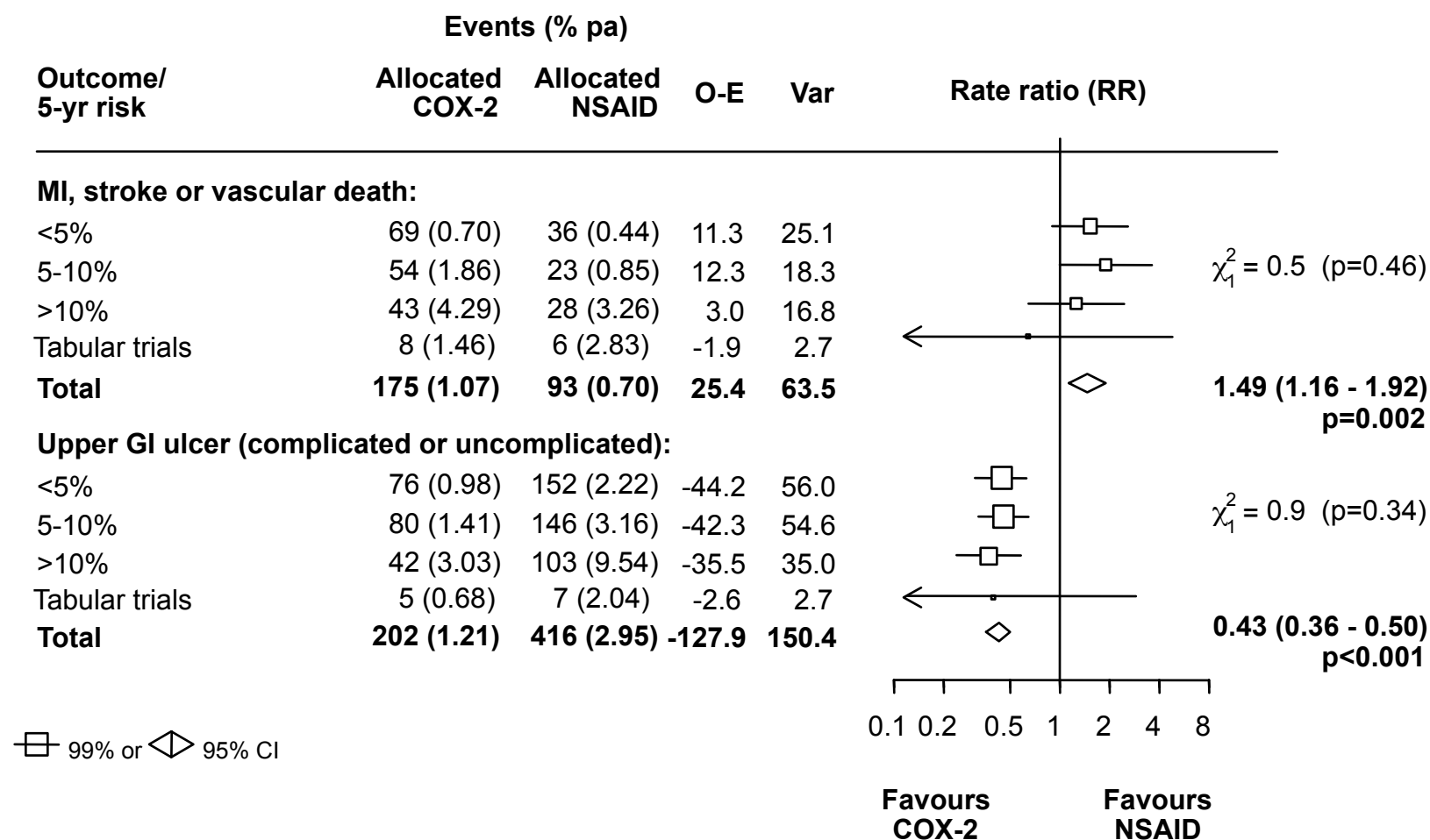


Figure 8.3: Effects of COXIBS vs NSAIDs without antiplatelet activity, by baseline 5-year risk on major vascular events and any upper gastrointestinal ulcers

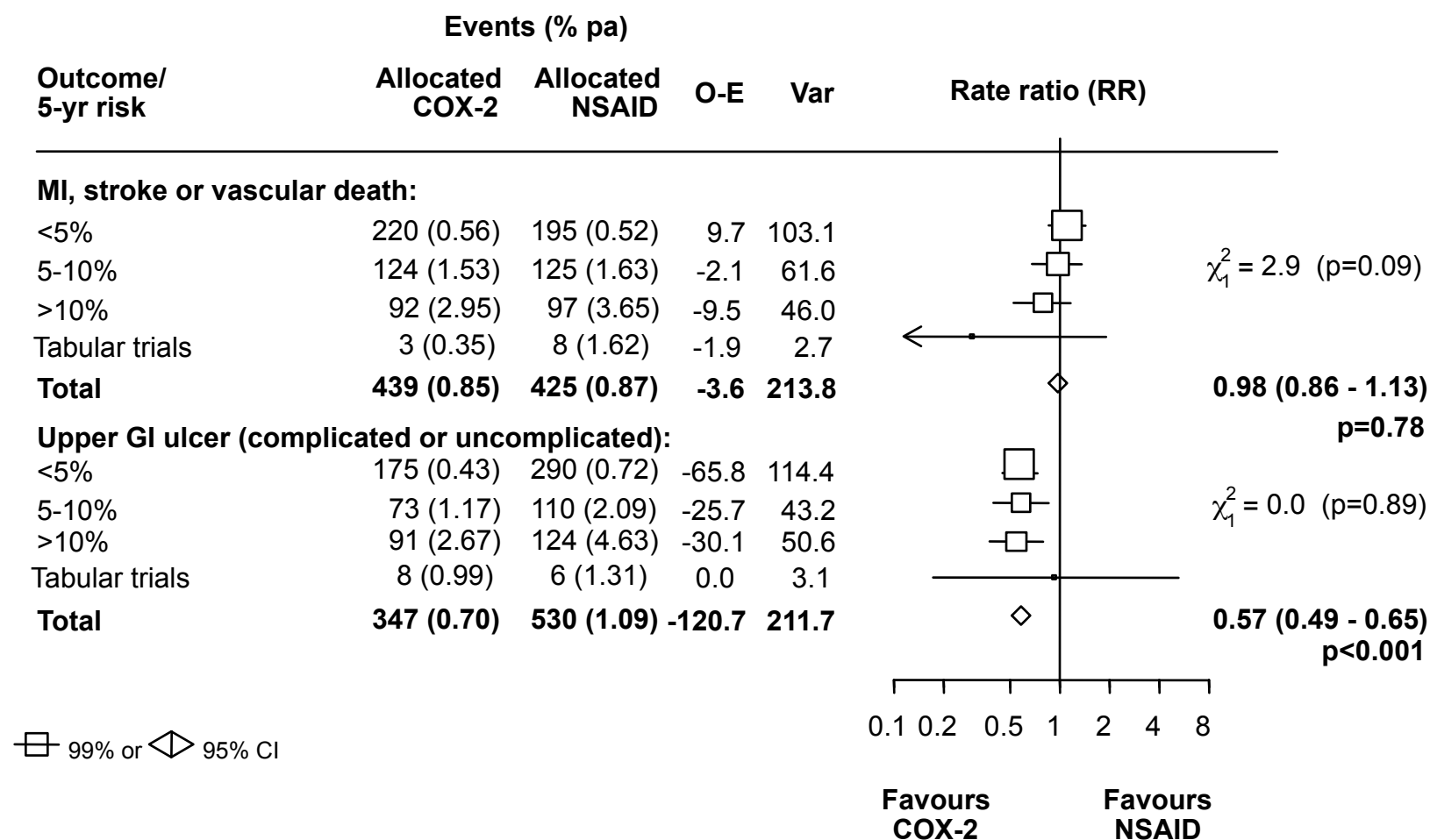
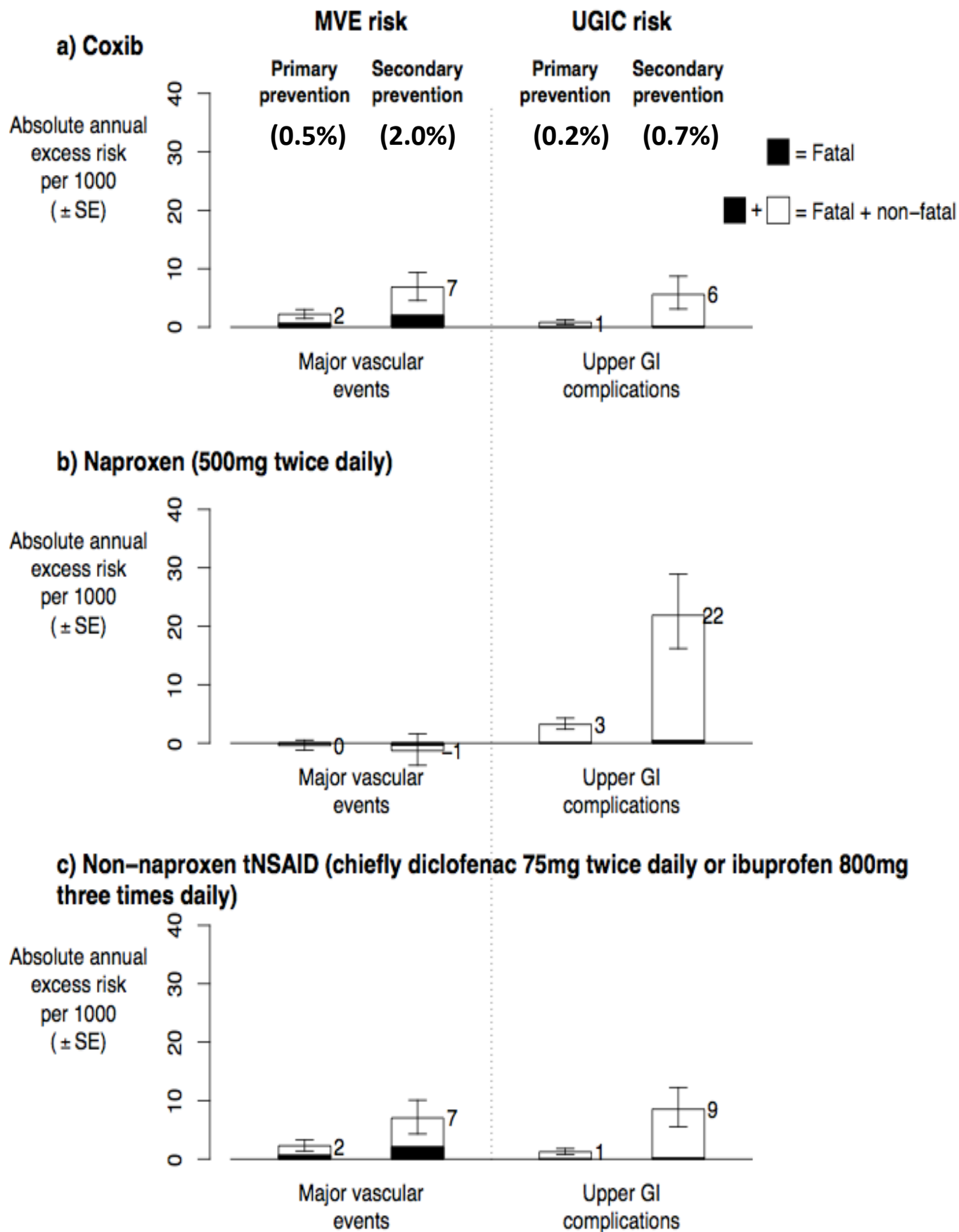


Figure 8.4: Absolute effects per 1000 of coxibs and tNSAIDs at different baseline risks of major vascular events and upper GI complications



CHAPTER 9: Discussion & conclusions

9.1 Summarising the main outcomes

9.1.1 Major vascular events

9.1.2 Upper GI complications and symptomatic upper GI ulcers

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9.9.2 Comparison with other meta-analyses of randomised trials

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9.10.2 Evidence-base for other analgesic therapies

9.11 Clinical implications

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9.12 Applying what is known from the pharmacology of NSAIDs

9.12.1 Naproxen and other NSAIDs with persistent antiplatelet activity

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9.14 The need for future large-scale randomised trials and overviews

9.15 Conclusions

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Table 9.1 Overall relative and absolute estimates of effects of major outcomes by type of drug

Table 9.2 Questions answered by this meta-analysis of randomised trials of coxibs and traditional NSAIDs

Table 9.3 Suggested use of coxibs versus naproxen according to upper gastrointestinal and vascular risks

9.1 Summarising the primary outcomes

9.1.1 *Major vascular events*

When we considered all the randomised trial (predominantly individual participant) data, allocation to a coxib was associated with a highly significant 1.3- to 1.4-fold increased risk of major vascular events versus placebo. This was largely due to a 1.8- to two-fold increased risk of myocardial infarction and a 1.6-fold increased risk of any vascular death. These increased risks of major vascular events were remarkably similar to allocation of a NSAID without persistent antiplatelet activity (eg, high-dose regimens of diclofenac). In contrast, allocation to a NSAID with persistent antiplatelet activity (chiefly naproxen 500mg bd), was associated with a 'neutral' (no clear evidence of beneficial or harmful) effect on major vascular events. Although we found no significant excess in the incidence of strokes or of its subtypes (ischaemic, haemorrhagic or unknown), the confidence intervals were wide (so we could not exclude a moderate effect).

9.1.2 *Upper gastrointestinal complications and symptomatic upper GI ulcers*

Allocation to a coxib was also associated with a highly significant 1.6- to 1.8-fold increased risk of upper GI complications (versus placebo), predominantly bleeds, showing that these agents are not without gastrotoxicity. Moreover, allocation to a traditional NSAID without persistent antiplatelet activity (eg, high-dose regimens of diclofenac) were associated with an additional excess risk, with a highly significant two-fold increased risk versus placebo of upper GI complications. However, NSAIDs with persistent antiplatelet activity, particularly naproxen, were associated with the highest relative risk: around a four-fold risk of upper GI complications versus placebo (with even a conservative estimate being three-fold).

Allocation to a coxib was associated with a highly significant two-fold excess risk of symptomatic ulcers, similar to the proportional effect of coxibs on upper GI complications. Correspondingly, allocation to a traditional NSAID was associated even more strongly with an increased risk of symptomatic ulcers: those without persistent antiplatelet activity (eg, diclofenac) had a two-fold risk and those with persistent antiplatelet activity (eg, naproxen) had the highest effect for symptomatic ulcers (2.3-fold).

9.1.3 *Hospitalisation for heart failure*

Allocation to both coxibs and traditional NSAIDs were associated with a highly significant two-fold excess risk of hospitalisation for heart failure. The majority of these heart failure events were not associated with other occlusive vascular events (suggesting they did not take place post-myocardial infarction). The similar rate ratios for heart failure for both coxibs and traditional NSAIDs, suggests a similar pathophysiological effect on COX-2-dependent cardiorenal prostaglandin synthesis, which mediates this vascular hazard.

9.1.4 *Other vascular complications*

Although there was no excess in the risk of any other vascular complications (combined as a composite endpoint) between the different coxibs and traditional NSAIDs, these are a heterogenous group of outcomes (eg, pulmonary embolus and unstable angina), which were not the principal outcome of most of the trials studied. Hence, there was a lack of power to adequately assess the effect of coxibs and traditional NSAIDs on other vascular complications.

9.1.5 *Cause-specific mortality*

There was limited power to assess cause-specific mortality with the drugs. However, because of their effect on vascular deaths, allocation to a coxib was associated with a 20% increase in overall mortality, with allocation to a traditional NSAID without persistent antiplatelet activity (eg, diclofenac or ibuprofen) associated with a similar moderate effect (albeit not statistically significant). Moreover, in those participants at higher vascular risk, vascular deaths will contribute to a larger proportion of overall deaths. In contrast, deaths due to upper GI complications appeared to be much less common than deaths due to vascular aetiologies, although the long-term prognostic significance of such incident events may be under-estimated because some patients may leave the trial after such an event. There was no evidence of an effect on deaths due to cancer with coxibs, although these results were predominantly driven by one study assessing colorectal cancer. (Kerr et al. 2007)

9.2 Putting risks into context

9.2.1 *Absolute risks of vascular and upper GI events*

Allocation to a coxib was associated with around three extra people having a major vascular event per 1000 per year in this population (one of these being fatal), with most of this excess attributable to myocardial infarction. Traditional NSAIDs without antiplatelet activity were associated with a similar absolute risk of major vascular events (3 per 1000 per year, 1 being fatal), whilst there was no absolute effect for these outcomes for NSAIDs with antiplatelet activity (ie, naproxen). Allocation to coxibs and all traditional NSAIDs were associated with around four extra people having an episode of hospitalisation for congestive heart failure per 1000 per year. (Table 9.1)

Allocation to a coxib was associated with around two extra people having an upper GI complication per 1000 per year in this population, with most of this excess attributable to bleeds. Traditional NSAIDs without antiplatelet activity were associated with a slightly increased upper GI complication risk (3 per 1000 per year) but those with antiplatelet activity were associated with the highest absolute risk (8 per 1000 per year) in this population.

9.2.2 *Mortality of different outcomes*

These results are summarised in Table 9.1 but it also needs to be considered that the outcomes studied in this meta-analysis are not strictly comparable in terms of severity. For example, a non-fatal admission with myocardial infarction, or, particularly, a stroke is more likely to result in long-term disability than is a non-fatal upper GI bleed or other complication.

Upper GI complications are still serious outcomes, with a hospital admission for an upper GI bleed associated with an annual mortality of around 10% in the most recent UK National Audit. (Hearnshaw et al. 2011). However, the major vascular events include deaths due to a vascular aetiology, which are substantially more common than deaths related to upper GI ulcers (which are predominantly non-fatal – 98% in this study). Even including the possibility of under-ascertainment of the relatively few upper GI deaths, the vascular

outcomes are still relatively more serious outcomes, with a higher risk of mortality and morbidity.

9.2.3 *Utility of different outcomes*

Estimates of the disutility of the different outcomes, and of analgesic efficacy, need to be considered as well as mortality and morbidity. There are only a few economic evaluations of the effects of coxibs and traditional NSAIDs that have tried to estimate utility in this topic (Spiegel et al. 2003; Chen et al. 2008), most recently by UK National Institute of Clinical Excellence calculations, summarised in the Appendix tables. (Latimer et al. 2009).

When considering quality of life years (QALYs, with 1 showing completely healthy), as utilised by NICE, vascular death obviously has the most profound effect (score of 0). For other vascular outcomes (QALY for first three months in brackets), myocardial infarction (0.37), and particularly strokes (0.35) were estimated to have a profound initial effect in the first three months, particularly those proportion of strokes that cause long-standing and severe disability. Interestingly, congestive heart failure (0.71) were estimated to have a transient NSAID effect on quality of life and utility in these analyses, which may be a relative underestimate given the mortality of this condition. (In the UK, a hospital admission for heart failure is associated with a risk of mortality of 12% in the ensuing year, so this is another important outcome to consider, especially in the elderly.) (National Heart Failure Audit 2012)

Corresponding utilities for upper GI ulcers were less severe than vascular events: Upper GI complications (QALY 0.46), ranging to symptomatic ulcers (0.55) and dyspepsia (0.88). Moreover in the longer term, after 3 months, upper GI bleeds and symptomatic ulcers have less of an effect (0.98). As symptomatic ulcers (and upper GI complications in these analyses) were mainly non-fatal, these QALYS could be overestimates of the effects.

There are few reliable means to assess the disutility of chronic pain, and to quantify the benefits of analgesic therapies. In the NICE analyses above, The Western Ontario and McMaster Universities Arthritis Index (WOMAC), a widely used proprietary set of standardized questionnaires was used to evaluate the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the

joints. Coxibs and traditional NSAIDs were estimated to lead to an equivalent improvement in WOMAC score, far more effective for analgesia than paracetamol. A mean utility weight method was also estimated for these analyses, in which coxibs and traditional NSAIDs were more effective than paracetamol (or placebo), although serious adverse events such as vascular and upper GI events were not included in these analyses. Given the imprecision of current studies to reliably assess alleviation of burden of pain, more accurate methods to reliably estimate the utilities of analgesia, especially when comparing therapies, are an important area for future research.

9.3 Comparison of the effects of coxibs and traditional NSAIDs

There was no strong evidence for heterogeneity by different types of coxibs for the doses tested in the comparisons made. Of course, we cannot exclude differences between coxibs, especially as these comparisons are dominated by few drugs (ie, celecoxib, lumiracoxib or rofecoxib), but any such differences would appear to be modest. For the traditional NSAIDs, those with antiplatelet activity were dominated by naproxen, and those without antiplatelet activity were dominated by diclofenac and ibuprofen.

The finding of little heterogeneity on vascular risk between the types of coxibs has scientific implications. Coxibs and traditional NSAIDs vary by cyclo-oxygenase selectivity, half-life and other pharmacological characteristics. However, the lack of significant difference for major vascular events suggests that the role of these pharmacological differences could play a smaller role than the overall class effect (ie, high-grade COX-2 inhibition). This may also apply to the effect of the different drugs on other possible mediators of vascular risk, such as blood pressure.

The pharmacological characteristics of specific drugs, such as COX-2 selectivity, may be of more relevance to upper gastrointestinal outcomes. Selective COX-2 inhibitors were, after all, developed to have a reduced effect on upper gastrointestinal outcomes compared to traditional NSAIDs. For example, lumiracoxib, which is relatively more COX-2 selective, was found to have a potential reduced effect on upper gastrointestinal ulcer risk compared to other coxibs. (Figure 7.15) As well as the finding of little heterogeneity on upper

gastrointestinal risk between the types of coxibs in other comparisons, however, it is noteworthy that the class effects of each type of regimen still appear to provide the largest effect for upper gastrointestinal outcomes.

9.4 The effects of different doses of coxibs and traditional NSAIDs

Except for a slightly increased effect of higher doses of celecoxib on major vascular events and of etoricoxib on upper GI complications, there was no strong evidence for a dose response effect. This is partly because there was not enough variation among the doses of the coxibs studied to evaluate the effect on risk. Nevertheless, as coxibs (and traditional NSAIDs) have effects on major vascular events and upper GI complications, then it would be biologically plausible that these effects would increase with higher doses. Hence, (as per current guidance) for those participants who need coxib therapy, reducing the daily dose to the lowest compatible with symptom control could be a practical means of reducing harms.

There was even less power to detect variation in the effects of different doses of traditional NSAIDs, but there are two important caveats. First, the doses used for traditional NSAIDs without persistent antiplatelet activity (ie, ibuprofen and diclofenac) were supratherapeutic compared to those used in everyday clinical practice. As dose response is uncertain for these traditional NSAIDs, then it is biologically plausible that the vascular and upper GI relative effects for these treatment regimens would also apply at lower doses, which have not been directly assessed in trials. Secondly, the 'neutral vascular effect' of naproxen, in relation to its persistent antiplatelet activity, may be directly related to dose. (Baigent and Patrono 2003) However, as with coxibs, when giving traditional NSAID therapy, reducing the daily dose to the lowest possible for the alleviation of symptoms could be a practical method to reduce possible harms in clinical practice.

9.5 The effects of duration of follow-up in analyses

As a subgroup analysis, the results separated by duration of follow-up need to be interpreted with some caution compared to the primary analyses. For major vascular

events, driven at least partly by the APPROVe trial results, (Bresalier et al. 2004) there was no evidence for a latent effect (ie, any time-dependent effect before any hazards emerged). For upper gastrointestinal ulcers, although the trend was for events to occur closer to allocation of a coxib or traditional NSAID, there was no evidence for a substantial alteration in risk over time.

Compared to other meta-analyses of trials, for example those of statins, (CTT Collaboration 2010) the duration of treatment with coxibs and traditional NSAIDs in this meta-analysis was much shorter. Whilst older relatively shorter studies of traditional NSAIDs contribute events for analyses less than six months, more recent larger and longer trials of coxibs, such as MEDAL, contribute events for more than 18 months (as well as preceding time intervals). Therefore, for both major vascular and upper GI outcomes, hazards related to coxibs or traditional NSAIDs can occur after only a short duration of use. This is consistent with the results of some of the short-term randomised trials of parecoxib/valdecoxib in coronary artery bypass graft patients. (Ott et al. 2003, Nussmeier et al. 2004) Moreover, although a latent effect was hypothesised after the original APPROVe results, hazards do not occur solely with prolonged exposure. Hence, for those participants who need symptom control, reducing exposure to coxibs and traditional NSAIDs to as short a duration as possible to alleviate symptoms may be a practical way of reducing the risk of hazards.

9.6 The effects of concomitant aspirin use

Although there have been some concerns about the effects of low-dose aspirin taken in conjunction with coxibs or traditional NSAIDs, (Strand et al. 2008) the subgroup results for coxib versus placebo with/without aspirin do not show any strong evidence of heterogeneity for either primary outcome. However, this comparison did have limited power, and this is not an appropriate design to directly address this hypothesis (ideally a comparison of aspirin versus placebo among patients taking or not taking coxib). (FitzGerald and Patrono 2001) However, it should be noted that there are three further caveats for the use of aspirin with coxibs and traditional NSAIDs. First, when considering the vascular benefits versus the bleeding risks, low-dose aspirin is only of likely net overall value in patients at high risk of occlusive vascular disease. (Baigent et al. 2009) Secondly, the

predominant hazardous effect of co-prescription appears to be on upper GI outcomes: increasing NSAIDs and antithrombotics increases relative risks substantially for upper GI ulcers and complications. (Weil et al. 2000) Finally, there is pharmacological evidence of coxibs/traditional NSAIDs, particularly ibuprofen and naproxen, counteracting the antiplatelet benefits of aspirin use when given together. Hence, although some patients may require aspirin and coxibs/NSAIDs concurrently (eg, a post-MI patient requiring analgesia for arthritis), there are both scientific and clinical rationale not to give both together.

9.7 Lack of variation of the effects in prognostic subgroups

The use of individual participant data demonstrates the contribution of the risk factors for the primary outcomes: whilst those factors for vascular outcomes are well-known and confirmed in this study (eg, smoking, prior atherosclerotic disease and older age), those for NSAID-related upper GI complications have been less well described and particularly include older age and a past history of an ulcer. Although subgroup analyses need to be interpreted with caution, there was little evidence of heterogeneity among the many tests conducted, especially when allowing for multiple testing. This provides valuable evidence of the lack of variation of the proportional effects of different drugs on vascular and upper GI risk, especially as it applies to different absolute risk categories. In turn, this allows reliable and clinically relevant estimates of the excess risk of giving a coxib or traditional NSAID to a participant, based on their absolute risk at baseline, to be made, as shown in Figures 8.4.

9.8 Methodological strengths and limitations

9.8.1 *The role of random error*

The chief limitation of this study, even though it comprises all the available randomised evidence, is the relatively small number of outcomes available for analysis, which limits the assessment of the hazards of the various coxibs and traditional NSAIDs in particular clinical circumstances. The relatively small increase in the absolute risk of vascular or upper GI

outcomes from taking these medications meant that even with individual participant and tabular data on more than 250,000 randomised persons, estimates for primary outcomes (eg, for naproxen) still have some statistical imprecision and cannot exclude moderate effects. Although the proportional risks are statistically reliable for the primary outcome for coxibs and most traditional NSAIDs, there is limited power to assess different drugs, dose response, time-to-event, and other subgroup analyses, and so the secondary outcomes need to be interpreted cautiously (as discussed above). For example, the lack of dose variation and limited duration of treatment means that these results require particular attention to clinical implications (ie, as low a dose as possible for as short as possible).

9.8.2 *Selection bias*

The data included in these analyses were taken from published and unpublished relevant unconfounded randomised trials after multiple electronic literature searches in order to reduce any publication bias. Whilst it is possible that small trials were missed, it is unlikely that this was the case for larger trials that would be more likely to alter the risk estimates. As is shown in Chapter 5, for coxib comparisons, individual participant data were available for the vast majority of trials identified, and for the large trials most have been analysed by intention-to-treat (with the exception of the TARGET trials). (Schnitzner et al. 2004)

A further potential source of bias was our *a priori* decision to limit eligibility to trials of at least four weeks' duration, although we did request data for studies of high vascular risk populations. Although requested from the sponsor, two small short term randomised trials of parecoxib (the intravenously administered pro-drug of valdecoxib) and valdecoxib versus placebo among patients having coronary artery bypass grafting, (Nussmeier et al. 2005; Ott et al. 2003) in which the risk of vascular events was increased threefold, were not provided. However, when these two trials were included in this meta-analysis, the summary rate ratio for a coxib versus placebo changed only slightly, similar to the findings of a previous meta-analysis (from 1.37 to 1.41). (Kearney et al. 2006) Hence, although we cannot exclude the possibility that, at least in the context of vascular surgery, the proportional increase in risk of a vascular event is higher with parecoxib or valdecoxib than with other coxibs, the exclusion of these trials had a small effect on the overall summary rate ratio for a coxib versus placebo.

9.8.3 *Information bias*

Data included, whether available as individual participant or tabular, were checked versus the published record or clinical study report, reducing the likelihood of substantial bias due to erroneous data. Moreover, for those contributing individual participant data, primary outcomes and other details were corroborated by the collaborating trialist after an extensive data checking procedure, further reducing any information bias. Unpublished studies contributed very few person-years and events, and there was no evidence of any heterogeneity compared to published studies for the primary outcomes, so publication bias is unlikely to contribute significantly (Table 5.3 and Appendix).

An advantage of using randomised trials is that differential misclassification (which can lead to under- or over-estimates of effects) should be minimal compared to non-randomised studies. However, not all of the trials independently adjudicated vascular events, so a bias towards the null, owing to non-differential misclassification of both vascular and upper gastrointestinal outcomes in those trials without independent adjudication, is possible. The assumption has been that this would result in an underestimate of the hypothesized relationship between coxib/traditional NSAID and the outcomes studied. Still, as more than 75% of the vascular events occurred in trials that were adjudicated, the potential for such misclassification was small. (Kearney et al. 2006)

9.8.4 *Direct and indirect comparisons*

The vast majority of the information comes from the direct comparison of coxibs (for which there are adequate data available for the primary outcomes), but there are relatively little data from the direct comparison of traditional NSAIDs versus placebo, leading to unreliable estimates for these medications. Therefore, in order to estimate the effects of traditional NSAIDs, indirect evidence was also utilised (derived from trials of a coxib versus NSAID and a coxib versus placebo, and weighted on numbers of outcomes). The use of the direct randomised comparisons gives reliable information on the effects of coxib versus placebo, (which was attenuated only slightly by the incorporation of indirect evidence). However, the incorporation of indirect evidence is of most value in clarifying the effects of traditional NSAIDs (due to the paucity of data from direct comparisons).

The validity of the adjusted indirect comparisons depends critically on the internal validity and similarity of the trials and participants included. (Song et al. 2003) Whilst using individual patient data have been proposed as the optimal method to reduce methodological biases when using indirect methods, (Glenny et al. 2005) most meta-analyses of randomised trials have not, however, done so (Donegan et al. 2010). Evaluating detailed baseline characteristics of the participants, as was available in these analyses, showed that the different coxib and traditional NSAID comparisons were similar at baseline, making combined estimates of the primary outcomes less prone to bias and more reliable. Although the preferred methodology is dependent on the available data (and direct evidence would, of course, be preferable), use of indirect comparisons using a common comparator, as in this case for coxibs and traditional NSAIDs, can provide valid estimates of effects, albeit interpreted with caution. (Edwards et al. 2010).

9.8.5 The effects of full compliance with allocated treatment

Allocation to a coxib was associated with around three extra people having a major vascular event per 1000 per year, with most of this excess attributable to myocardial infarction: the annual excess incidence associated with full compliance with a coxib could however be much larger. For example, in the APPROVe and MEDAL studies, approximately one third of randomised patients discontinued study treatment before the end of the study. If this discontinuation rate was typical, the absolute excess incidence produced by full compliance with a selective COX 2 inhibitor (or NSAIDs without antiplatelet activity) might be four or five additional patients having a major vascular event per 1000 treated per year ($3/1000/0.67=0.0045$). Similarly, the absolute excess incidence produced by full compliance with a NSAID with antiplatelet effects might be around twelve additional patients having an upper GI complication per 1000 treated per year ($8/1000/0.67=0.012$). The results from this overview may therefore be an underestimate of effects in absolute terms.

9.8.6 Generalisability and external validity

As the proportional risks in major vascular events and upper gastrointestinal complications were statistically reliable and seemed generally homogeneous over the wide range of settings and subgroups studied in these trials, the effects of coxib and traditional NSAID therapy should be expected to apply to an even wider range of patients than those

categories for which the present meta-analysis provides direct or indirect evidence. Although it would be inappropriate to base conclusions about the effects of coxib or traditional NSAID therapy in each small subcategory of patients solely on the results from that subcategory, the overall results (primary outcomes) could be used.

External validity in this case is the extent to which the randomised results of this study for coxibs and traditional NSAIDs can be generalized to other situations and to other people. Factors that can affect randomised controlled trials' external validity include: (i) where the trial was performed; (ii) characteristics of the patients (e.g., a trial may include patients whose prognosis is better than average, or may exclude the elderly and those with comorbidities); (iii) study procedures (e.g., in a trial patients may receive follow-up care difficult to achieve in the "real world"); and (iv) incomplete reporting of adverse effects. (Rothwell et al. 2006)

In this case, although 80% of IPD participants were of Caucasian ethnicity, as this sample contains all the available randomised evidence, it is still likely to be generalisable to other populations (eg, those in China, India etc.), particularly as there is no strong biological rationale for any differences. It would, of course, be preferable to have more randomised trials in these less studied populations rather than having to generalise. The characteristics of the patients in the trials would be expected to include those with a better prognosis due to exclusion criteria, but also includes groups such as the elderly and those with comorbidities (as shown in baseline features), so it should not affect external validity *per se*. Participants in randomised trials are also followed up more closely than those in the "real world", giving more reliable hypothetical estimates of effects. Moreover, by conducting as detailed a meta-analysis of randomised trials as possible, these results are able to provide reliable estimates rather than incomplete and selective reporting of individual results. Overall, the findings of this meta-analysis of randomised trials can reasonably be extrapolated to a far wider range of patients than those studied, with the caveat that the further the extrapolation, the more desirable it is to have direct evidence.

9.9 Comparisons of this systematic overview with other studies

9.9.1 *Comparisons with the tabular meta-analysis of randomised trials*

This meta-analysis of individual participant data confirms many of the previous findings of the tabular meta-analysis of randomised trials, in particular the moderate vascular effects of coxibs and some traditional NSAIDs. (Kearney et al. 2006) However, the present meta-analysis of the coxibs and traditional NSAIDs includes more trials and participants, and particularly, is powered by more primary outcomes, which improves power to detect effects. Incorporation of the individual participant data allowed detailed reliable subgroup analyses to be conducted, particularly to assess risk factors and to separate participants into different risk categories.

As the proportional effects of coxibs and traditional NSAIDs do not differ substantially by other characteristics, we could put the absolute risks into context. The time-to-event analyses, which could not be conducted in the tabular meta-analysis, are also able to demonstrate that any latent effect is substantially smaller than previously hypothesised. Most importantly, this study is able to put the upper gastrointestinal effects of coxibs and traditional NSAIDs in the context of the vascular (and heart failure) effects. The principal questions answered by this study are shown in Table 9.2.

9.9.2 *Comparison with other meta-analyses of randomised trials*

This study is also substantially larger than other published meta-analyses of randomised trials of coxibs and traditional NSAIDs, most of which have focused on vascular effects. Most of the other meta-analyses of randomised trials have only included published studies and many have evaluated individual coxibs or traditional NSAIDs, and so have been unable to assess any class effects. (A table of other meta-analyses is shown in the Appendix).

The most recent large meta-analysis of randomised trials, published in January 2011, actually comprises substantially fewer participants (116 429 patients versus more than 250 000 in the CNT Collaboration) and outcomes than that collected in this study. (Trelle et al. 2011) That meta-analysis suggested that naproxen might be the safest NSAID to use in terms of vascular outcomes, which corresponds with our findings. However, any meta-analysis critically depends on the underlying data, and this study used large published trials

only, which may have resulted in imprecise estimates. As well as methodological differences (eg, random effects meta-analysis models potentially giving undue weighting to smaller studies), these authors also highlighted borderline positive subgroup results. This study placed a lot of emphasis on their findings for stroke ($n=377$), which was a secondary outcome: ibuprofen was associated with the highest risk (relative risk 3.36, 95% credibility interval 1.00 to 11.6), followed by diclofenac (RR 2.86, 1.09 to 8.36). However, our estimates for stroke differ substantially, suggesting that coxibs and traditional NSAIDs as a group have no discernible effect on stroke subtypes.

There are even fewer meta-analyses evaluating upper gastrointestinal outcomes from randomised trials, but the most up to date is a Cochrane collaboration study. (Rostom et al. 2006) However, this tabular meta-analysis also had substantially fewer trials, participants, and upper GI outcomes than the results presented in this thesis. Results from their study showed that compared with traditional NSAIDs, coxibs produced significantly fewer gastroduodenal ulcers (relative risk, 0.26, 95% confidence interval, 0.23 to 0.30) and clinically important ulcer complications (RR 0.39, 0.31-0.50). However, whilst our results are in the same direction, they are of a more moderate proportional effect, owing to incorporation of more recent larger trials. Moreover, our results show that the distinction between traditional NSAIDs with and without antiplatelet activity considerably alters the implications of the upper GI safety profile, but their meta-analysis did not examine this.

There are only two other meta-analyses of coxibs and traditional NSAIDs that have used individual participant data, both of which are much smaller than the analyses presented in this thesis. Ross et al. conducted a cumulative participant-level pooled analysis of data from all randomised, placebo-controlled trials of rofecoxib conducted before September 2004, identifying 30 randomised, placebo-controlled trials of rofecoxib that enrolled a combined 20 152 participants. (Ross et al. 2009) Their main outcome measurement was incidence of any investigator-reported death from any cause or cardiovascular thromboembolic (CVT) adverse event. Cumulative meta-analysis demonstrated a borderline trend toward increased vascular outcomes associated with rofecoxib compared with placebo as early as December 2000, i.e., after the VIGOR hypothesis-generating result.

The Cross Trial Safety Assessment Group performed a patient-level pooled analysis of adjudicated data from 7950 patients in 6 placebo-controlled trials comparing celecoxib with placebo for conditions other than arthritis with a planned follow-up of at least 3 years. (Solomon et al. 2008) The primary end point was the combination of cardiovascular death, myocardial infarction, stroke, heart failure, or thromboembolic event. With 16,070 patient-years of follow-up, the hazard ratio (HR) for the composite end point combining the doses tested was 1.6 (95% confidence interval 1.1 to 2.3). The risk, which increased with dose regimen ($P=0.0005$), was lowest for the 400-mg once daily dose (HR 1.1; 0.6 to 2.0), intermediate for the 200-mg twice daily dose (HR 1.8; 1.1 to 3.1), and highest for the 400-mg twice daily dose (HR 3.1; 1.5 to 6.1). In their model, those participants in the highest tertile of baseline risk had a disproportionately greater risk of celecoxib-related vascular events (P for interaction = 0.034). Although the Cross trialists observed evidence of differential vascular risk as a function of the celecoxib dose regimen and baseline cardiovascular risk, our findings suggest that any such effect for all coxibs or traditional NSAIDs were substantially more modest, if they exist at all.

9.9.3 *Comparisons with other (non-randomised) epidemiological studies*

Resources will never be available to design large simple randomised trials to address all the questions of clinical interest. The use of observational studies to assess the effects of coxibs and traditional NSAIDs can generate large numbers of non-randomised participants in databases, but it cannot avoid moderate (or even in some cases such as recall, large) biases. Many of the observational studies conducted to assess the effects of coxibs were retrospective, and cannot prove a temporal component. Even within carefully designed prospective studies, biases and confounders can be of a similar magnitude to estimates of effect, and so causal relationships cannot be inferred. (Collins and Macmahon 2001)

In the case of coxibs and traditional NSAIDs, many observational studies have been conducted, including case-control and observational studies. The largest meta-analysis of observational studies to date (McGettigan & Henry 2006) comprised information on almost 190 000 participants in 30 case control studies and more than 2.7 million exposed participants in 21 prospective observational studies. When compared to the findings of the randomised evidence, this showed similarities: for example, the estimates of major vascular

events suggested a moderate effect for most coxibs and traditional NSAIDs, and a lower risk for naproxen (shown in Appendix). However, although the risks of vascular events associated with celecoxib were lower than rofecoxib and diclofenac in the observational data, the methodological design means that adjustments for key differences between the individual studies and participants cannot be made. (Baigent C. et al. 2010) Assessing the evidence from randomised trials to the level of individual participant data, our results of little heterogeneity between coxibs are more reliable, with the overall drug class effect being more important.

9.9.4 Comparisons with guidelines

As well as the many organ-specific guidelines (eg, osteoarthritis) that exist, those specifically for the use of traditional NSAIDs before the advent of coxibs initially focussed on prevention and treatment of upper gastrointestinal ulcers. (Champion et al. 1997; Lanza 1998) After the concerns about the vascular effects of coxibs in 2004, guidelines were released by regulatory authorities (eg, the MHRA), which used the findings from the tabular meta-analysis in communicating risks to the public. Many guidelines around this time focussed on the vascular effects of these agents, such as those from the American Heart Association, which recommended naproxen as the NSAID therapy of choice. (Antman et al. 2007) However, guidelines since that time have also tried to reliably put upper gastrointestinal risks into perspective, but have been unable to do so quantitatively: in addition, there has been uncertainty related to the upper gastrointestinal risk profile of coxibs and traditional NSAIDs. (Bhatt et al. 2009; Rostom et al. 2009; Lanza et al. 2010) In particular, both vascular and upper gastrointestinal risks related to coxibs and traditional NSAIDs are cited as warnings in prescribing information given to practitioners by the regulatory authorities (eg, the FDA and the EMEA). Of note, as well as major vascular events and upper GI ulcers, there has been little attention on other findings such as congestive heart failure and cause-specific mortality. The findings of the CNT Collaboration (presented in this thesis) will hopefully aid future guidelines related to upper GI and vascular risks of coxibs and traditional NSAIDs and their prudent use.

9.10 Public health implications

9.10.1 Drug safety and cost effectiveness

Drug safety (akin to vaccine safety) is of particular importance in making public health recommendations to large populations (in this case, increasing numbers of older adults who require analgesia for arthritis). However, unlike other situations (eg, aspirin in the primary prevention of occlusive vascular disease) where one is dealing with large, apparently disease-free populations, the question facing someone who requires analgesia is made more complex by the fact they are in pain and need treatment, as well as other competing risks and comorbidity. The absolute risks of coxib or traditional NSAID therapy are also relatively small (running into a few events per thousand person years for average), which, in the context of an individual seeking pain relief, might be of less importance than their analgesic properties. This question depends critically on the absolute risk of the individual in question – for example, a young active healthy sportsperson's absolute risks are small. Nevertheless, even if limited to low-risk groups, when considering the population exposure, this could translate into many preventable adverse vascular and gastrointestinal events related to coxibs and traditional NSAIDs.

Cost also requires consideration, and most traditional NSAIDs are available generically around the world, and detailed estimates of cost-effectiveness could be of relevance in the future. Although coxibs have been more expensive than traditional NSAIDs in the past, they are likely to be available generically in the next few years. However, detailed estimates of cost-effectiveness are of limited relevance without reliable evaluation of clinical effectiveness. Of note, previous UK National Institute of Clinical Excellence analyses assessing prescription of a proton pump inhibitor for people with osteoarthritis taking a traditional NSAID or coxib found this strategy to be cost effective. (Latimer et al. 2009) This analysis was particularly sensitive to vascular and upper gastrointestinal adverse event data, highlighting that the specific choice of coxib or traditional NSAID agent should, therefore, take into account these individual risks.

9.10.2 Evidence base for other analgesic therapies

One might instinctively read the results of this thesis and note that as all the therapies being considered have some risk, the most appropriate choice might be that a patient is not prescribed a coxib or NSAID at all. Of course, this would only apply if there was no discernible benefit but this would not be ethical in the case of someone who requires pain relief unless other analgesia was offered. However, other therapeutic options for analgesia are limited: paracetamol is a weaker analgesic, and opiates (eg, morphine), although quite powerful, has many side effects.

For paracetamol, the most recent published meta-analysis evaluated fifteen short-term randomised trials (median trial duration of 6 weeks), but only included 5986 participants. (Towheed et al. 2006) In the comparator-controlled trials, paracetamol was less effective overall than traditional NSAIDs in terms of pain reduction. However, patients taking traditional NSAIDs (19%) versus the paracetamol group (13%) were more likely to experience an adverse gastrointestinal event (RR 1.47; 95% CI 1.08 to 2.00).

Opiate drugs also have a number of well-known serious adverse events that hamper their use, including symptoms such as nausea, vomiting, pruritus and constipation, and addiction is also a potential hazard. Tolerance and withdrawal can occur with long-term use, and respiratory depression is a serious concern, especially in those requiring large doses. In a meta-analysis assessing opioids for chronic non-cancer pain, there were 41 randomised trials (mean 5 weeks), involving a total of 6019 patients. (Furlan et al. 2006) Whilst other drugs, predominantly traditional NSAIDs and coxibs, produced better functional outcomes than opioids, the latter were the optimal treatment for pain relief in this study.

As well as the limited evidence from randomised trials, an observational study of arthritis patients suggested that, compared with traditional NSAIDs, use of opioid therapy was associated with an elevated relative risk for vascular events (hazard ratio 1.77; 95% CI 1.39-2.24). (Solomon et al. 2010) Whilst this may be due to the baseline characteristics of participants, other biases or confounders, long-term assessments of opioid-related adverse effects are not well understood and, ideally, require large-scale randomised trials, as would other widely available analgesics, eg, tramadol.

9.11 Clinical implications

9.11.1 The context of management of vascular disease

When assessing a patient who requires a coxib or traditional NSAID for pain relief, appropriate evidence-based measures can be implemented to reduce the absolute risk of occlusive vascular disease. For example, cholesterol-lowering therapies such as statins (including higher doses to lower LDL cholesterol further) have been evaluated in previous meta-analyses of randomised trials. (Cholesterol Treatment Trialists' (CTT) Collaboration 2005; Cholesterol Treatment Trialists' (CTT) Collaboration 2010) Given that coxib and traditional NSAID vascular effects are at least partly mediated by blood pressure, the role of pharmacological and non-pharmacological anti-hypertensive therapies are of especial importance. (Lewington et al. 2002; Neal, MacMahon, & Chapman 2000) In particular, ACE inhibitors have a proven therapeutic value in congestive heart failure, albeit they can cause nephrotoxicity and so need to be used with care with coxibs and NSAIDs. (Teo et al. 2002)

Although there is net uncertainty about the judicious role of aspirin in the primary prevention of occlusive vascular disease, antithrombotic therapies (eg, clopidogrel as well as aspirin, and anticoagulants) have a definite role in secondary prevention. (Antiplatelet Trialists' Collaboration 1994; Antithrombotic Trialists' Collaboration 2002; Baigent et al. 2009) However, the bleeding risks with these antithrombotics, of which there is still some uncertainty for specific subtypes, are likely to be increased substantially with coxib or traditional NSAID therapy, and also merit careful consideration. (Weil et al. 2000; Bhala et al. 2011) In addition to these potential pharmacological therapies, a consideration of vascular risk reduction also includes other measures such as smoking cessation, diet and exercise. (Crowe et al. 2011; Doll et al. 2004)

9.11.2 The context of management of upper gastrointestinal disease

In comparison to vascular diseases, the evidence base from randomised trials for upper gastrointestinal disease is more limited. Although formal comprehensive meta-analyses of randomised trials are required, gastroprotectant medical therapies (including proton pump inhibitors [PPI], histamine-2 receptor antagonists [H2RA], and prostaglandin analogues eg, misoprostol) have a definite role in ulcer treatment and prevention. (Brown et al. 2006;

Hooper et al. 2004) There would be a definite rationale to combining these gastroprotectant therapies with coxibs and NSAIDs for prevention of complications, symptomatic ulcers but also for symptomatic relief (eg, heartburn and dyspepsia). There have been some large randomised trials carried out combining a traditional NSAID and PPI versus a coxib, demonstrating that gastroprotectants can be co-prescribed to reduce the risk of ulcer complications. (Chan et al. 2010) *Helicobacter pylori* eradication therapies in appropriate patients also have a role for the prevention of upper GI ulcers. (Vergara et al. 2005) Other non-pharmacological methods that are relevant for upper GI ulcers include smoking cessation and, possibly, moderation of alcohol. (Doll et al. 2004)

9.11.3 *The context of other effects of coxibs and traditional NSAIDs*

As well as their effects on vascular and upper gastrointestinal outcomes with coxibs and traditional NSAIDs, other potential effects of these drugs require consideration. For example, hypotheses on colorectal cancer prevention (in polyp trials) were actually the driver for the large coxib versus placebo studies. (Bresalier et al. 2005) Recent meta-analyses of randomised trials on the long-term effects of aspirin on cancer outcomes have also brought the COX-2 specific effects under further scrutiny. (Rothwell et al. 2010; Rothwell et al. 2011) However, any potential cancer prevention effects of coxibs and traditional NSAIDs also need to be brought into absolute context with the more common vascular and upper GI events.

Whilst other serious outcomes may be the focus of future cycles of coxibs and traditional NSAIDs, they are also much less common. For example, lower gastrointestinal bleeding outcomes are approximately one fifth as common as those for upper gastrointestinal bleeding. (Laine et al. 2006) Similarly, renal and arrhythmic adverse events, which have been assessed in other meta-analyses, are less common than the vascular events studied. (Zhang, Ding, & Song 2006) Some outcomes are even rarer - for example, hepatic serious adverse events (Laine et al. 2009) picked up in post-marketing were the driver for the withdrawal of lumiracoxib, but occurs very rarely (less than 20 per 100,000 persons) so only a small number of events would be expected, even when assessing all the randomised evidence.

9.12 Applying what is known from clinical pharmacological studies

9.12.1 *Naproxen and NSAIDs with persistent antiplatelet activity*

As the plasma half life of naproxen is around 14 hours, a regimen of 500 mg twice daily results in sustained inhibition of COX 1 dependent thromboxane biosynthesis, whereas both ibuprofen and diclofenac have much shorter half lives (one to two hours), and standard twice or thrice times daily regimens have only transient effects. A few traditional NSAIDs with prominent effects on the COX-1 isozyme, such as indobufen and flurbiprofen, have also been tested as potential antiplatelet agents in small studies, but no adequately powered long-term randomised trials have assessed these drugs. (Antithrombotic Trialists' Collaboration 2002) We therefore hypothesised that the vascular effects of naproxen, indobufen and flurbiprofen would differ from those of other traditional NSAIDs without persistent antiplatelet activity. This study confirms the vascular findings of this separation of traditional NSAIDs by antiplatelet activity, as suggested in the previous meta-analysis, (Kearney et al. 2006) but also confirms that such activity has a role in upper gastrointestinal complications. These findings confirm the need to dichotomise by antiplatelet activity, particularly between naproxen and other traditional NSAIDs, when prescribing these medications. Further mechanistic studies to examine the biological basis of antiplatelet activity of naproxen and other such traditional NSAIDs are an important area of future research: in particular, does the dose of naproxen (500mg bd in most of the studies evaluated) play an important role, and what are the mechanisms by which such drugs translate to increased gastrointestinal hazards.

9.12.2 *NSAIDs and mechanisms for vascular outcomes*

Coxibs, and traditional NSAIDs without antiplatelet activity predominantly mediate effects on major vascular events by around a proportional increase of three quarters on coronary heart disease: conversely, traditional NSAIDs with antiplatelet activity do not have such effects. What could be the mechanisms by which a predominant effect on coronary heart disease outcomes? Selective COX-1 inhibition has been shown to have an antithrombotic effect mediated by a relatively specific, potent, and irreversible inhibition of platelet COX-1, which reduces thromboxane A₂ biosynthesis, a powerful trigger of platelet aggregation. (Patrino et al. 2003) Since naproxen inhibits the synthesis of both TXA₂ and prostacyclin,

but coxibs inhibits the synthesis of COX-2–dependent prostacyclin only, it was suggested that rofecoxib might cause arterial thrombosis because of an accumulation of unopposed TXA₂ (which is prothrombotic) at the platelet–vascular endothelial interface, thus favouring occlusive thrombus formation. (FitzGerald, Cheng, & Austin 2001) Although alteration of the homeostatic balance of endothelial prostacyclin and platelet-derived TXA₂ by coxibs and other tNSAIDs by means of the differential effects of COX-1 and COX-2 inhibition regulating thrombus formation remains a plausible mechanism (Grosser et al. 2006) the mechanistic underlying pathophysiology of NSAID-associated coronary risk by this means remains speculative.

What are the effects of coxibs and traditional NSAIDs on blood pressure? Meta-analyses of randomised trials suggest that coxibs increase systolic blood pressure by around 3.8 mmHg versus placebo. (Aw et al. 2005) This change in blood pressure also appears to occur consistently for up to 3 years follow-up in the longer term APC and PreSAP studies. (Solomon et al. 2006) Traditional NSAIDs, including naproxen, also lead to a similar increase in blood pressure as coxibs (ie, around 4 mmHg on average). (Aw et al. 2005; Chan et al. 2009) Extrapolation from the available epidemiologic evidence in the Prospective Studies Collaboration meta-analyses, (Lewington et al. 2002) suggests that this increment in blood pressure would cause around a 10% higher risk of myocardial infarction, and around a 20% increased risk of stroke and congestive heart failure in this meta-analysis. Perhaps surprisingly, the randomised trial evidence does not indicate any clearly increased risk of ischaemic or haemorrhagic strokes. However, the absence of any stroke risk for drug regimens that are all known to increase blood pressure, is unlikely to be biologically plausible: few strokes were recorded and blood pressure may be the principal mechanism by which vascular effects are mediated.

One of the key findings in this study are the effects of COX inhibition on heart failure outcomes, which are likely to be mediated by renal prostaglandin upregulation by all coxib and traditional NSAID therapies. Thus, an incomplete antithrombotic effect of COX-1 inhibition may counteract the prothrombotic effects of COX-2 inhibition afforded by NSAIDs leading to an increased risk of myocardial infarction and heart failure events.

9.12.3 Interaction of aspirin, other antithrombotics and NSAIDs

Traditional NSAIDs commonly bind to the Arginine120 of the platelet cyclooxygenase channel and may prevent aspirin from entering this site, antagonising its cardioprotective effects. (Ouellet, Riendeau, & Percival 2001). *In vivo* studies in healthy volunteers taking aspirin reported significant inhibition of platelet function with co-administration of ibuprofen due to competition for the binding site. (Catella-Lawson et al. 2001) (Renda et al. 2006) Although the vascular effects of concomitant aspirin and NSAIDs have not been assessed formally in large randomised trials, translation of this interaction into clinical outcomes has been suggested in prospective observational studies. (MacDonald & Wei 2003; Ray et al. 2002) Small crossover studies suggest that naproxen (at doses of 220mg and 500 mg twice daily) also interferes with the effect of aspirin on platelet COX-1 inhibition. (Capone et al. 2004; Capone et al. 2008) This lends support to the hypothesis that traditional NSAIDs, especially ibuprofen but also naproxen, interact with the cardioprotective effects of aspirin.

In those with known occlusive vascular disease, the use of aspirin is more likely to outweigh symptomatic analgesic treatment, so extreme caution is required if ibuprofen and naproxen need co-prescribing. Moreover, other antithrombotics such as clopidogrel are likely to be required in immediate secondary prevention, which also increase bleeding risks. Although it is not known if coxibs and diclofenac have an interaction with aspirin with regard to deleterious vascular effects, co-prescription of all coxibs and traditional NSAIDs with aspirin and other antithrombotics does lead to an increased risk of upper gastrointestinal bleeding. (Lanas et al. 2006). Hence, due to increased bleeding risks, as well as concerns about interactions on vascular outcomes, traditional NSAIDs (and ibuprofen and naproxen in particular) and coxibs should not be given to those taking aspirin and other antithrombotics if possible.

9.13 Applying these results in clinical practice.

Applying the results of Figure 8.4 into clinical practice, there are a number of important points to consider when prescribing coxibs and traditional NSAIDs to those who require analgesia. First of all, appropriate vascular and upper gastrointestinal risk stratification of patients should be carried out. Appropriate Interventions to reduce the absolute risk of upper GI disease (eg, gastroprotectant therapy [PPI, H2RA or misoprostol], *Helicobacter pylori* eradication etc.) should be used. Likewise, interventions to reduce the absolute risk of occlusive vascular disease, without affecting bleeding risk (eg, smoking cessation, cholesterol-lowering and blood pressure-lowering therapies etc.) should also be used. Coxibs and traditional NSAIDs should be used at the lowest effective dose and for the shortest period of time possible.

Among those at low risk of both vascular and upper GI complications, the risks of a coxib or any traditional NSAID regimen appear similar (with the lower vascular risk of naproxen offset by a somewhat higher risk of upper GI complications). With increasing vascular risk among those at lowest upper GI risk, the excess risk of upper GI complications resulting from naproxen appears less hazardous than the excess of major vascular events resulting from a coxib. As major vascular events are of increased severity, and more likely to be fatal, naproxen is the NSAID treatment regimen of choice in many scenarios, particularly as vascular risk increases. With increasing upper GI risk among those at lowest vascular risk, however, a coxib appears to be the most reasonable choice, particularly due to naproxen's relatively higher upper GI risk profile.

In participants for whom there is an substantially increased risk of both vascular and upper GI events, even with means of reducing both vascular risk (eg, with statins and antihypertensives) and upper GI risk (eg, with a proton-pump inhibitor), clinicians may prefer to use naproxen or avoid coxibs or traditional NSAIDs altogether. In those with overt vascular disease (secondary prevention), the situation becomes more complex as aspirin and other antithrombotics (eg, clopidogrel) are likely to be required. As coxibs and traditional NSAIDs (especially ibuprofen & naproxen) may interfere with the antiplatelet effect of aspirin, and they increase the risk of bleeding with aspirin and other antithrombotics (eg, clopidogrel), co-prescription should ideally be avoided. Moreover,

coxibs and traditional NSAIDs should both be avoided in patients with congestive heart failure, another rationale for avoiding use of these therapies in patients with overt occlusive vascular disease. Table 9.3 sets out suggested clinical guidelines for prescribing coxibs or traditional NSAIDs, for use by general practitioners and other clinicians. Dissemination of the findings of this thesis in subsequent scientific publications could help clarify therapeutic decision-making in this arena.

9.14 The need for future large-scale randomised trials and future overviews

Randomised trials of all sizes will be required to reliably evaluate uncertainties in the future. However, with such large numbers of participants assessed in this overview, in order to make a substantial change to the risk estimates for the primary outcomes studied there will have to be very large studies of coxibs and traditional NSAIDs. For ethical reasons, patients cannot have a commonly available NSAID for analgesia chosen at random for them if either they or their doctor are (for any reasons) reasonably certain that another treatment is preferable. Hence, randomisation can be offered only if both doctor and patient feel substantially uncertain as to which of the trial options is most beneficial. This uncertainty principle as the key entry criteria for a randomised trial, particularly for the clinician managing the patient trying to balance between competing risks such as vascular and upper GI effects. Future trials may need to focus on the risk benefit equipoise between coxibs and naproxen, as this is the key choice generated by this study. Future Coxib and traditional NSAID Trialists' (CNT) Collaboration cycles will incorporate other ongoing large randomised trials, eg, for celecoxib, the SCOT trial versus other NSAIDs (n=16,000) (MacDonald 2009) and the PRECISION trial versus ibuprofen or naproxen (n=20,000). (Becker et al. 2009)

Another aspect where there is continued uncertainty is the use of traditional NSAIDs, such as ibuprofen and diclofenac at lower doses than those studied in this overview. Despite little evidence of a formal dose response for major vascular events in these analyses, if clinicians were keen to keep using these therapies, then designing randomised trials to assess these lower doses would add to the available evidence (however, such studies would need to be very large in order to accrue sufficient outcomes).

A new class of anti-inflammatory drugs, COX-inhibiting nitric oxide donators (CINODs), has also been designed for potential similar anti-inflammatory effects as NSAIDs. CINODs release nitric oxide, providing purported protective effects in the gastrointestinal tract and attenuating the detrimental effects on blood pressure normally associated with NSAIDs. From these analyses, a new anti-inflammatory therapy that combined the neutral vascular effects of naproxen with blunted hazards on both heart failure and upper gastrointestinal outcomes would be an attractive proposition, but such a therapy would also require formal evaluation in large-scale randomised trials.

Reliable assessments of the concomitant role of gastroprotectants (for which a related meta-analysis, the Gastroprotectant Trialists' [GPT] Collaboration, is currently being conducted) are one of the important questions that this study has generated. Although there is uncertainty about the optimal role for concomitant aspirin, given the increasing bleeding risks, randomised trials combining coxibs or traditional NSAIDs with antithrombotic agents would not necessarily be appropriate. Future Antithrombotic Trialists' (ATT) Collaboration cycles will, however provide a systematic overview of the effects of these newer agents.

9.15 Conclusions

When patients are faced with a need for a NSAID for their analgesia, traditional NSAIDs with a persistent antiplatelet activity (eg, naproxen) would initially appear to be the agents of choice given a neutral effect on major vascular outcomes. In comparison, traditional NSAIDs without antiplatelet activity (eg, diclofenac or ibuprofen) and coxibs are both associated with a moderate (30-40%) effect on major vascular outcomes, in particular myocardial infarction and vascular death. Evidence-based therapies to reduce thrombotic vascular risk should be considered when prescribing coxibs and traditional NSAIDs. Moreover, coxibs and all traditional NSAIDs are associated with a similar two-fold increased risk of congestive heart failure.

However, traditional NSAIDs like naproxen, likely due to its antiplatelet activity, are also associated with around a four-fold relative increase in upper gastrointestinal complications.

Coxibs are also not without harm of upper gastrointestinal complications, being associated with 60-80% increase, and traditional NSAIDs without antiplatelet activity (eg, diclofenac) associated with around a two-fold increase, particularly in bleeding. Even so, as upper GI complications are relatively less harmful in terms of morbidity and mortality than major vascular events, and are also potentially amenable to therapies such as gastroprotectants, naproxen is likely to be the therapy of choice in most cases. However, in those with a heightened risk of upper GI complications, ideally without a corresponding increased vascular risk (eg, a young patient with a recent ulcer bleed without other vascular risk factors), the risk/benefit balance may favour prescription of coxibs over naproxen.

Although there was no strong evidence of a latent interval, those who require therapy with coxibs or traditional NSAIDs should take them for as short a time as possible, and with as low a dose as possible. Moreover, these findings appear consistent in proportional effect through the many different subgroups of participants enrolled in the trials, suggesting the baseline absolute risks of the patient are the key factors to consider when prescribing.

Careful consideration is required for the future role of many easily available traditional NSAIDs, such as diclofenac and ibuprofen, given their adverse profile on major vascular events, congestive heart failure, and upper gastrointestinal outcomes. For those who require analgesia, although naproxen is the traditional NSAID of choice due to its antiplatelet activity, coxibs may also have a role for a selected group at high risk of upper gastrointestinal complications. In order to prevent premature mortality and morbidity when prescribing coxibs or traditional NSAIDs, appropriate risk stratification and suitable preventative interventions, particularly in the context of the individual's absolute vascular and upper gastrointestinal risks, need to be taken into account. Some people may consider the hazards of NSAIDs an acceptable trade-off in return for effective pain relief, even if they are at increased risk of vascular and upper gastrointestinal complications, and the results of this thesis can provide further evidence to guide patients and practitioners when faced with these decisions.

Table 9.2 Questions answered by this meta-analysis of randomised trials of coxibs and traditional NSAIDs

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1. **Reliable estimates** of the effects of coxibs and traditional NSAIDs on major vascular events, other vascular complications (eg, heart failure) and upper GI complications can be generated from direct and indirect comparisons of randomised trial evidence.
 2. There are **no strong evidence of a latent effect** of coxibs and traditional NSAIDs on vascular and upper GI events: ie, there could be a hazard soon after usage or with prolonged usage, so the shortest possible dose should be used.
 3. There are **no strong evidence that the proportional effects** of coxibs and traditional NSAIDs on vascular and upper GI events **vary amongst patient subgroups for the clinical features studied** (eg, age, gender, baseline disease, aspirin use etc.).
 4. The **risk factors** that increase the risk of vascular and upper GI outcomes relevant to coxibs and traditional NSAIDs from randomized studies have been identified: these include age, gender, diabetes, smoking and past medical history (particularly the latter for upper GI ulcers).
 5. There is **no strong evidence for trends towards proportional increases** in vascular and upper GI events with higher baseline absolute risks and higher coxib/traditional NSAID when considering all the randomized studies: however, baseline absolute risks of events and medications prescribed are important determinants of these effects.
 6. The **balance of benefits and risks of different coxibs and traditional NSAIDs** in terms of absolute effects on vascular and upper GI events among different types of patients requiring analgesia should consider: (i) that **in the context of, naproxen is associated with 'neutral' vascular effects but is the most ulcerogenic NSAID studied**; (ii) that **coxibs should be considered for patients at high risk of upper GI events with a low risk of vascular events**; (iii) that **other interventions to reduce vascular and upper GI risk should also be used** in conjunction; (iv) that **use of any coxib or traditional NSAID should be as short and at as low a dose as possible**.

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Appendices

- 1: Timelines
- 2: Letter for invitation to the CNT Collaboration
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APPENDIX

TIMELINE FOR COXIBS AND TRADITIONAL NSAIDS FOCUSSED ON MAJOR TRIALS

5th century BC Greek physician Hippocrates suggests the use of a bitter powder extracted from willow bark for the treatment of aches, pains and fever.

1763 AD Reverend Edward Stone documents the use of willow bark in fifty patients in Chipping Norton, Oxfordshire. In a letter to the Royal Society, it was found to be a 'powerful astringent and very efficacious in curing agues and intermitting disorders.' He had discovered salicylic acid, the active ingredient in aspirin.

1899 A less corrosive compound of salicylic acid, acetylsalicylic acid, produced by reacting sodium salicylate with acetyl chloride, was developed by Felix Hoffman and later marketed by Bayer as 'aspirin'.

1961 Ibuprofen was derived from propionic acid by the research arm of Boots Group (UK) and the drug was launched as a treatment for arthritis in the United Kingdom in 1969.

1971 Sir John Vane demonstrates that inhibition of prostaglandin synthesis is the mechanism of action of aspirin and NSAIDs, for which he is later awarded the Nobel Prize for medicine and physiology.

1970-80's Newer NSAIDs developed and launched. For example, diclofenac was developed by Ciba-Geigy (now Novartis) in 1973 and introduced in the UK in 1979. Naproxen was marketed in 1976 by Syntex (now Roche).

1989-91 The cyclo-oxygenase 2 (COX-2) isozyme is identified by Daniel Simmons' team at Brigham Young University and Philip Needleman's team at Washington University Medical School, and later developed by the latter at Monsanto pharmaceuticals.

1991-95 The first generation of COX-2 inhibitors are developed, and begin evaluation in randomised clinical trials. Celecoxib (made by G.D. Searle and Co., later

Pharmacia, now Pfizer) and rofecoxib (made by Merck) are tested, especially for their relative effects on upper gastrointestinal outcomes compared to traditional NSAIDs.

1998-1999 Celecoxib and rofecoxib are approved by the FDA. Sales of coxibs start to increase with concentrated marketing and advertising. Small human volunteer studies suggest a possible difference between coxibs and traditional NSAIDs in thrombotic effects. Large outcome studies of coxibs with supratherapeutic doses are required by the US Food and Drug Administration (FDA) to prove safety data.

2000 The CLASS (celecoxib) and VIGOR (rofecoxib) randomised trials show that use of coxibs decreases the risk of an upper GI complication (ulcer, perforation or bleed). However, in VIGOR, there are five times more myocardial infarctions in the rofecoxib versus the naproxen arm (20 versus 4).

2001 Valdecoxib (made by G.D. Searle and Co., later Pharmacia, now Pfizer) is approved by the FDA.

2004 The TARGET study of lumiracoxib (made by Novartis) versus ibuprofen or naproxen is published, reporting gastrointestinal and vascular outcomes. The APPROVe trial of polyp prevention confirms a vascular risk of rofecoxib versus placebo. Merck withdraws rofecoxib from the market. The APC trial confirms an increased vascular risk for celecoxib versus placebo, raising concerns about a class effect of coxibs. In the intense media spotlight that follows, many patients who require continued pain relief are switched over from coxibs to traditional NSAIDs.

2005 The FDA requests the withdrawal of valdecoxib (and its prodrug parecoxib) due to severe adverse skin reactions and myocardial infarction risks in short-term coronary artery bypass graft operations. The FDA reviews the vascular safety of other approved coxibs, allowing their continuing use. The first federal case of litigation for vascular effects of Vioxx begins.

2006 The meta-analysis of published and unpublished tabular data by Kearney *et al.* of trials confirms that coxibs are associated with a moderately increased risk of major vascular events. High-dose naproxen is not associated with such an excess, but other high-dose NSAIDs without an antiplatelet effect (eg, diclofenac and ibuprofen) are associated with similar moderate vascular risks.

2007 Etoricoxib is evaluated versus diclofenac in the MEDAL programme and approved in more than 70 countries worldwide (including the UK but not the USA). Lumiracoxib is withdrawn from some markets due to case reports of acute liver failure on post-marketing surveillance.

2008 The Cross Trial Safety Analysis assessed the vascular risk of celecoxib in six randomised placebo-controlled trials and observed evidence of differential risk as a function of dose regimen and baseline vascular risk.

2008 - present The pharmaceutical sponsors and investigators of randomised trials of coxibs and traditional NSAIDs have agreed to provide data to facilitate an individual participant data meta-analysis of all such trials (the Coxib and traditional NSAID Trialists' [CNT] Collaboration).

COXIB AND TRADITIONAL NSAID TRIALISTS' (CNT) COLLABORATION

CTSU, Richard Doll Building
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Oxford OX3 7LF, UK
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Fax: +44-(0)1865-743985
Email: cnt@ctsuo.ox.ac.uk

OUR REF: S«study_id»-P«investigator_id»-C«contact_id»

«title» «initials» «surname»

«address1»

«address2»

«address3»

«address4»

«address5»

«country»

«DATE_LETTER»

Dear «title» «surname»

Invitation to contribute individual participant data from to the CNT Collaboration.

We are writing to invite you to join the Coxib and traditional NSAID Trialists' (CNT) Collaboration. The Collaboration plans to assemble a database of individual participant data from all published and unpublished randomized controlled trials (of longer than 4 weeks duration) that have compared coxibs or traditional NSAIDs, or both. We hope that the ... will consider providing data from the ... Trial. The chief aim of the Collaboration will be to assess the effects of coxibs and NSAIDs on major clinical outcomes, including serious vascular events and upper gastrointestinal complications. These analyses will be periodically updated when new trials become available. The project is being coordinated by the Clinical Trial Service Unit (CTSU) at the University of Oxford and is independent from the pharmaceutical industry.

Please find enclosed a number of documents for your attention:

- 1). Protocol for the Collaboration (including statements on confidentiality and publishing policy)
- 2). Data request
- 3). Current list of included trials

The coxib manufacturers (Merck, Novartis and Pfizer) have all agreed to contribute individual participant data from trials that they have sponsored. Please indicate whether, in principle, you would be willing to contribute and return the proforma at the end of this letter by email, post or fax, preferably **before** We plan to commence data collection in the final quarter of this year. If you have any comments or questions about the Collaboration, then we would be delighted to discuss it with you on the telephone, or by email.

With kind regards,

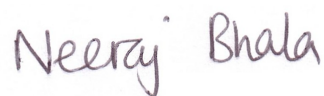
Yours sincerely,

Colin Baigent



Professor of Epidemiology
University of Oxford

Neeraj Bhala



MRC Research Fellow
University of Oxford

Carlo Patrono



Professor of Pharmacology
Catholic University of Rome

COXIB AND NSAID TRIALISTS' (CNT) COLLABORATION

...
[...]

Please indicate your intentions by ticking one box:

YES, we plan, in principle, to collaborate ☐

NO, we do not plan to collaborate ☐

Please return, by email, fax or post to:

CNT Secretariat, CTSU, Richard Doll Building, Oxford OX3 7LF, UK
Email: cnt@ctsu.ox.ac.uk Tel: +44 1865 743743 Fax: +44 1865 743985

COXIB AND TRADITIONAL NSAID TRIALISTS' (CNT) COLLABORATION

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OUR REF: S«study_id»-P«investigator_id»-C«contact_id»

«title» «initials» «surname»

«address1»

«address2»

«address3»

«address4»

«address5»

«country»

«DATE_LETTER»

Dear «title» «surname»

Invitation to participate in the Coxib and traditional NSAID Trialists' (CNT) Collaboration for the study:

«ref_short»

We are writing to invite you to contribute data from the above trial to an international study which will reliably assess the treatment effects of non-steroidal anti-inflammatory drugs (NSAIDs). The Coxib and traditional NSAID Trialists' (CNT) Collaboration will conduct meta-analyses of all published and unpublished randomised controlled trials with at least one unconfounded comparison involving a selective cyclo-oxygenase 2 inhibitor (coxib) or a traditional NSAID. The chief aim of the CNT Collaboration will be to assess the effects of coxibs and traditional NSAIDs on serious vascular events (such as myocardial infarction and stroke) and on upper gastrointestinal ulcer complications and symptomatic ulcers. These collaborative meta-analyses are being coordinated by the Clinical Trial Service Unit (CTSU) at the University of Oxford, with the guidance of a distinguished Steering Committee (see below), and data are being collected, analysed and reported entirely independent of the pharmaceutical industry.

Our preferred format for data from your trial would be "individual participant data", ie, an electronic datafile in a standard format (with data on baseline features and major outcomes for each trial participant) as this will allow more detailed analyses to be conducted. However, we recognise that this may not be possible for some trials, perhaps because the data have been discarded or because statistical resources are limited. If so, we would like you to provide summary outcomes data, which we will request at a later date. Tabular data such as this will still add considerable value to the currently available evidence.

We do hope that you will be able to participate in the CNT Collaboration, which will provide the most reliable evidence available on the balance of benefits and hazards for both coxibs and traditional NSAIDs. In the first instance, please could you indicate whether you plan to collaborate by completing the attached Form A and, if you do plan to do so, provide a few details about your trial in the attached Form B (trial design) and Form C (trial methodology).

We would very much appreciate your participation in this project. Your assistance will enable the CNT Collaboration to better inform clinicians and patients of the effects of these medications in real life practice.

Should you have any comments or questions, please do not hesitate to contact Dr Neeraj Bhala on cnt@cts.ox.ac.uk or at the address above.

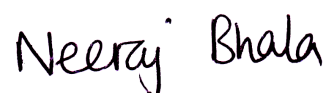
With kind regards.
Yours sincerely,

Colin Baigent



Professor of Epidemiology
University of Oxford

Neeraj Bhala



MRC Research Fellow
University of Oxford

Carlo Patrono



Professor of Pharmacology
Catholic University of Rome

Other members of the CNT Steering Committee:

Steve Abramson	New York University School of Medicine, USA
Nadir Arber	Tel Aviv Sourasky Medical Center, Israel
John Baron	Dartmouth Medical School, New Hampshire, USA
Claire Bombardier	Toronto General Hospital, Canada
Chris Cannon	Brigham and Women's Hospital, Boston, USA
Jonathan Emberson	Clinical Trial Service Unit, University of Oxford, UK
Michael Farkouh	Mount Sinai Hospital, New York, USA
Garret FitzGerald	University of Pennsylvania Medical School, USA
Paul Goss	Massachusetts General Hospital, Boston, USA
Ernest Hawk	M. D. Anderson Cancer Center, Houston, USA
Chris Hawkey	University of Nottingham, UK
Charles Hennekens	Florida Atlantic University, Boca Raton, USA
Marc Hochberg	University of Maryland, Baltimore, USA
Patricia Kearney	Trinity College Dublin, Ireland
Loren Laine	USC School of Medicine, Los Angeles, USA
Angel Lanas	University of Zaragoza, Spain
Peter Lance	University of Arizona Cancer Center, Tucson, USA
Andreas Laupacis	St. Michael's Hospital, Toronto, Canada
Tom Schnitzer	Northwestern University, Chicago, USA
Scott Solomon	Brigham and Women's Hospital, Boston, USA
Peter Tugwell	University of Ottawa, Canada
Janet Wittes	Statistics Collaborative, Washington DC, USA

COXIB AND TRADITIONAL NSAID TRIALISTS' (CNT) COLLABORATION

Form A: Agreement to participate

Publication: «brief_ref»

OUR REF: S«study_id»-P«investigator_id»-C«contact_id»

Please indicate your intentions by ticking one box:

YES, we plan, in principle, to collaborate. We plan to provide:

- individual participant data

☐

- tabular data only

☐

NO, we do not plan to collaborate

☐

Please return, by email, fax or post to:

CNT Secretariat, CTSU, Richard Doll Building, Roosevelt Drive, Oxford OX3 7LF, UK
Email: cnt@ctsu.ox.ac.uk Tel: +44(0) 1865 743614 Fax: +44(0) 1865 743985

**COXIB AND TRADITIONAL NSAID TRIALISTS'
(CNT) COLLABORATION
Form B: Trial Design**

Publication: «brief_ref»

OUR REF: S«study_id»-P«investigator_id»-C«contact_id»

Person completing this form: _____

Main Contact		Data Manager	
Name		Name	
Address		Address	
Tel		Tel	
Fax		Fax	
Email		Email	

Indication for entry into trial: _____

Sample size: (Please give total number randomised, i.e., intention to treat) _____

Study comparisons - Please document all arms of your trial and include dose(s) of drug(s), as well as numbers of participants. For trials with more than one randomisation please provide details on a separate sheet.

	First randomised drug (and dose)	No. of participants
Arm 1		
Arm 2		
Arm 3		
Arm 4		

Please give details of any other non-trial treatments that were given routinely to all patients (e.g. aspirin):

Trial duration: (in weeks) _____

Recruitment period: _____

Actual or scheduled treatment period: _____

Actual or scheduled follow-up period: _____

(Please give average duration or period if variable)

Trial sponsor: _____

Any further details: _____

COXIB AND TRADITIONAL NSAID TRIALISTS'

(CNT) COLLABORATION

Form C: Trial Methodology

Publication: «brief_ref»

OUR REF: S«study_id»-P«investigator_id»-C«contact_id»

Please tick or highlight the appropriate method listed below for the named study.

i) Method of Randomisation

- ☐ 1 IVRS (Interactive Voice Response System)
- ☐ 2 Telephone central office
- ☐ 3 Pharmacy coded containers administered sequentially
- ☐ 4 Onsite computer accessible only after entering patients details
- ☐ 5 Sealed envelopes, sequentially numbered and opaque
- ☐ 6 Closed list of random numbers
- ☐ 7 Other method
- ☐ 8 Unknown whether randomised or not

If method of randomisation is described as 'other', please provide details here:

ii) Method of Blinding

- ☐ 1 Double blinded (neither subject nor investigator aware of allocation)
- ☐ 2 Single blinded (only investigator aware of allocation)
- ☐ 3 Open trial (both subject and investigator aware of allocation)
- ☐ 4 Other method
- ☐ 5 Unknown whether blinded or not

If method of blinding is described as 'other', please provide details here:

iii) Method of Treatment Allocation Concealment

- ☐ 1 Double-dummy (for two-by-two factorially designed studies in which both study treatments are compared with visually identical inactive placebos)
- ☐ 2 Single-dummy (inert standard treatment versus active study drug, both visually identical)
- ☐ 3 Open comparison (formulations/treatments visibly different)
- ☐ 4 Other method
- ☐ 5 Unknown whether treatment allocation concealed or not

If method of concealment is described as 'other', please provide details here:

Other comments:

COXIB AND TRADITIONAL NSAID TRIALISTS' (CNT) COLLABORATION

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Tel: +44-(0)1865-743614
Fax: +44-(0)1865-743985
Email: cnt@ctsuo.ox.ac.uk
OUR REF: S-P-C

Address

Date

Dear

Coxib and traditional NSAID Trialists' (CNT) Collaboration Outcomes for the study:

Study Title

Thank you for kindly agreeing to collaborate in the Coxib and traditional NSAID Trialists' (CNT) Collaboration, which will conduct meta-analyses of all published and unpublished randomised controlled trials with at least one unconfounded comparison involving a selective cyclo-oxygenase 2 inhibitor (coxib) or a traditional NSAID, assessing the effects of these medications on serious vascular events (such as myocardial infarction and stroke) and on upper gastrointestinal ulcer complications and symptomatic ulcers. Hence, we would like you to provide summary outcomes data by filling out the accompanying material (Form D) - this tabular data will still add considerable value to the currently available evidence.

Please use the following rules when filling out outcomes:

1. Please record only those events considered by the investigator to have been DEFINITE or PROBABLE. Exclude events considered to have been "possible" (but not probable). For each outcome, please use the trialists' own definition. Please include any patients who were randomised and later withdrawn, lost to follow-up, or deemed ineligible after randomisation.
2. Upper gastrointestinal (UGI) complicated ulcer events are defined as perforation, obstruction or haemorrhage (bleed). If a patient has a symptomatic ulcer diagnosed without these occurring, it is uncomplicated. An UGI ulcer should be considered FATAL only if the patient definitely did die from an UGI ulcer.
3. Only events that occurred within each patient's originally scheduled study follow-up period should be recorded. If a patient experienced more than one event of a given type (e.g. two consecutive myocardial infarctions) only the first event should be counted. If a patient experienced more than one different type of event (e.g. a myocardial infarction and a stroke) both events should be recorded.

We very much appreciate your participation in this project. Your continued efforts and assistance will enable the CNT Collaboration to better inform clinicians and patients of the effects of these medications in real life practice.

Should you have any comments or questions, please do not hesitate to contact Dr Neeraj Bhala on cnt@ctsu.ox.ac.uk or at the address above.

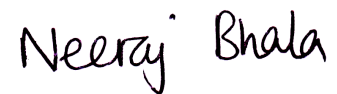
With kind regards.
Yours sincerely,

Colin Baigent



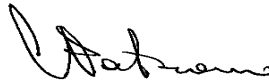
Professor of Epidemiology
University of Oxford

Neeraj Bhala



MRC Research Fellow
University of Oxford

Carlo Patrono



Professor of Pharmacology
Catholic University of Rome

Other members of the CNT Steering Committee:

Steve Abramson	New York University School of Medicine, USA
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John Baron	Dartmouth Medical School, New Hampshire, USA
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Michael Farkouh	Mount Sinai Hospital, New York, USA
Garret FitzGerald	University of Pennsylvania Medical School, USA
Paul Goss	Massachusetts General Hospital, Boston, USA
Ernest Hawk	M. D. Anderson Cancer Center, Houston, USA
Chris Hawkey	University of Nottingham, UK
Charles Hennekens	Florida Atlantic University, Boca Raton, USA
Marc Hochberg	University of Maryland, Baltimore, USA
Patricia Kearney	Trinity College Dublin, Ireland
Loren Laine	USC School of Medicine, Los Angeles, USA
Angel Lanas	University of Zaragoza, Spain
Peter Lance	University of Arizona Cancer Center, Tucson, USA
Andreas Laupacis	St. Michael's Hospital, Toronto, Canada
Tom Schnitzer	Northwestern University, Chicago, USA
Scott Solomon	Brigham and Women's Hospital, Boston, USA
Peter Tugwell	University of Ottawa, Canada
Janet Wittes	Statistics Collaborative, Washington DC, USA

COXIB AND TRADITIONAL NSAID TRIALISTS' (CNT) COLLABORATION FORM D (TABULAR OUTCOMES)

Publication:
OUR REF:

Trial name				
Trial reference	TREATMENT GROUPS			
Drug name(s) including placebo:				
Dose:				
Frequency:				
NUMBERS OF PATIENTS RANDOMISED (before any subsequent exclusions)				
EVENTS: Please record the number of patients in which the following events occurred at least once during the scheduled treatment period. Write "0" if no events occurred and "N/A" if the events were not recorded.				
VASCULAR OUTCOMES	Were vascular outcomes adjudicated?		Yes	No
Myocardial infarction (MI)				
Ischaemic stroke				
Haemorrhagic stroke				
Any stroke (known or unknown aetiology)				
Coronary death OR non-fatal MI				
Vascular death OR non-fatal MI OR non-fatal stroke				
UPPER GASTROINTESTINAL (UGI) ULCERS	Were UGI outcomes adjudicated?		Yes	No
UGI ulcer complication (perforation, obstruction, or bleed [haemorrhage])				
Symptomatic UGI ulcer (ie, uncomplicated ulcer but no perforation, obstruction, or bleed [haemorrhage])				
MORTALITY: Please record the number of patients that died, by each underlying cause (if known)				
Any VASCULAR cause				
Any NON-VASCULAR cause				
UNKNOWN cause of death				
Coronary heart disease				
Stroke				
Upper gastrointestinal (UGI) ulcer				
Cancer				

CNT Secretariat, Clinical Trial Service Unit, Richard Doll Building, Oxford OX3 7LF, UK
 Email: cnt@ctsu.ox.ac.uk Tel: +44 1865 743743 Fax: +44 1865 743985

COXIB AND TRADITIONAL NSAID TRIALISTS' (CNT) COLLABORATION:

A collaborative meta-analysis of individual participant data from all randomised trials with at least one unconfounded comparison involving a selective cyclo-oxygenase-2 inhibitor (coxib) or a traditional non-steroidal anti-inflammatory drug (tNSAID).

Background

Traditional non-steroidal anti-inflammatory drugs (tNSAIDs) and newer selective cyclo-oxygenase-2 inhibitors (coxibs) are widely used for analgesia, but they have potentially serious vascular and gastrointestinal risks. A meta-analysis of tabular data from randomised trials of at least 4 weeks' duration involving a coxib versus placebo, or a coxib versus a traditional NSAID, has provided some limited information about the risk of vascular events associated with these drugs.¹ Although this has been used by regulatory authorities in informing treatment choices for the public, a meta-analysis of individual participant data from these trials would be substantially more informative. The pharmaceutical sponsors of coxib trials and their investigators have agreed to provide data to form a collaboration (the Coxib and traditional NSAID Trialists' [CNT] Collaboration), in order to assemble and maintain a database of individual participant data from all unconfounded trials, published and unpublished, of at least four weeks duration which have involved a coxib or tNSAID. The chief aim of this Collaboration will be to conduct analyses of the effects of coxibs and tNSAIDs on the most common adverse effects of coxibs and tNSAIDs, namely "serious vascular events" and "symptomatic ulcer or upper gastrointestinal (GI) complications". We aim to update the results of this meta-analysis when the results of new trials become available.

The main benefits of an individual participant data meta-analysis include an ability to address some important outstanding questions, suggest new hypotheses and help identify future research questions. Some of the outstanding questions about anti-inflammatory drugs that will be informed by this collaborative meta-analysis include:

- Do the proportional effects on serious vascular events and upper GI complications vary amongst patient subgroups, for example by age, gender and other clinical features which influence the risk of vascular and upper gastrointestinal disease?
- Do cardiovascular hazards occur soon after drug initiation, or do they require prolonged exposure?
- Do different coxib and tNSAID regimens differ clearly in their vascular and upper gastrointestinal toxicity? In particular, do these analyses support the hypothesis, first raised by the Cross Trial Safety Assessment Group in celecoxib versus placebo trials, that there is a trend towards larger proportional increases in vascular risk with higher coxib dose and higher baseline risk of vascular disease?²
- What is the balance of benefit and risk of different coxibs and tNSAIDs in terms of absolute effects on vascular events and gastrointestinal effects among different types of patients?

Methods

Study eligibility: Eligible studies will be randomised trials of at least four weeks' duration in which there is a comparison of a coxib versus placebo, a coxib versus tNSAID, one coxib versus another coxib, a dose-comparison of a particular coxib, tNSAID versus placebo, one tNSAID versus another tNSAID, or a dose comparison of a particular tNSAID. We aim to collect information on all available tNSAIDs, including those with additional properties (e.g., variable inhibition of COX-1, nitric oxide [NO] release, etc.) The first cycle of analyses will include all trials for which final clinical study reports are available before January 1st 2009.

Trials of less than 4 weeks duration will not be included in the primary comparisons, because most such studies are small, early phase trials, and will contribute few events but consume a disproportionately large proportion of the project's resources. However, there have been a few short-term studies among patients at high risk of vascular disease (for example, two studies of valdecoxib among patients receiving a coronary artery bypass graft^{3,4}), which involved enough vascular events to warrant sensitivity analyses of the early vascular risks associated with coxibs derived from these trials as well. We will therefore seek data from all short-term trials among patients with established vascular disease (in addition to data from longer term trials).

Identification of eligible trials: Potentially eligible trials will be identified using electronic literature searches.¹ The manufacturers of coxibs (Merck, Pfizer and Novartis) and tNSAIDs (including the manufacturers of newer nitric oxide-donating agents such as NicOx) will be asked to identify any additional trials involving their own drug, published or unpublished, of which they are aware.

Data collection and checking: We will seek individual participant data for all randomised individuals in relevant trials, irrespective of whether they actually took allocated treatment. The requested data will comprise: baseline characteristics and concomitant medications recorded at randomisation, details of randomly allocated treatments (and the dates they commenced), dates of major vascular and gastrointestinal outcomes; dates of treatment discontinuation. The data will be checked carefully for internal consistency and completeness of individual participant records, and for other indicators of possible anomalies. All queries regarding particular trials will be referred back to the sponsors or principal investigators of the trials, and computer generated outputs consisting of detailed summary tabulations and consistency checks will be returned to each collaborator for review and confirmation.

Outcomes & Adjudication

Data will be sought on definite or probable cardiovascular and upper gastrointestinal outcomes, as defined and adjudicated in each trial (or adjudicated independently after trial completion [see Sections C and D of the data request]). If adjudicated cardiovascular and/or gastrointestinal outcomes are not available, then the best available information on these outcomes will be recorded. In those trials where outcomes were not adjudicated but MedDRA codes have been used to code serious adverse events, those codes will be used to identify particular vascular and GI outcomes from pre-specified coding lists (see Appendices 1 & 2).

Analytical strategy

The available trials involve a number of different designs. Electronic literature searches have already established that, prior to the development of the coxibs, there were relatively few placebo controlled trials of traditional NSAIDs, or trials comparing one traditional NSAID with another, and most of these were small and short-term (typically less than 12 weeks). A majority of these trials were published over 25 years ago, and it is likely to be difficult to obtain individual participant data. It is probable, therefore, that trials that precede the development of coxibs will provide little reliable information on the effects of particular tNSAIDs on specific vascular and GI outcomes.

By contrast, there is an order of magnitude more information on these outcomes recorded in more recently completed trials involving a comparison of a coxib vs placebo or a coxib vs a tNSAID (or both).

Given this distribution of information on particular outcomes in the available trials, the primary analysis strategy will be to conduct meta-analyses of all trials involving the following comparisons:

- Coxib versus placebo
- Coxib versus tNSAID
- One coxib versus another coxib
- tNSAID versus placebo
- One tNSAID versus another tNSAID
- Dose comparisons for particular coxibs or tNSAIDs

Details of the analysis strategy are provided in the Statistical Appendix. Briefly, estimates of the effects of particular coxibs will be obtained from comparisons of a coxib versus placebo. Estimates of the effects of each tNSAID will be derived by combining *direct comparisons* (i.e., trials comparing the particular tNSAID versus placebo, which will involve small numbers of events) and *indirect comparisons* (i.e., estimates derived indirectly by combining the more statistically precise results of trials comparing a coxib versus placebo with those of trials of a coxib versus the particular tNSAID under study). In exploratory analyses, we will use a variety of model-based approaches (sometimes called “network meta-analysis”) to derive estimates of the relative effects of each tNSAID and coxib using all of the available trial data.

Rate ratios and their confidence intervals for each of the pre-specified comparisons will be derived using the Peto “one step” approximation. Standard methods for analysis of survival data in individual participant data meta-analyses will be used.⁶

The primary outcomes will be:

- “Vascular events” as defined by Antiplatelet Trialists’ (APT) Collaboration⁵ (nonfatal myocardial infarction, nonfatal stroke or vascular death)
- “Upper gastrointestinal complications (bleed, perforation or obstruction)”

Secondary outcomes will be:

(i) Vascular

- Vascular mortality
- Myocardial infarction
- Stroke (subdivided into haemorrhagic and non-haemorrhagic causes)
- Heart failure requiring hospitalisation
- Pulmonary embolus
- Peripheral arterial event
- Coronary revascularisation
- Resuscitated cardiac arrest
- Unstable angina requiring hospitalisation

(ii) Upper gastrointestinal

- Upper gastrointestinal complication (bleed)
- Upper gastrointestinal complication (perforation)
- Upper gastrointestinal complication (obstruction)
- Upper gastrointestinal symptomatic uncomplicated ulcer

(iii) Cause-specific mortality

- Vascular causes (coronary heart disease, other cardiac, stroke, other vascular)
- Upper gastrointestinal causes (bleed, perforation, obstruction, other)
- Other non-vascular causes (cancer, other)

Secondary analyses will also include assessments of effects on individual components of the primary outcomes. A Poisson model will be devised to assess independent determinants of major vascular and upper gastrointestinal events, using a method employed previously by the Cholesterol Treatment Trialists’ (CTT) Collaboration.⁷ Subgroup analyses will include assessments of effects on specific outcomes among categories defined by:

- (i) baseline demographic features
- (ii) concomitant treatments at baseline (e.g. aspirin, gastroprotectants etc.)
- (iii) participants at low-, intermediate-, and high-risk of vascular events (as defined by a Poisson model)
- (iv) participants at low-, intermediate-, and high-risk of gastrointestinal events (as defined by a Poisson model)
- (v) particular indications for an anti-inflammatory drug (e.g. osteoarthritis, rheumatoid arthritis, cancer prevention etc.)
- (vi) adjudicated and non-adjudicated trials
- (vii) trials of painful and non-painful conditions
- (viii) cancer prevention and treatment trials

Where possible, assessments of dose-response will be made for particular coxibs or tNSAIDs, using all available data. These will include, in particular, any period involving multiple dose comparisons from “extension trials” (where a short-term placebo-controlled period, sometimes with several different doses, was followed by a longer comparison of a coxib vs tNSAID).

In addition, exploratory analyses will be carried out to assess, where possible, the evolution in rate ratios after drug discontinuation. We will also assess differences between analyses that exclude events occurring prior to the first drug dose and those involving all post-randomisation follow-up.

Publication policy

All publications will be in the name of the Coxib and traditional NSAID Trialists' (CNT) Collaboration, with the names of collaborators listed at the end of the paper. Publications will be circulated for comments and approval before submission to peer review.

Confidentiality

All trial data will be regarded as strictly confidential, and will not be provided to any third party without the prior written permission of the owners of the data.

Funding

Collaborators will be asked to fund their own travel costs for meetings (accommodation and meals will be provided), although a fund will be set up to assist those who would not otherwise be able to attend.

Proposed timeline

3 rd quarter, 2008	Circulation of protocol and data request
3 rd to 4 th quarter, 2008	Discussions with trial sponsors
	Electronic searches and trial selection
1 st to 3 rd quarter, 2009	Steering Group teleconference (Oxford)
	Final protocol and data request circulated
	Data collection commences
Up to 4 th quarter, 2010	Data checking and analysis
1 st quarter, 2011	Preliminary results meeting (Oxford)
Up to 4 th quarter, 2011	Additional analyses suggested by collaborators
	Circulation and revision of manuscript(s)
	Submission of primary manuscript

Additional substudies

In addition, to the unconfounded comparisons of coxibs and traditional NSAIDs which are detailed above, we will collect tabular data on other therapeutic and confounded comparisons. These include coxib versus paracetamol; NSAID versus paracetamol; coxib versus aspirin; NSAID versus aspirin; NSAID and gastroprotectant (eg, proton pump inhibitor [PPI], histamine-2 receptor antagonist [H2-RA] or misoprostol) versus coxib alone; coxib and gastroprotectant versus coxib alone; and NSAID and gastroprotectant versus NSAID alone.

References

- 1). Kearney P, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclooxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006; 332: 1302-5.
- 2). Cross Trial Safety Assessment Group. Solomon SD, Wittes J, Finn PV, et al. Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials: the cross trial safety analysis. *Circulation*. 2008 Apr 22;117(16):2104-13.
- 3). Multicenter Study of Perioperative Ischemia (McSPI) Research Group; Ischemia Research and Education Foundation (IREF) Investigators. Ott E, Nussmeier NA, Duke PC, et al. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg*. 2003 Jun;125(6):1481-92.
- 4). Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med*. 2005 Mar 17;352(11):1081-91.
- 5). Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106.
- 6). Early Breast Cancer Trialists' Collaborative Trial. Treatment of early breast cancer: worldwide evidence 1985-1990. Oxford: Oxford University Press, 1990.
- 7). Cholesterol Treatment Trialists' (CTT) Collaborators. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005 Oct 8;366(9493):1267-7

How to send data to the CNT secretariat

Reminder of confidentiality

All data sent to the secretariat will be held securely and treated in the strictest confidence. The data will not be used in any publication without the explicit permission of the responsible trialist.

Ways of sending data

As long as it will not cause delay the easiest way for us to receive the data is by encrypted email (cnt@ctsu.ox.ac.uk). If you choose to use a different medium for sending data, please accompany it with

1. a full description of the format
2. the software package (including version number) used to write the file
3. the number of data records included

Preferred data format

Please record ALL patients originally randomised, i.e. include any who were ineligible, withdrawn, unevaluable, lost or “protocol-deviant”.

Please provide data as an *ASCII text file* and not the storage format used by any proprietary software package. The preferred format is comma separated variable (CSV) file, or similar text file delimited by a suitable character (*tabs* for example). We can also accept the data as a SAS transport file. If you are providing data in your own format (i.e. different to that described below) then it is very useful if variable names are included as column headings in the file.

If particular data are not available, simply leave the relevant columns blank: it is not necessary to include a “missing data” code. However, if it is easier for you to include a code for missing data, please tell us precisely what that code is: it is particularly important that we can differentiate between the codes for “no event” and “missing data”.

If you are unable to provide actual dates (for example, due to privacy laws), then please provide the number of days since randomisation (and omit the date of randomisation). Otherwise, please use the convention DDMMYYYY (or similar day-month-year ordered format) for dates. If a date is incompletely known, either leave the day blank and give month and year, or leave the day and month blank and just give year. Please leave dates of specific events blank when a patient did not experience such an event.

A. Baseline data recorded PRIOR to randomisation	Coding
Patient identifier note 1	
Gender	1 = male 2 = female
Ethnicity	1 = caucasian 2 = other
Date of birth or age at randomisation note 2	
Indication for treatment note 3	1 = rheumatoid arthritis 2 = osteoarthritis 3 = back pain 4 = gout 5 = cancer treatment 6 = cancer prevention 7 = treatment/prevention of Alzheimer's disease 8 = other condition 9 = unknown
History of atherosclerosis (coronary heart disease note 4 , cerebrovascular disease note 5 , or other arterial disease note 6)	1 = yes 0 = no
History of diabetes mellitus	1 = yes 0 = no
History of upper gastrointestinal ulcer note 7	1 = yes 0 = no
<i>Helicobacter pylori</i> status at baseline note 8	1 = positive 0 = negative
Height (cm)	
Weight (kg)	
Current cigarette smoker note 9	1 = yes 0 = no
Current drinker of alcohol note 10	1 = yes 0 = no
Current user of aspirin	1 = yes 0 = no
Current user of gastroprotective agent note 11	1 = proton pump inhibitor 2 = histamine 2 receptor blockers 3 = misoprostol 9 = other 0 = no
Baseline haemoglobin (g/dl) note 12	

Baseline total cholesterol (mmol/L) note 12	
Baseline creatinine (μmol/l) note 12	
Baseline systolic blood pressure (mm Hg) note 13	
Baseline diastolic blood pressure (mm Hg) note 13	
B. Randomisation and treatment allocation	
Date of randomisation note 14	
Date commenced <i>first</i> treatment note 14	
First randomised treatment allocation note 14	
Date ended first treatment note 14	
Date commenced <i>second</i> treatment note 14	
Second randomised treatment allocation note 14	
Date ended second treatment note 14	

C. Cardiovascular events occurring AFTER randomisation (record information on first event of each type)

Only the first cardiovascular event occurring in each category is to be recorded. Please record all events that occurred on or before the pre-specified censoring date for that event type (in some trials, this was some time after treatment ended [e.g. 28 days]). *Definite or probable* events should be included, but please exclude “possible” events. Please use the trialists’ definition of an outcome – although there will inevitably be minor differences in definition between trials, all comparisons are within trial, and heterogeneity between trials will be explored. Record either adjudicated events or, if a specific event was not adjudicated, the best available matching event from your file (and give us details of how this has been done). Where the MedDRA system has been employed, please use the list of terms in Appendix 1 to define events.

First myocardial infarction (MI) <i>after</i> randomisation	1 = yes 0 = no
Date of first MI note 15	
Whether MI was fatal or non-fatal note 16	1 = fatal 0 = non-fatal
First stroke <i>after</i> randomisation note 17	1 = yes 0 = no
Type of stroke <i>after</i> randomisation	1 = intracerebral haemorrhage 2 = subarachnoid haemorrhage 3 = subdural haematoma 4 = ischaemic (including embolic) stroke 9 = unknown
Date of first stroke note 15	
Whether stroke was fatal or non-fatal note 16	1 = fatal 0 = non-fatal
First episode of heart failure requiring hospitalisation <i>after</i> randomisation note 18	1 = yes 0 = no
Date of first heart failure event note 15	
Whether heart failure event was fatal or non-fatal note 16	1 = fatal 0 = non-fatal
First pulmonary embolus (PE) <i>after</i> randomisation note 19	1 = yes 0 = no
Date of first PE note 15	
Whether PE was fatal or non-fatal note 16	1 = fatal 0 = non-fatal
First peripheral arterial disease event <i>after</i> randomisation note 20	1 = yes 0 = no

Date of first peripheral arterial disease event note 15	
Whether peripheral arterial disease event was fatal or non-fatal note 16	1 = fatal 0 = non-fatal
First coronary revascularisation <i>after</i> randomisation note 21	1 = yes 0 = no
Date of first coronary revascularisation note 15	
Whether coronary revascularisation was fatal or non-fatal note 16	1 = fatal 0 = non-fatal
First resuscitated cardiac arrest <i>after</i> randomisation note 22	1 = yes 0 = no
Date of first resuscitated cardiac arrest note 15	
Whether resuscitated cardiac arrest was fatal or non-fatal note 16	1 = fatal 0 = non-fatal
First episode of unstable angina <i>after</i> randomisation note 23	1 = yes 0 = no
Date of first unstable angina event note 15	
Whether unstable angina was fatal or non-fatal note 16	1 = fatal 0 = non-fatal

D. Upper gastrointestinal (UGI) events occurring AFTER randomisation (record information on first event of each type)

Only the first UGI event occurring in each category is to be recorded. Please record all events that occurred on or before the pre-specified censoring date for that event type (in some trials, this was some time after treatment ended [e.g. 28 days]). *Definite or probable* events should be included, but please exclude “possible” events. Please use the trialists’ definition of an outcome – although there will inevitably be minor differences in definition between trials, all comparisons are within trial, and heterogeneity between trials will be explored. Record either adjudicated events or, if a specific event was not adjudicated, the best available matching event from your file (and give us details of how this has been done). Where the MedDRA system has been employed, please use the list of terms in Appendix 2 to define events.

First symptomatic (but <u>un</u> complicated) UGI ulcer <i>after</i> randomisation note 24	1 = yes 0 = no
Date of first symptomatic (but <u>un</u> complicated) UGI ulcer note 25	
First upper gastrointestinal UGI ulcer complication <i>after</i> randomisation note 24	1 = yes 0 = no
Date of first UGI ulcer complication note 25	
Type of UGI ulcer complication	1 = UGI haemorrhage 2 = UGI obstruction 3 = UGI perforation 4 = other 9 = unknown
Whether UGI ulcer complication was fatal or non-fatal note 26	1 = fatal 0 = non-fatal

E. Study discontinuation	
Study treatment discontinued permanently prior to scheduled end	1 = yes 0 = no
Date study treatment discontinued if prior to scheduled end note 27	
F. Follow-up information	
Date of scheduled end of treatment note 28	
Date of last follow-up for cardiovascular events note 29	
Date of last follow-up for gastrointestinal events note 30	
Date of last follow-up for vital status note 31	
Vital status on that date	1 = dead 0 = alive
ICD (or other code) for death note 32	

Explanatory notes

A. Baseline data recorded prior to randomisation

- 1 Please use a unique code that will enable you to retrieve a patient's data if the secretariat requests clarification.
- 2 Please provide either the date of birth or age (in complete years) at randomisation.
- 3 Please provide primary indication for drug treatment.
- 4 This consists of a history of myocardial infarction, unstable angina, heart failure, resuscitated cardiac arrest or coronary revascularisation.
- 5 This is defined as a history of stroke (ischaemic, haemorrhagic [including subarachnoid haemorrhage or subdural haematoma], or unknown).
- 6 This consists of a history of peripheral arterial disease, peripheral arterial intervention, or other arterial disease (e.g., aortic aneurysm, ischaemic colitis, splenic infarction).
- 7 This consists of a history of symptomatic UGI ulcer or UGI ulcer complication (i.e. perforation, obstruction or haemorrhage), defined anatomically as being including and proximal to the duodenum (i.e., the ligament of Treitz).
- 8 If known, please record *H. pylori* status at randomisation. Otherwise please leave blank.
- 9 Please record 'yes' if patient reports that they are a current smoker, 'no' otherwise (and leave blank if unknown).
10. Please record 'no' if patient reports that they are currently teetotal, 'yes' otherwise (and leave blank if unknown).
- 11 If using the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) Classification System, please use Appendix 3.
- 12 Please use either serum or plasma measurements. Where several blood results are available, please record the last prior to randomisation.
- 13 Where several measurements are available, please record the last prior to randomisation.

B. Randomisation and treatment allocation

- 14 Each patient's trial medication should be recorded with a simple character string: date of randomisation; date commenced first randomised treatment; code for first treatment; date ended first treatment. Then, if the trial involved a second randomised comparison: date commenced second treatment; code for second allocated treatment; date ended second treatment. (For example, a trial involving a single comparison of coxib vs. placebo would involve 4 items for each patient, whilst a trial involving an initial comparison of coxib vs. placebo followed by coxib vs. NSAID would involve 7 items).

If you are unable to provide actual dates (for example, due to privacy laws), then please provide the number of days since randomisation instead (and omit the date of randomisation).

C. Cardiovascular events occurring after randomisation

- 15 If a cardiovascular event did not occur, please leave the corresponding “date of event” blank.
- 16 A cardiovascular event (after randomisation) is defined to be fatal if death was primarily attributed to that event, but otherwise an event should be recorded as non-fatal.
- 17 This can be either ischaemic, haemorrhagic (including subdural haematoma or subarachnoid haemorrhage), or of unknown aetiology. Stroke is defined clinically as 'a neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours'.
- 18 This consists of an episode of heart failure or pulmonary oedema requiring hospitalisation.
- 19 This consists of a pulmonary embolus or pulmonary thrombosis.
- 20 This consists of a peripheral arterial disease event, peripheral arterial intervention, or other arterial disease event (e.g., aortic aneurysm, ischaemic colitis, splenic infarction).
- 21 This consists of a coronary angioplasty (with or without a stent), coronary artery bypass graft, or other coronary revascularisation.
- 22 This consists of a confirmed resuscitated cardiac arrest, occurring in or out of hospital.
- 23 This consists of an episode of unstable angina requiring hospitalisation.

D. Upper gastrointestinal (UGI) events occurring after randomisation

- 24 UGI complicated events are defined as perforation, obstruction or haemorrhage (bleed). If patient has had a symptomatic ulcer diagnosed without these occurring, it is uncomplicated.
- 25 If an UGI event did not occur, please leave the corresponding “date of event” blank.
- 26 An UGI event (after randomisation) is defined to be fatal if death was primarily attributed to that event, but otherwise an event should be recorded as non-fatal.

E. Study discontinuation

- 27 If a permanent study treatment discontinuation did not occur, please leave the corresponding “date of event” blank.

F. Vital status at last follow-up

- 28 Please record the date that a patient was scheduled to complete study treatment.
- 29 Please record the last date of follow-up (i.e. censoring date) for cardiovascular events.
- 30 Please record the last date of follow-up (i.e. censoring date) for gastrointestinal events.
- 31 Please record the date of death, or the last date on which the patient was known

to be alive.

- 32 If possible, code the cause of death using the 9th or 10th revision of the International Classification of Diseases. If this is not possible, please provide details of your coding scheme.

Coxib and traditional NSAID Trialists' (CNT) collaboration

APPENDIX 1

MedDRA Terms for unadjudicated cardiovascular endpoints

<u>Confirmed Endpoint</u>	<u>Investigator Reported Term (MedDRA PT, LLT or SMQ)</u>
Myocardial Infarction	Myocardial infarction Acute myocardial infarction Myocardial infarction, Coronary artery disease Non-Q wave MI Acute non-Q wave MI Post procedural myocardial infarction
Haemorrhagic Stroke	Haemorrhagic stroke Intracranial haemorrhage Haemorrhagic transformation stroke Haemorrhagic cerebral infarction Haemorrhage intracranial Haemorrhagic infarction Cerebral haemorrhage Cerebral haemorrhage traumatic Pituitary haemorrhage Thalamus haemorrhage Brain stem haemorrhage Intraventricular haemorrhage Basal ganglia haemorrhage Cerebellar haemorrhage Brain stem haemorrhage Haemorrhagic cerebrovascular conditions (SMQ)
Subarachnoid Haemorrhage	Subarachnoid haemorrhage
Subdural Haematoma	Subdural haematoma Subdural haemorrhage

Ischaemic Stroke	Ischaemic stroke Brain stem infarction Cerebral infarction Cerebral thrombosis Cerebrovascular accident Stroke Embolic stroke Thrombotic stroke Thromboembolic stroke Cerebral artery occlusions Cerebral artery thrombosis Ischaemic cerebral infarction Thrombotic cerebral infarction Embolic cerebral infarction Lacunar infarction Pituitary infarction Thalamic infarction Cerebellar infarction Cerebral thrombosis Cerebral artery thrombosis Cerebral artery embolism Post procedural stroke Ischaemic cerebrovascular conditions (SMQ)
Heart Failure	Cardiac failure Pulmonary oedema Acute pulmonary oedema Heart failure Cardiac failure acute Cardiac failure congestive Left ventricular failure Acute left ventricular failure Cardiopulmonary failure Ventricular failure
Pulmonary Embolus	Pulmonary embolus Pulmonary thrombosis

Peripheral Arterial Disease	Arterial thrombosis Peripheral occlusive disease Arterial thrombosis limb Arterial occlusive disease Arterial embolism limb Iliac artery thrombosis Subclavian artery thrombosis
Peripheral Arterial Intervention	Peripheral revascularisation Vascular operation Vascular stent insertion
Other Arterial Disease	Colitis ischaemic Infarction, Splenic infarction Aortic aneurysm Aortic aneurysm repair Aortic aneurysm rupture Intra-thoracic aortic aneurysm repair
Coronary Revascularisation	Coronary revascularisation Coronary artery bypass Coronary angioplasty Coronary arterial stent insertion Coronary endarterectomy Percutaneous coronary intervention Arterial bypass operation Angioplasty CABG/coronary artery bypass graft Percutaneous coronary (intervention) Balloon (in context of angioplasty) PTCA/Percutaneous transluminal coronary angioplasty
Resuscitated Cardiac Arrest	Cardiac arrest Cardio-respiratory arrest Circulatory collapse
Unstable angina	Angina unstable Angina pectoris Postinfarction angina Microvascular angina

Coxib and traditional NSAID Trialists' (CNT) collaboration

APPENDIX 2

MedDRA Terms for unadjudicated upper gastrointestinal (UGI) endpoints

<u>Confirmed Endpoint</u>	<u>Investigator Reported Term (MedDRA PT, LLT or SMQ)</u>
Symptomatic UGI Ulcer	Peptic ulcer Duodenal ulcer Gastroduodenal ulcer Gastric ulcer Gastric ulcer helicobacter Oesophageal ulcer Stress ulcer Gastrointestinal ulcer, site unspecified
UGI Perforation	Peptic ulcer perforation Duodenal ulcer perforation Duodenal perforation Gastric ulcer perforation Gastric perforation Oesophageal ulcer perforation Oesophageal perforation Gastrointestinal ulcer perforation, site unspecified Gastrointestinal perforation, site unspecified Perforated ulcer Perforated duodenal ulcer repair
UGI Obstruction	Peptic ulcer perforation, obstructive Peptic ulcer, obstructive Duodenal ulcer perforation, obstructive Duodenal ulcer, obstructive Duodenal obstruction Duodenal stenosis Gastric ulcer perforation, obstructive Gastric ulcer, obstructive Gastric ulcer haemorrhage, obstructive Obstruction gastric Pyloric stenosis

UGI Haemorrhage	Peptic ulcer haemorrhage Duodenal ulcer haemorrhage Gastric ulcer haemorrhage Oesophageal ulcer haemorrhage Gastrointestinal ulcer haemorrhage Gastric haemorrhage Gastroduodenal haemorrhage Oesophageal haemorrhage Upper gastrointestinal haemorrhage Gastrointestinal haemorrhage Intra-abdominal haemorrhage

Coxib and traditional NSAID Trialists' (CNT) collaboration

APPENDIX 3

**WHO ATC codes for concomitant medications
[Current user of gastroprotective agent]**

<u>Medication</u>	<u>ATC Term</u>	<u>ATC Code</u>
Proton pump inhibitors	Proton pump inhibitors	A02BC
Histamine 2 receptor blockers	H2-receptor antagonists	A02BA
Misoprostol	Prostaglandins	A02BB
Other	Combination for eradication of <i>Helicobacter pylori</i> Other drugs for peptic ulcer and gastro-oesophageal reflux disease	A02BD A02BX

APPENDIX Search Strategy

Description of Eligible Studies

- properly randomized trials
- of at least 4 week's duration (though studies less than this will be assessed to check actual duration)
- Unconfounded comparisons of either
 - n Coxib versus placebo
 - n Coxib versus tNSAID
 - n One coxib versus another coxib
 - n tNSAID versus placebo
 - n One tNSAID versus another tNSAID
 - n Dose comparisons for particular coxibs or tNSAIDs

Outcomes

From the selected trials data sought on definite or probable outcomes, as defined by each trial (whether adjudicated or not).

1. Cardiovascular outcomes:
 - myocardial infarction
 - stroke (subdivided into haemorrhagic or ischaemic)
 - vascular death
 - coronary revascularization procedure (PCI or CABG)
 - hospitalization for unstable angina
 - hospitalization for congestive heart failure
 - peripheral arterial thrombosis (including peripheral arterial procedure)
 - pulmonary embolus
2. Gastrointestinal outcomes
 - Upper GI bleed
 - Upper GI perforation
 - Upper GI obstruction
 - Upper GI symptomatic (uncomplicated) ulcer
3. Mortality by cause
 - Vascular causes (CHD, other cardiac, stroke, other vascular)
 - Non-vascular causes (cancer, upper GI bleed, other)

Search Strategy

The Search was performed according to the revised Cochrane Collaboration search strategy for electronic searches of randomized trials (Robinson and Dickersin)

(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos [mh] OR placebo*[tw] OR random*[tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control*[tw] OR

AND all treatments in the list of coxibs and traditional NSAIDs (including nitric oxide-sparing [ie, CINOD]) shown below:

Drugs to be included in the search:

All the drugs below were identified as ones that could be included in the electronic search.

Coxibs

- Celecoxib
- Etoricoxib
- Lumiracoxib
- Parecoxib
- Rofecoxib
- Tiracoxib
- Valdecoxib
- AZD3582

Traditional NSAIDs

- Aceclofenac
- Alclofenac
- Apazone
- Benoxaprofen
- Diclofenac
- Diflunisal
- Dipyrrone
- etodolac
- Fenbufen
- Fenoprofen
- Floctafenine
- Flurbiprofen
- Ibuprofen
- indobufen
- Indomethacin
- Isoxicam
- Ketoprofen
- Ketorolac
- Lornoxicam
- Meclofenamate
- Meclofenamic acid
- Mefenamic acid

- Meloxicam
- Nabumetone
- Naproxen
- Nimesulide
- Oxyphenbutazone
- Oxyprozin/oxaprozin
- Phenylbutazone
- Piroxicam
- Sulindac
- Tenoxicam
- Tiaprofenic acid
- Tiroxicam
- Tolmetin

CINODS

- Naproxcinod
- Cyclooxygenase inhibitor-NO
- Cinods

Drugs deemed not for inclusion

- Bromelains
- Clonixin
- Curcumin
- Glycyrrhizic acid
- Iofazimine
- Niflumic acid
- Prenazone
- Sulf/phas/x/zalas/zine (s/x/za)
- Suprofen
- Carprofen
- Dapsone
- Fentanyl (opioid)
- Feprazone
- Flufenamic acid
- Glucosamine
- Mesalamine (Mesalazine)
- Morphine (opioid)
- Nalbuphine (opioid)
- Pentazocine
- Pentoxifylline
- Pirprofen
- Pranoprofen
- Proglumetacine
- Proquazone
- Tolfenamic acid

Initial Medline Search via OvidSP in MEDLINE® In-process & Other Non-indexed Citations and Ovid MEDLINE ® 1950 to Present (March 2008)

Search Term	Search No	Details of search	Trials returned	comment
Randomized trial according to the Revised Cochrane Collaboration search strategy for PubMed of				

Robinson and Dickersin.				
Randomized controlled trial	1	randomized controlled trial.mp. or Randomized Controlled Trial/	251388	
Controlled trial	2	controlled clinical trial.mp. or Controlled Clinical Trial/	80986	
Random allocation	3	random allocation.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	60218	
Double blind	4	double-blind method.mp. or Double-Blind Method/	60218	
Single blind	5	single-blind method.mp. or Single-Blind Method/	94676	
Clinical trial	6	clinical trial.mp. or Clinical Trial/	11623	
Clinical trials	7	clinical trials.mp. or Clinical Trial/	473913	
Blind or mask	8	((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).ti.	566684	
	9	((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).ab.	85579	
Latin square	10	latin square.mp.	2554	
Placebo	11	placebo\$1.mp.	121659	
Random	12	random\$7.mp.	541329	
Comparative study	13	comparative study.mp.	1380680	
Evaluation	14	evaluation studies.mp. or Evaluation Studies/	216592	
Prospective study	15	prospective studies.mp. or Prospective Studies/	243292	
Follow-up study	16	follow-up studies.mp.	358182	
Crossover	17	cross-over studies.mp. or Cross-Over Studies/	21407	
Case-control	18	Case-Control Studies/	93991	
	19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18		
Coxib (MEDLINE)				
Coxib	20	Coxibs.mp or Cyclooxygenase 2 Inhibitors/	4932	
	21	Cyclooxygenase 2 inhibitors/	4676	
	22	Cyclooxygenase 2 inhibitor\$.mp	5307	
	23	20 or 21 or 22	5538	
RCT and Coxib	24	19 and 23	1348	
Deduplicate	25	Remove duplicates from 24	1327	
NSAIDS				
Naproxen		Naproxen.mp or Naproxen/	1562	With RCT strategy and limited to adults
Ibuprofen		Ibuprofen.mp or Ibuprofen/	1253	Ditto
Diclofenac		Diclofenac.mp or diclofenac/	2095	Ditto
Indomethacin		Indomethacin.mp or Indomethacin/		Ditto
Nabumetone		Nabumetone.mp or nabumetone/		Ditto
Meloxicam		Meloxicam.mp or meloxicam/		Ditto
Tiroxicam		Tiroxicam.mp or tiroxicam/		Ditto
Diflunisal		Diflunisal.mp or diflunisal/	114	Ditto
Apazone		Apazone.mp or apazone/	947	Ditto
Clonixin		Clonixin.mp or clonixin/	476	Ditto
Dipyrrone		Dipyrrone.mp or dipyrrone/	3526	Ditto
Etodolac		Etodolac.mp or etodolac/	1653	Ditto
Fenoprofen		Fenoprofen.mp or fenoprofen	2210	Ditto

Meclofenamic acid		Meclofenamic acid.mp or meclofenamic acid/	2380	Ditto
Mefenamic acid		Mefenamic acid.mp or mefanamic acid/	3628	Ditto
Oxyphenbutazone		Oxyphenbutazone.mp or oxyphenbutazone/	2571	Ditto
Floctafenine		Floctafenine.mp or floctafenine/	30	Ditto
Flurbiprofen		Flurbiprofen.mp or flurbiprofen/	1573	Ditto
Isoxicam.mp		isoxicam.mp or isoxicam/	114	Ditto
Ketoprofen		Ketoprofen.mp or ketoprofen/	1033	Ditto
Ketorolac		Ketorolac.mp or ketorolac/	1016	Ditto
Loxoprofen		Loxoprofen.mp or loxoprofen/	35	Ditto
Nimesulide		Nimesulide.mp or nimesulide/	413	Ditto
Oxyprozin/oxaprozin		Oxyprozin.mp or oxyprozin/	1	Ditto
Phenylbutazone		phenylbutazone.mp. or Phenylbutazone/	1072	Ditto
Piroxicam		Piroxicam.mp or piroxicam/	1285	Ditto
Sulindac		Sulindac.mp or sulindac/	526	Ditto
Tenoxicam		Tenoxicam.mp or tenoxicam/	303	Ditto
Tiaprofenic acid		Tiaprofenic acid.mp or Tiaprofenic acid/	121	Ditto
Tolmetin		Tolmetin.mp or tolmetin/	639	Ditto
CINODS				
AZD3582		AZD3582.mp or AZD 3582.mp	11	Ditto
Cinod		Cinod.mp or cinods.mp	11	Ditto
Naproxcinod		Naproxcinod.mp	8	Ditto
Cyclooxygenase inhibitor-NO		Cyclooxygenase inhibitor-NO.mp or cyclooxygenase inhibitor nitric oxide.mp	2	Ditto
TOTAL			31935	

EMBASE Search via OvidSP: completed March 2008 in EMBASE 1980 to present

Search Term	Search No	Details of search	Trials returned	comment
Randomized trial according to the Revised Cochrane Collaboration search strategy for PubMed of Robinson and Dickersin.				
Randomized controlled trial	1	randomized controlled trial.mp. or Randomized Controlled Trial/	409964	
Controlled trial	2	controlled clinical trial.mp. or Controlled Clinical Trial/	126521	
Random allocation	3	random allocation.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	60820	
Double blind	4	double-blind method.mp. or Double-Blind Method/	162908	
Single blind	5	single-blind method.mp. or Single-Blind Method/	18997	
Clinical trial	6	clinical trial.mp. or Clinical Trial/	986867	
Clinical trials	7	clinical trials.mp. or Clinical Trial/	1097526	
Blind or mask	8	((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).ti.	42992	
	9	((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).ab.	167696	

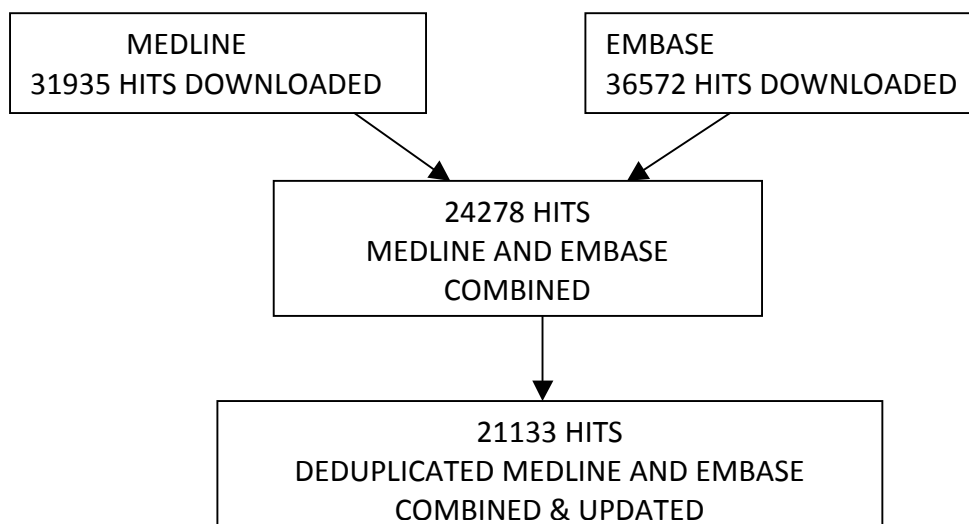
Latin square	10	latin square.mp.	3648	
Placebo	11	placebo\$.mp.	281026	
Random	12	random\$.mp.	940084	
Comparative study	13	comparative study.mp.	1507871	
Evaluation	14	evaluation studies.mp. or Evaluation Studies/	268648	
Prospective study	15	prospective studies.mp. or Prospective Studies/	324669	
Follow-up study	16	follow-up studies.mp.	363524	
Crossover	17	cross-over studies.mp. or Cross-Over Studies/	41435	
Case-control	18	Case-Control Studies/	111432	
	19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	3676931	
Coxib				
Coxib	20	Coxibs.mp or Cyclooxygenase 2 Inhibitors/	16317	Limit to humans
	21	Cyclooxygenase 2 inhibitors/	15995	Ditto
	22	Cyclooxygenase 2 inhibitor\$.mp	16845	Ditto
	23	20 or 21 or 22	17138	Ditto
RCT and Coxib	24	19 and 23	5763	Ditto
Deduplicate	25	Remove duplicates from 24	5043	Dito
NSAIDS				
Naproxen		Naproxen.mp or Naproxen/	4037	With RCT strategy and limited to adults
Ibuprofen		Ibuprofen.mp or Ibuprofen/	5377	Ditto
Diclofenac		Diclofenac.mp or diclofenac/	6524	Ditto
Indomethacin		Indomethacin.mp or Indomethacin/		Ditto
Nabumetone		Nabumetone.mp or nabumetone/		Ditto
Meloxicam		Meloxicam.mp or meloxicam/		Ditto
Tiroxicam		Tiroxicam.mp or tiroxicam/		Ditto
Diffunisal		Diffunisal.mp or diflunisal/	393	Ditto
Apazone		Apazone.mp or apazone/	170	Ditto
Clonixin		Clonixin.mp or clonixin/	69	Ditto
Dipyrone		Dipyrone.mp or dipyrone/	976	Ditto
Etodolac		Etodolac.mp or etodolac/	583	Ditto
Fenoprofen		Fenoprofen.mp or fenoprofen	330	Ditto
Meclofenamic acid		Meclofenamic acid.mp or meclofenamic acid/	225	Ditto
Mefenamic acid		Mefenamic acid.mp or mefenamic acid/	585	Ditto
Oxyphenbutazone		Oxyphenbutazone.mp or oxyphenbutazone/	153	Ditto
Floctafenine		Floctafenine.mp or floctafenine/	35	Ditto
Flurbiprofen		Flurbiprofen.mp or flurbiprofen/	1301	Ditto
Isoxicam.mp		isoxicam.mp or isoxicam/	65	Ditto
Ketoprofen		Ketoprofen.mp or ketoprofen/	1771	Ditto
Ketorolac		Ketorolac.mp or ketorolac/	2167	Ditto
Loxoprofen		Loxoprofen.mp or loxoprofen/	81	Ditto
Nimesulide		Nimesulide.mp or nimesulide/	894	Ditto
Oxyprozin/oxaprozin		Oxyprozin.mp or oxyprozin/	148	Ditto
Phenylbutazone		phenylbutazone.mp. or Phenylbutazone/	691	Ditto
Piroxicam		Piroxicam.mp or piroxicam/	2117	Ditto
Sulindac		Sulindac.mp or sulindac/	1589	Ditto
Tenoxicam		Tenoxicam.mp or tenoxicam/	574	Ditto
Tiaprofenic acid		Tiaprofenic acid.mp or Tiaprofenic	238	Ditto

		acid/		
Tolmetin		Tolmetin.mp or tolmetin/	340	Ditto
CINOD				
AZD3582		AZD3582.mp or AZD 3582.mp nitronaproxen	51	Ditto
Cinod		Cinod.mp or cinods.mp	22	Ditto
Naproxcinod		Naproxcinod.mp	18	Ditto
Cyclooxygenase inhibitor-NO		Cyclooxygenase inhibitor-NO.mp or cyclooxygenase inhibitor nitric oxide.mp	0	Ditto
TOTAL			36572	

Deduplication of MEDLINE and EMBASE combined

The following options for the duplicate search were selected from the 'Duplicate Search' menu (tools, then options) in Reference Manager:

Authors, primary
Date, primary
Periodical



Other electronic searches performed:

www.clinicalstudyresults.org

WWW.CLINICALTRIAL.GOV

Details of new trials from other searches

	Clinicalstudyresults.org		CNT TRIAL NUMBER	Clinicaltrials.gov		CNT NUMBER
	No. searched	No. of new studies		No. searched	No. of new studies	
Celecoxib	86	11	836	191	1	910
			865			
			866			
			867			
			877			
			878			
			879			
			880			
			881			
			883			
			900			
Etoricoxib	16	1	890	16	2	906
						907 X1
						908 X2
Rofecoxib	16	1	889	16	1	905
Lumiracoxib	0	1	893	16	0	
Parecoxib	9	0		11	0	
Valdecoxib	20	3	862	20	0	
			863			
			864			
Total New Trials	147	17		270	4	

APPENDIX: Comparing numbers of trials, participants and vascular outcomes in the coxib versus placebo and coxib versus traditional NSAID comparisons in recent meta-analyses of randomised trials

	Kearney <i>et al.</i> BMJ 2006	Trelle <i>et al.</i> BMJ 2011	CNT Collaboration
Number of trials	138	31	246
Participants	145,000	115,000	190,000
Person-years	88,000	115,000	180,000
Any myocardial infarctions	426	554	728
Any strokes	317	377	528
Vascular death	239	312	481

APPENDIX: Comparing numbers of trials, participants and upper gastrointestinal outcomes in the coxib versus placebo and coxib versus traditional NSAID comparisons in recent meta-analyses of randomised trials

	Rostom <i>et al.</i> CGH 2007	CNT Collaboration
Number of trials	69	245
Participants	93,000	190,000
Any upper GI ulcers	800	1730*
Any upper GI complications	279	638

*Excludes symptomatic uncomplicated upper GI ulcers that occurred on the same day as an upper GI complication

APPENDIX: Comparing numbers of trials, participants and vascular outcomes in the coxib versus placebo and coxib versus traditional NSAID comparisons in recent meta-analyses

	McGettigan <i>et al.</i> CASE CONTROL	PloS Med 2011 COHORTS	CNT Collaboration RANDOMISED
Number of studies	30	21	246
Participants	189,946	2,700,000	190,000
Person-years	-	795,852	180,000
Cases	17,000	-	728

APPENDIX: Estimates of vascular outcomes in a meta-analysis of observational studies of coxibs and traditional NSAIDs

	McGettigan <i>et al.</i> PloS Med 2011 Relative risk (RR)	(95% CI)
Rofecoxib	1.45	1.33 – 1.59
Diclofenac	1.40	1.27 – 1.55
Indomethacin	1.30	1.19 – 1.41
Ibuprofen	1.19	1.11 – 1.25
Celecoxib	1.17	1.08 – 1.27
Naproxen	1.09	1.02 – 1.16

Estimated costs and utilities

Adverse effect	Symptomatic ulcer	Upper GI bleed	Myocardial infarction	Stroke	Heart failure
Cost of adverse events (£ per 3 months, 2007-8)					
Initial 3 months	640	2862	1437	2268	1770
After initial 3 months	19	19	134	435	134
Utility weights for adverse events					
Initial 3 months	0.55 (0.47 to 0.65)	0.46 (0.37 to 0.56)	0.37 (0.28 to 0.47)	0.35 (0.25 to 0.45)	0.71 (0.61 to 0.81)
After initial 3 months	0.98	0.98	0.88 (0.78 to 0.98)	0.71 (0.61 to 0.80)	0.98

Latimer et al. BMJ 2009

Estimated treatment effect/utility gain

Meta-analysis results	Mean WOMAC total score (95% CI)	Mean utility weight* (95% CI)
No treatment	25.54	0.69
Paracetamol	23.08 (21.24 to 24.91)	0.70 (0.69 to 0.71)
All coxibs and traditional NSAIDs**	18.01 (16.79 to 19.22)	0.72 (0.72 to 0.73)
*Assuming no adverse events		
**All of these therapies are considered equivalent		

Latimer et al. BMJ 2009

Estimated UK drug costs

Therapy	Dose	Drug cost (£ per 3 months, 2007/8)
No treatment	-	-
Paracetamol	3000mg	10.64
Diclofenac	100mg	4.35
Napoxen	750mg	8.58
Ibuprofen	1200mg	8.01
Celecoxib	200mg	44.97
Etoricoxib	30mg	64.65

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Guidelines: coxibs/NSAIDs

Organisation	Publication, year	Vascular	Upper GI
Asia-Pacific consensus	Champion et al. 1997	No	Yes
American consensus	Lanza 1998	No	Yes
UK Medicines & Healthcare Regulatory Agency 2005		Yes	(No)
American Heart Association	Antman et al. 2007	Yes	(No)
American College Cardiology	Bhatt et al. 2009	(Yes)	Yes
Canadian Assoc Gastro	Rostom et al. 2009	(Yes)	Yes
American College Gastro	Lanza et al. 2010	(Yes)	Yes
US Food and Drug Administration (current)		Yes	Yes
European Medicine Authority (current)		Yes	Yes

GUIDELINES

<http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice-A-F/CardiovascularsafetyofCOX-2inhibitorsandnon-selectiveNSAIDs/index.htm>

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/10/news_detail_001637.jsp&mid=WC0b01ac058004d5c1

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103420.htm>

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Figure 1: Effects of coxib therapy vs placebo, by published/unpublished data

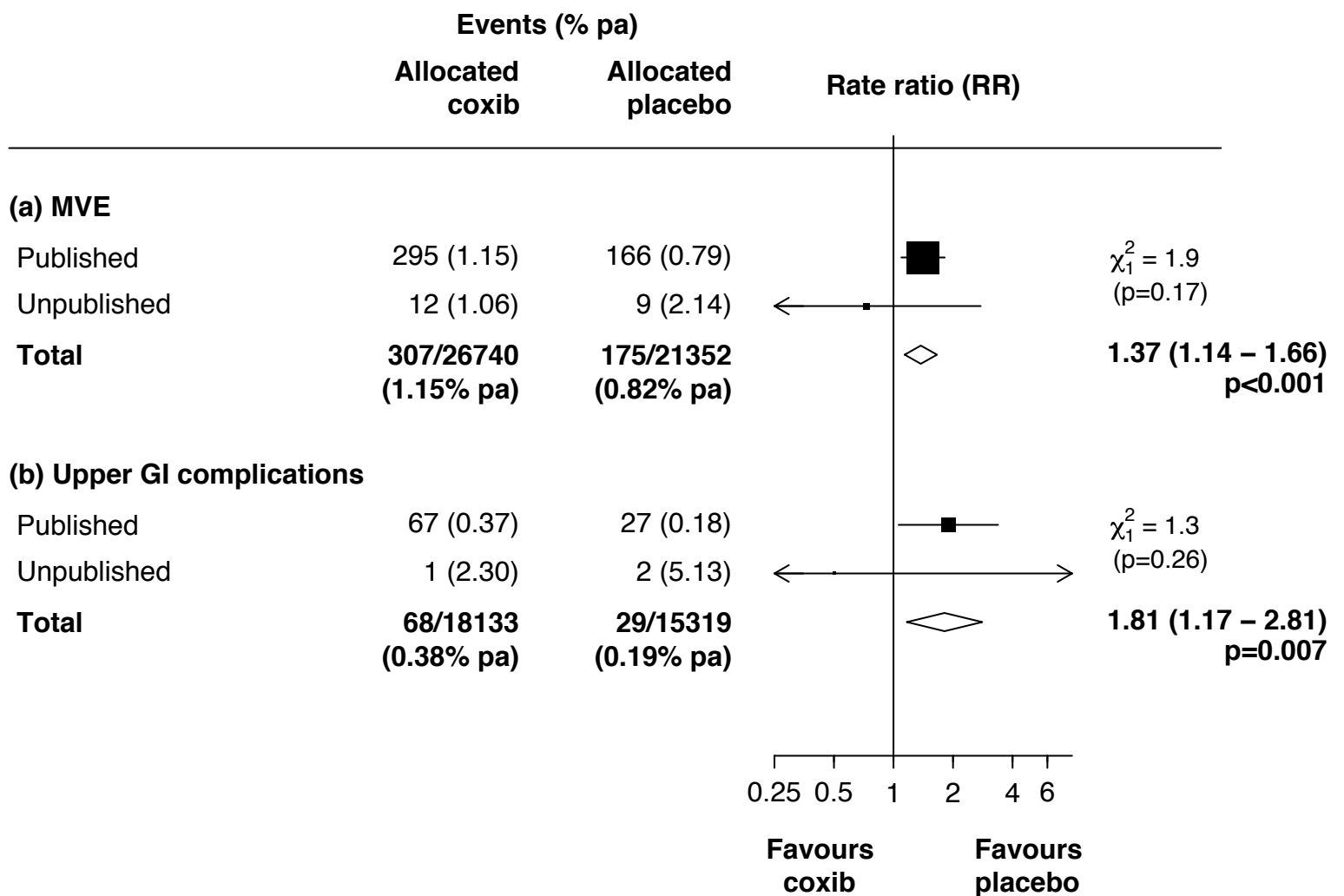


Figure 2: Effects of coxib therapy vs naproxen, by published/unpublished data

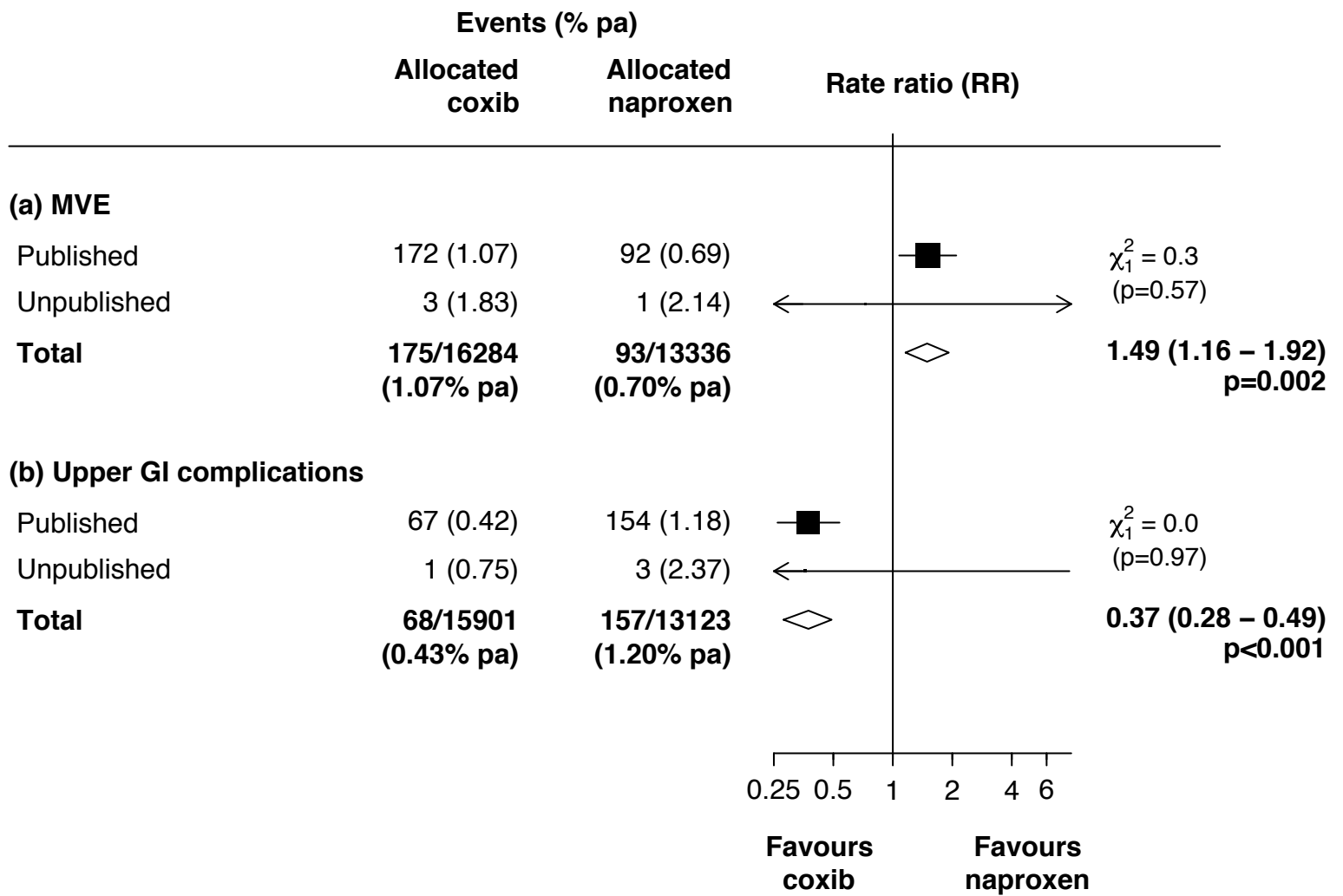
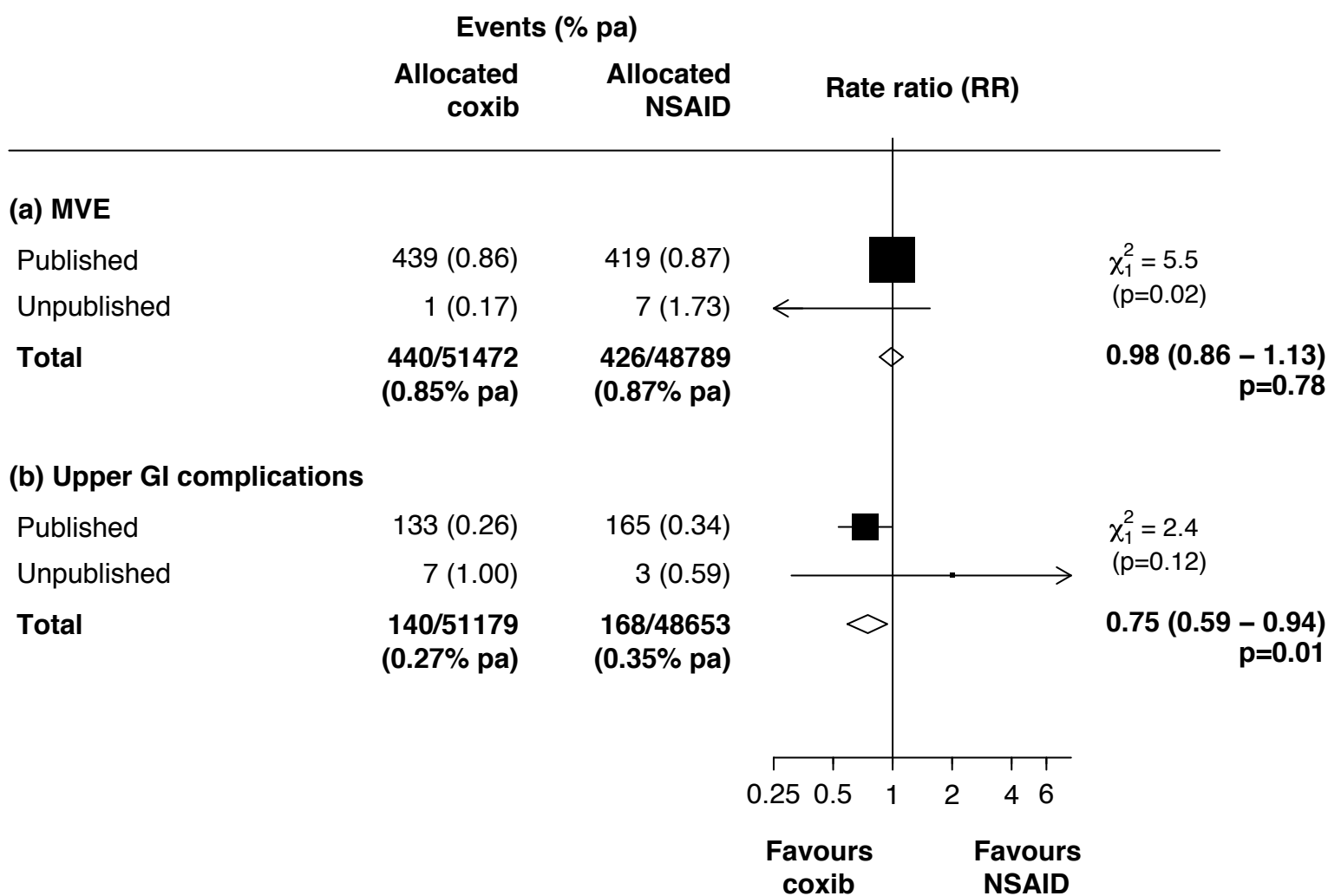


Figure 3: Effects of coxib therapy vs non-naproxen NSAIDs, by published/unpublished data



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10/10/2010

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