woven into the fabric of humanity. The UN Human Rights Council has unequivocally stated that LGBT rights are human rights.[8]

An inclusive foreign policy is gaining traction and could generate considerable health benefits. Although an inclusive foreign policy has advanced most rapidly in high-income nations where discrimination and violence are less common, 29 US states[9] and 12 European countries[2] still have laws that discriminate against homosexual individuals. Advancement of LGBT rights is about embracing health and wellness for all, irrespective of sexual orientation or gender.

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We declare that we have no conflicts of interest.

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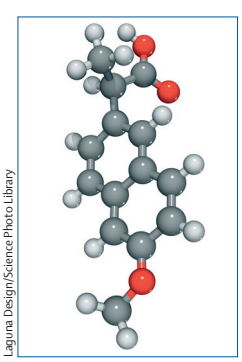
High-dose non-steroidal anti-inflammatories: painful choices



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Naproxen

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No therapeutic intervention is risk-free. However, the risk of heart attack and death associated with the use of high-dose non-steroidal anti-inflammatory drugs (NSAIDS) are probably not fully appreciated by many patients using these drugs. In *The Lancet*, Colin Baigent and colleagues[1] from the Coxib and traditional NSAID Trialists' (CNT) Collaboration have used meta-analyses to assess the vascular and gastrointestinal effects of NSAIDs, including selective COX-2 inhibitors (coxibs) and traditional NSAIDs. Their findings should facilitate informed individual decision making about the use of NSAIDs for chronic painful conditions.

The authors assembled over 600 clinical trials that included more than 300 000 participants, and used direct and indirect meta-analytic techniques to add certainty and precision to estimates of NSAID-associated vascular and gastrointestinal adverse events.[1] Their results indicate that high doses of all coxibs, diclofenac, and ibuprofen increase the risk of major vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death), and that high-dose naproxen is not associated with either an increased risk or significant aspirin-like protection for these outcomes. However, all NSAIDs (both coxibs and traditional NSAIDs, including naproxen) double the risk of congestive heart failure, and increase the risk of peptic ulcer complications and other gastrointestinal bleeding. Less information was available on other NSAIDs, but there is no evidence that there are any with a safer risk profile than the more studied drugs.

Clinical trials are not the whole story. Indeed, observational studies often identify and quantify important safety concerns missed by clinical trials of short duration, done in select and small populations. An early pooled analysis of observational studies of NSAIDs and gastrointestinal complications[2] yielded more clinically useful information than a contemporaneous meta-analysis of clinical trials.[3] The increased risk of major cardiovascular events with rofecoxib compared with naproxen in a large randomised safety trial[4] was interpreted optimistically as due to naproxen's antiplatelet effects.[5] However, laboratory studies offered biological plausibility for the adverse vascular effects of coxibs[6] and several observational studies supported concerns about rofecoxib[7,8] well before publication of confirmatory clinical trials.

Observational studies can also help fill knowledge gaps left by clinical trials. Baigent and colleagues' meta-analysis offers considerable certainty about relative and absolute major vascular risks of high doses of the most commonly prescribed NSAIDs, but leaves large gaps about risks associated with lower NSAID

doses, longer durations of use, and residual effects after stopping treatment. Although the CNT collaborators raised concerns about inherent biases of observational studies, concerns about unmeasured differences between drug users and comparator non-users in observational analyses can be addressed in part by using a comparator drug with a similar indication, by comparing current with recent and past use, and by sensitivity analyses that assess the effect that unmeasured confounders might have on study results.[9]

McGettigan and Henry[10] reviewed 51 observational studies, which included more than 2·7 million NSAID users. Low doses of rofecoxib, celecoxib, and diclofenac increased the risk of major vascular events by 20–30%, and risk increased with higher doses. Vascular risk with ibuprofen was confined to higher doses and naproxen was risk-neutral at low as well as high doses. In both clinical trials and observational studies, risk was evident quickly after drug initiation. Observational studies have also shown that risk does not wane over years of use, but falls quickly after drug cessation.[11] Likewise, adverse gastrointestinal effects are confined almost exclusively to current use.[12]

For 1000 patients at moderate risk of heart disease, one would expect about three major vascular events, including one death, due to a year of high-dose NSAIDs (except naproxen). For 1000 patients at moderate risk of gastrointestinal complications, a year of high-dose NSAIDs would result in four to 16 gastrointestinal complications. These risks translate to a high drug-related burden of morbidity and mortality in populations where NSAID use is common. Individuals taking NSAIDs, especially at high doses, incur substantial risk when drug use persists for extended periods. Someone at moderate risk for both outcomes would have a 4–19% chance of a treatment-related vascular or gastrointestinal complication over 10 years of high-dose NSAID use.

Although naproxen seems a good choice for patients at high risk of cardiovascular disease, the concomitant use of antiplatelet agents or warfarin greatly increases bleeding risks, which can be only partially prevented by adding a proton-pump inhibitor. Low-dose ibuprofen seems to be fairly safe for both cardiovascular and gastrointestinal complications, but higher doses greatly increase the risk of both outcomes.

Unfortunately, older adults at high risk of many NSAID-associated adverse effects comprise a substantial portion of people with chronic pain. For those at high risk of heart failure or with chronic kidney disease, NSAIDs are generally avoided. Opioids are an option for some patients; however, these drugs also have serious risks and, like NSAIDs, evidence for their efficacy in chronic pain is sparse.[13,14] No available NSAID improves arthritis or prevents progression of painful conditions. Providers should offer patients evidence-based non-pharmacological treatments (eg, application of heat or cold, exercise, weight loss, or self-management programmes), NSAID and non-NSAID topical treatments, and NSAID regimens that minimise risk (low-risk agents, at low dose, or of short duration).[13,15] Identification of safe and effective strategies for chronic pain is sorely needed.[16] In the meantime, long-term use of high-dose NSAIDs should be reserved for those who receive considerable symptomatic benefit from the treatment and understand the risks.

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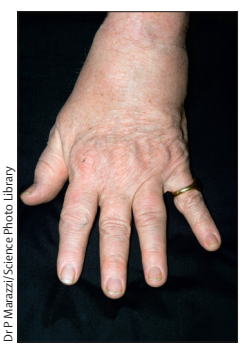
Ustekinumab for psoriatic arthritis: close to the PSUMMIT?



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Psoriatic arthritis

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Psoriasis is a debilitating immune-mediated inflammatory disease complicated, in roughly 20% of cases, by a seronegative arthritis known as psoriatic arthritis. The burden of disease is pronounced for patients with psoriasis and is compounded by coexisting arthritis. Environmental interactions in genetically susceptible individuals underlie the development of both psoriasis and psoriatic arthritis. Genetic overlap between the disorders is great, as evidenced by data from genome-wide association scans,[1] which have identified shared susceptibility loci, including single nucleotide polymorphisms in interleukins 12 and 23.[2,3] However, attempts to explore the factors that underpin the development of psoriatic arthritis have proved difficult because detailed phenotyping of both skin and joint disease is rarely done in studies.

For many years, psoriatic arthritis has been neglected relative to rheumatoid arthritis, and treatment algorithms based on robust evidence specifically from clinical trials of psoriatic arthritis are few. Thus, studies such as that by Iain McInnes and colleagues[4] in *The Lancet* are welcome. McInnes and colleagues present the 52 week data from a phase 3, randomised, double-blind, placebo-controlled trial[1] of ustekinumab in patients with active psoriatic arthritis—the PSUMMIT 1 trial. Ustekinumab, a human monoclonal antibody, inhibits the p40 subunit common to interleukins 12 and 23 and is highly effective for treatment of moderate-to-severe psoriasis.[5,6] Immunological investigations have also shown the importance of T-helper-17 (Th17) cells (inhibited by interleukin 23) in the immunopathogenesis of both psoriasis and psoriatic arthritis.[7] The efficacy of ustekinumab might also be related to the effects of interleukin 12 on T-helper-1 (Th1) cells. Phase 2 data showed that ustekinumab was efficacious in treatment of psoriatic arthritis.[8]

In PSUMMIT 1, 615 patients with active psoriatic arthritis (ie, ≥5 of 66 joints swollen, ≥5 of 68 joints tender, C-reactive protein ≥3·0 mg/L) despite 3 months or more of disease-modifying antirheumatic treatment or 4 weeks or more of non-steroidal anti-inflammatory drugs, or both, were randomly assigned to 45 mg ustekinumab, 90 mg ustekinumab, or placebo at baseline, week 4, and every 12 weeks thereafter. At week 16, patients with less than 5% improvement from baseline in both tender and swollen joint counts entered masked early escape—ie, patients receiving placebo switched to 45 mg ustekinumab and those receiving 45 mg ustekinumab switched to 90 mg ustekinumab; patients already receiving 90 mg ustekinumab continued their masked dose regimen. The primary endpoint was the proportion of patients with at least a 20% improvement in the American College of Rheumatology (ACR) response criteria at week 24.

More patients in the ustekinumab groups (87 of 205 [42·4%] in the 45 mg group and 101 of 204 [49·5%] in the 90 mg group) than in the placebo group (47 of 206 [22·8%]) achieved 20% improvements in the ACR criteria at week 24 ($p<0·0001$ for both comparisons). Response rates after 24 weeks improved further, but this part of the trial was not placebo controlled. Significant benefits were also noted with ustekinumab relative to placebo in terms of 50% and 70% responses to the ACR response criteria, quality-of-life indices, and skin indices. Ustekinumab was generally well tolerated, although three major adverse cardiovascular events—specifically, myocardial infarction at 8 weeks and 22 weeks, and stroke at 29 weeks after initiation of ustekinumab—were noted. A possible link between major adverse cardiovascular events and interleukin 12/23 blockers, especially in the first 12 weeks of treatment, is much debated in the dermatology specialty,[9] but interpretation

Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

*Coxib and traditional NSAID Trialists' (CNT) Collaboration**

Summary

Background The vascular and gastrointestinal effects of non-steroidal anti-inflammatory drugs (NSAIDs), including selective COX-2 inhibitors (coxibs) and traditional non-steroidal anti-inflammatory drugs (tNSAIDs), are not well characterised, particularly in patients at increased risk of vascular disease. We aimed to provide such information through meta-analyses of randomised trials.

Methods We undertook meta-analyses of 280 trials of NSAIDs versus placebo (124 513 participants, 68 342 person-years) and 474 trials of one NSAID versus another NSAID (229 296 participants, 165 456 person-years). The main outcomes were major vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death); major coronary events (non-fatal myocardial infarction or coronary death); stroke; mortality; heart failure; and upper gastrointestinal complications (perforation, obstruction, or bleed).

Findings Major vascular events were increased by about a third by a coxib (rate ratio [RR] 1·37, 95% CI 1·14–1·66; p=0·0009) or diclofenac (1·41, 1·12–1·78; p=0·0036), chiefly due to an increase in major coronary events (coxibs 1·76, 1·31–2·37; p=0·0001; diclofenac 1·70, 1·19–2·41; p=0·0032). Ibuprofen also significantly increased major coronary events (2·22, 1·10–4·48; p=0·0253), but not major vascular events (1·44, 0·89–2·33). Compared with placebo, of 1000 patients allocated to a coxib or diclofenac for a year, three more had major vascular events, one of which was fatal. Naproxen did not significantly increase major vascular events (0·93, 0·69–1·27). Vascular death was increased significantly by coxibs (1·58, 99% CI 1·00–2·49; p=0·0103) and diclofenac (1·65, 0·95–2·85, p=0·0187), non-significantly by ibuprofen (1·90, 0·56–6·41; p=0·17), but not by naproxen (1·08, 0·48–2·47, p=0·80). The proportional effects on major vascular events were independent of baseline characteristics, including vascular risk. Heart failure risk was roughly doubled by all NSAIDs. All NSAID regimens increased upper gastrointestinal complications (coxibs 1·81, 1·17–2·81, p=0·0070; diclofenac 1·89, 1·16–3·09, p=0·0106; ibuprofen 3·97, 2·22–7·10, p<0·0001; and naproxen 4·22, 2·71–6·56, p<0·0001).

Interpretation The vascular risks of high-dose diclofenac, and possibly ibuprofen, are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk than other NSAIDs. Although NSAIDs increase vascular and gastrointestinal risks, the size of these risks can be predicted, which could help guide clinical decision making.

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*Collaborators are listed at the end of the report

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs in the world. They are chiefly used to treat pain, but their long-term use is limited by serious gastrointestinal side-effects. NSAIDs inhibit the two recognised forms of prostaglandin G/H synthase (also referred to as cyclo-oxygenase [COX]), namely COX-1 and COX-2.[1] Since the analgesic and anti-inflammatory effects of NSAIDs are mediated by inhibition of COX-2, and their gastrointestinal side effects mostly by inhibition of COX-1, NSAIDs which selectively inhibit COX-2 might reduce the risk of gastrointestinal toxicity compared with other NSAIDs. Several such COX-2 selective drugs (collectively known as coxibs) were developed in the 1990s, and early trials comparing coxibs versus traditional NSAIDs (tNSAIDS) seemed to confirm that coxibs at doses with similar analgesic efficacy had less gastrointestinal toxicity.[2,3] Unfortunately, however, subsequent placebo-controlled trials also showed unequivocally that coxibs were associated with an increased risk of atherothrombotic vascular events.[4,5]

Soon after these placebo-controlled trials were reported, a meta-analysis of randomised trials comparing a coxib versus placebo or a coxib versus tNSAID indicated that some tNSAIDs might also have adverse effects on atherothrombotic events, but that these hazards might depend on the degree and duration of suppression of platelet COX-1.[6] In these analyses, high-dose naproxen (generally 500 mg twice a day), which is alone among NSAID regimens in being able to induce near-complete suppression of platelet thromboxane biosynthesis throughout the 12-h dosing interval in some individuals,[7] did not seem to increase the risk of atherothrombosis, but other high-dose tNSAID regimens with only transient effects on platelet COX-1 were associated with a small, but definite, vascular hazard.[6]

Similar findings have emerged in non-randomised observational studies of NSAIDs.[8,9] The US Food and Drug Administration requires that the summaries of product characteristics of all NSAIDs carry a boxed warning about the risks of cardiovascular disease,[10] whereas the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) decided that coxibs (but not tNSAIDs[11]) should be contraindicated in patients with coronary heart disease or stroke, and used with caution in patients with risk factors for coronary heart disease.[12] Because randomised trials avoid selection bias, they could provide more reliable estimates of the size, timing, and severity of any moderate cardiovascular hazards of NSAID regimens than observational studies (which are better suited to detecting large effects). Accordingly, we initiated a collaborative meta-analysis of individual participant data (or, if not available, tabular data) from randomised trials of NSAIDs (the Coxib and traditional NSAID Trialists' [CNT] Collaboration). The main objective was to characterise and quantify the cardiovascular and gastrointestinal risks of particular NSAID regimens among different types of patients, particularly those at increased risk of vascular disease.

Methods

For **details of our study methods** see http://www.ctsu.ox.ac.uk/research/meta-trials/cnt

See Online for appendix

Identification of trials and eligibility assessment

Searches of Medline and EMBASE were done using the Cochrane strategy[13] (see appendix p 27 for details of search terms), with searches up to January, 2009, supplemented by subsequent periodic scrutiny of clinical trial registers (including www.clinicaltrials.gov and www.clinicaltrialresults.org), review of reference lists of relevant papers, and enquiry among collaborators and pharmaceutical companies. For the present analyses, trials with results available prior to January, 2011, were eligible if they were properly randomised (ie, they used a randomisation method with robust allocation concealment), of at least 4 weeks duration, and: involved a comparison of an NSAID versus placebo (or open control) or one NSAID regimen versus another NSAID regimen; and no other systematic differences in drug treatment between treatment arms were planned. All trials were reviewed for eligibility by two authors and information on key trial characteristics, including information pertaining to the risk of bias (method of randomisation, treatment masking, and publication status) were extracted and recorded. The secretariat sought individual participant data (or, where not available, aggregate data) from all eligible trials. Aggregate data in a standard format were either provided by trialists or, more commonly, data fields were extracted from publications and checked by at least two authors. Four companies agreed to provide individual participant data from published and unpublished trials, including those involving celecoxib (Pfizer), rofecoxib or etoricoxib (Merck), lumiracoxib (Novartis), and GW403681 (GlaxoSmithKline). Individual participant data from trials of valdecoxib (Pfizer) were requested but not provided, although aggregate data from these trials were included in our analyses. The US National Cancer Institute and the European Organisation for Research and Treatment of Cancer also provided individual participant data from any trials of NSAIDs they had sponsored.

Prespecified analyses

Intention-to-treat analyses of first events during the scheduled treatment periods were planned. Wherever available, adjudicated outcomes were used, but in a few trials only un-adjudicated outcomes based on standard Medical Dictionary of Regulatory Authorities (MedDRA) codes were available. The primary vascular outcome was major vascular events, defined as non-fatal myocardial infarction, non-fatal stroke, or death from a vascular cause; subsidiary vascular outcomes included major coronary events (non-fatal myocardial infarction or death from coronary disease); stroke (subdivided into haemorrhagic, ischaemic, or unknown types), and hospitalisation for heart failure. Deaths were subdivided into vascular, non-vascular, and unknown causes. The primary gastrointestinal outcome was upper gastrointestinal complications, defined as an upper gastrointestinal perforation, obstruction, or bleed. For subgroup analyses of the effects of NSAIDs or for defining ulcer risk categories, we used symptomatic upper gastrointestinal events, defined as a symptomatic ulcer or upper gastrointestinal complication, to supplement statistical power.

Statistical analysis

Meta-analyses of each comparison were done using standard logrank methods where individual patient data were available, or standard methods for 2×2 contingency tables otherwise.[14,15] For each trial, the observed minus expected statistic (o−e) and its variance (v) were calculated. These (o−e) values, one from each trial, were summed to produce a grand total (G), with variance (V) equal to the sum of their separate variances. The one-step estimate of the log of the event rate ratio is G/V. The χ^2_{n-1} statistic for heterogeneity between the effects in n different trials is $S-(G^2/V)$, where S is the sum over all the trials of $[o-e]^2/v$. To help allow for multiple subdivisions of the data, only summary rate ratios (indicated by open diamonds in figures) have 95% CI; all other rate ratios have 99% CIs. Rate ratios in different subgroups were compared by standard χ^2 tests for heterogeneity or, where the subgroups could be arranged in some meaningful order (eg, by dose), χ^2 tests for trend.

Rate ratios for the comparison tNSAID versus placebo were obtained by combining estimates obtained directly (from the small number of trials including such a comparison) with estimates obtained indirectly (from a comparison of trials of coxib *vs* tNSAID with trials of coxib *vs* placebo). For the calculation of indirect estimates of rate ratios for a tNSAID versus placebo, we used the following method.[16] Let A be the set of trials involving a direct randomised comparison of a coxib

versus placebo (but not also including the tNSAID of interest as a third group) and B the set of trials involving a direct randomised comparison of a coxib versus the tNSAID of interest (but not also including placebo as a third group). From A, we calculated the average log event rate ratio G_A/V_A for coxib versus placebo and, from B, the average log event rate ratio G_B/V_B for coxib versus tNSAID. These two results are independent of one another because A and B are non-overlapping sets of trials, so (subject to certain regularity assumptions) the log event rate ratio for tNSAID vs placebo can then be estimated indirectly by $G_A/V_A - G_B/V_B$ (with variance

	Data available			No data available*	Total
	IPD provided	Tabular data only	Total data available		
Coxib *vs* placebo					
Number of trials	113	71	184	6	190
Number of participants	73 635 (83%)	14 732 (17%)	88 367 (>99%)	238 (<1%)	88 605
Person-years†	46 407 (88%)	6 059 (12%)	52 466 (>99%)	164 (<1%)	52 630
Number of major vascular events (number of upper gastrointestinal complications)	436 (91)	46 (6)	482 (97)	..	..
tNSAID *vs* placebo					
Number of trials	47	111	158	30	188
Number of participants	18 018 (43%)	20 063 (48%)	38 081 (91%)	3756 (9%)	41 837
Person-years†	8253 (49%)	7964 (47%)	16 217 (96%)	700 (4%)	16 917
Number of major vascular events (number of upper gastrointestinal complications)	45 (34)	25 (26)	70 (60)	..	..
Coxib *vs* tNSAID					
Diclofenac					
Number of trials	27	6	33	2	35
Number of participants	58 891 (95%)	2681 (4%)	61 572 (>99%)	240 (<1%)	61 812
Person-years†	89 311 (99%)	1333 (1%)	90 644 (>99%)	21 (<1%)	90 665
Number of major vascular events (number of upper gastrointestinal complications)	762 (211)	11 (11)	773 (222)	..	..
Ibuprofen					
Number of trials	20	2	22	0	22
Number of participants	21 398 (96%)	827 (4%)	22 225 (100%)	0	22 225
Person-years†	11 508 (99%)	160 (1%)	11 668 (100%)	0	11 668
Number of major vascular events (number of upper gastrointestinal complications)	81 (82)	2 (0)	83 (82)	..	..
Naproxen					
Number of trials	34	14	48	1	49
Number of participants	42 222 (87%)	6484 (13%)	48 706 (>99%)	66 (<1%)	48 772
Person-years†	30 040 (95%)	1591 (5%)	31 631 (>99%)	20 (<1%)	31 651
Number of major vascular events (number of upper gastrointestinal complications)	254 (213)	14 (12)	268 (225)	..	..
Any tNSAID *vs* any other tNSAID					
Number of trials	1	334	335	49	384
Number of participants	733 (1%)	67 774 (89%)	68 507 (90%)	7247 (10%)	75 754
Person-years†	134 (1%)	22 284 (94%)	22 418 (94%)	1323 (6%)	23 741
Number of major vascular events (number of upper gastrointestinal complications)	3 (0)	21 (105)	24 (105)	..	..
Coxib *vs* other coxib					
Number of trials	32	3	35	0	35
Number of participants	25 442 (98%)	489 (2%)	25 931 (100%)	0	25 931
Person-years†	9033 (99%)	60 (1%)	9093 (100%)	0	9093
Number of major vascular events (number of upper gastrointestinal complications)	59 (19)	1 (0)	60 (19)	..	..

IPD=individual participant data. tNSAIDS=traditional non-steroidal anti-inflammatory drugs. *There were also seven trials involving a comparison of a coxib versus placebo, seven trials involving a comparison of a tNSAID versus placebo, one trial involving a comparison of a coxib versus ibuprofen, four trials involving a comparison of two different tNSAIDs, and one trial involving a comparison of two different coxibs for which the number of randomised patients was unknown. †Person-years for mortality.

Table: **Availability of data for analyses**

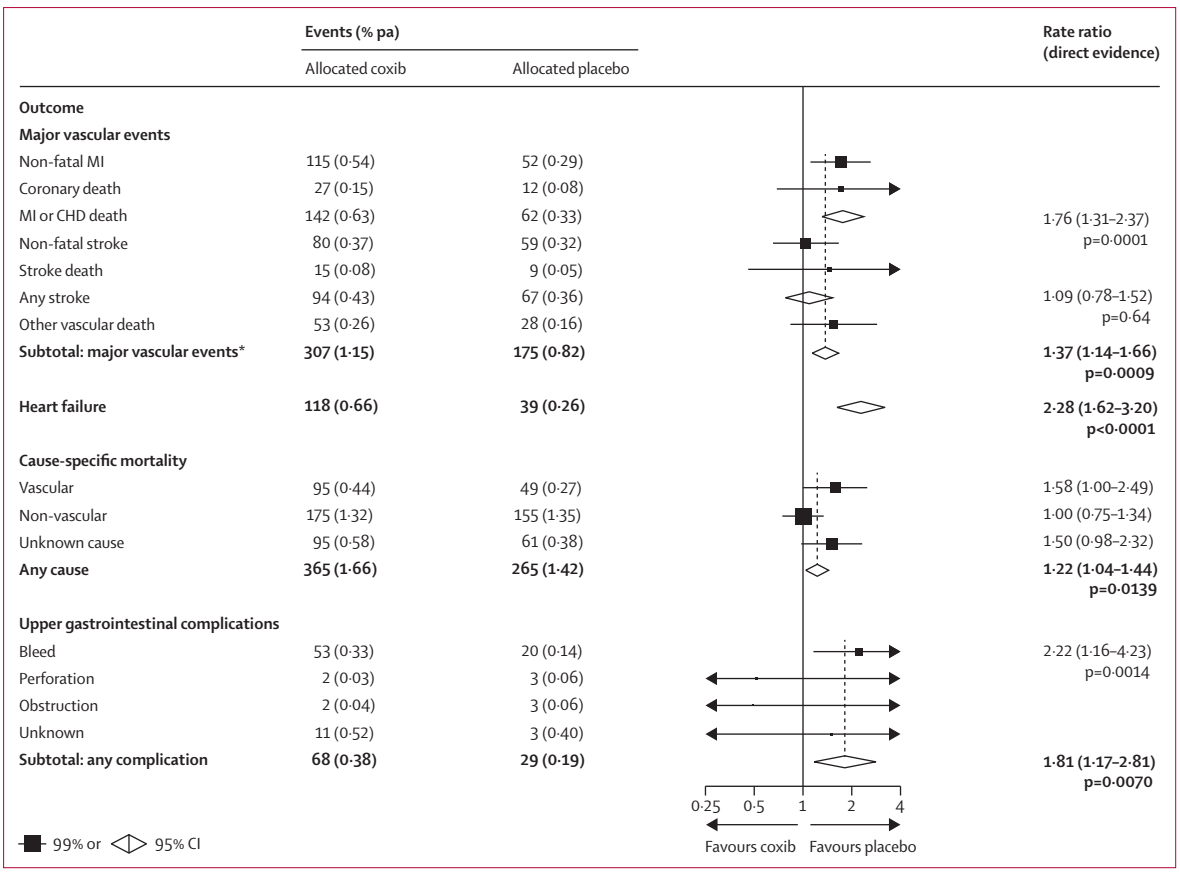

Figure 1: **Effects of coxib therapy on major vascular events, heart failure, cause-specific mortality, and upper gastrointestinal complications**
Actual numbers for participants are presented, together with the corresponding mean yearly event rate (in parentheses). Participants can contribute only once to the total of major vascular events. Rate ratios (RRs) for all outcomes are indicated by squares and their 99% CIs by horizontal lines. Subtotals and their 95% CIs are represented by diamonds. Squares or diamonds to the left of the solid line indicate benefit. MI=myocardial infarction. CHD=coronary heart disease. Major vascular event=myocardial infarction, stroke, or vascular death. *Includes a further 25 *vs* 21 major vascular events in patients randomised into trials for which only tabular information was available.

$1/V_A + 1/V_B$). The overall (combined) estimate of the effect of tNSAID versus placebo was calculated as the inverse variance weighted average of the direct and indirect estimates.

For each comparison, we assessed heterogeneity of treatment effect in subgroups defined by: demographic features (eg, age, sex); past medical history; physical measurements (eg, blood pressure); concomitant treatments at baseline (eg, aspirin); and 5-year predicted risks of major vascular events (low [<5%], intermediate [5–10%], or high [>10%]) or of symptomatic upper gastrointestinal events (low [<5%], intermediate [5–10%], or high [>10%]). The predicted risks of each of the primary outcomes were modelled using Poisson regression, following a method described previously (appendix p28).[17] Bonferroni corrections were applied for tests of heterogeneity to allow for multiple comparisons.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We found 24 278 titles and abstracts, from which we identified 639 randomised trials for analysis (appendix p 4). The main NSAID regimens contributing information on major vascular events, and their key pharmacological properties, are shown in the appendix (p 1). Data from comparisons of coxib versus placebo were available in 184 trials (88 367 participants, 52 466 person-years), and coxib versus tNSAID in 113 trials (diclofenac in 33 trials, 61 572 participants, 90 644 person-years; ibuprofen in 22 trials, 22 225 participants, 11 668 person-years; naproxen in 48 trials, 48 706 participants, 31 631 person-years; and another tNSAID in 14 trials, 6192 participants, 928 person-years; table). Almost all (roughly 99%) of primary outcomes occurred in trials involving a coxib or high-dose tNSAID (diclofenac 150 mg daily, ibuprofen 2400 mg daily, or naproxen 1000 mg daily), and most such trials provided individual participant data (table).

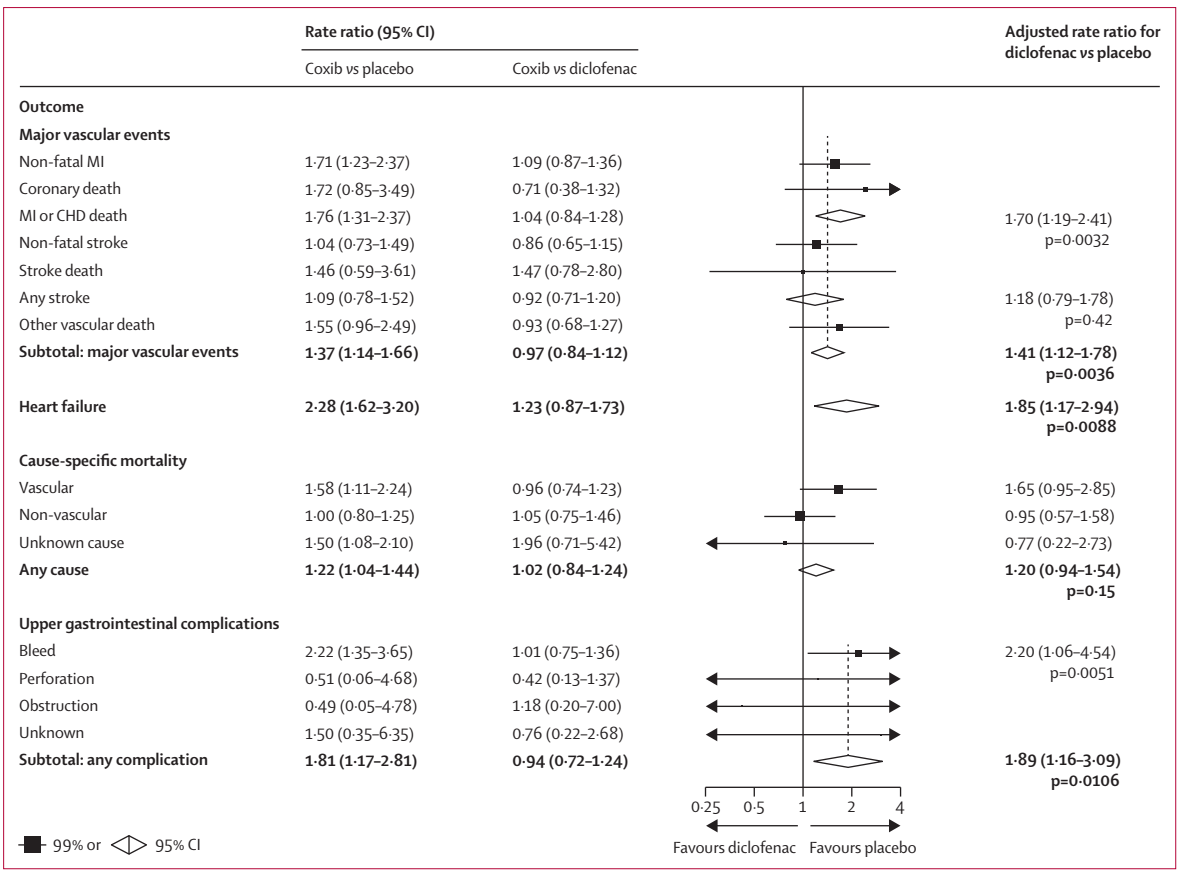

Figure 2: **Effects of diclofenac on major vascular events, heart failure, cause-specific mortality, and upper gastrointestinal complications (indirect comparisons)**
Rate ratios (RRs) are for comparisons of a tNSAID versus placebo, calculated indirectly from ratio of RRs for a coxib versus placebo and RRs for a coxib versus tNSAID, each of which is shown in the vertical columns (see statistical methods). MI=myocardial infarction. CHD=coronary heart disease.

In trials providing individual participant data, the mean age at randomisation was 61 years, about two-thirds were female, and 79% were white (appendix p 2). Few patients had a history of atherosclerosis (9%), of diabetes (9%), or of upper gastrointestinal peptic ulcer (7%). Mean body-mass index was 29 kg/m², blood pressure was 132/79 mm Hg, haemoglobin 137 g/L, creatinine 79 μmol/L, and total cholesterol 5·3 mmol/L. About a fifth of participants reported using aspirin at randomisation, 17% a proton-pump inhibitor, and 13% were current smokers. Overall, the indication for treatment with an NSAID was rheumatoid arthritis or osteoarthritis in around four-fifths of participants, but in trials of a coxib versus placebo the indication was the prevention of colorectal adenomata or of Alzheimer's disease in around a quarter of participants.

Compared with placebo (or, in a few cases, allocation to no NSAID treatment), the risk of major vascular events was increased by about a third in those allocated to a coxib (307 [1·15% per annum] coxib *vs* 175 [0·82% per annum] placebo; rate ratio [RR] 1·37, 95% CI 1·14–1·66, p=0·0009) or diclofenac (1·41, 1·12–1·78, p=0·0036), chiefly due to an increase of about three-quarters in the risk of major coronary events (coxibs 1·76, 1·31–2·37, p=0·0001; diclofenac 1·70, 1·19–2·41, p=0·0032; figures 1, 2). Ibuprofen also significantly increased major coronary events (2·22, 1·10–4·48, p=0·0253), but not major vascular events (1·44, 0·89–2·33, p=0·14; figure 3). By contrast with other tNSAIDs (heterogeneity p=0·04), high-dose naproxen was not associated with any significant excess risk of major vascular events (0·93, 0·69–1·27; figure 4), and nor was there an increase in major coronary events (0·84, 0·52–1·35). There was no evidence that any NSAID significantly increased the risk of stroke (figures 1–4).

The risk of hospitalisation due to heart failure was roughly doubled by all NSAID regimens studied (coxib 2·28, 95% CI 1·62–3·20, p<0·0001; diclofenac 1·85, 1·17–2·94, p=0·0088; ibuprofen 2·49, 1·19–5·20, p=0·0155; naproxen 1·87, 1·10–3·16, p=0·0197; figures 1–4).

The risk of vascular death was significantly increased by coxibs (1·58, 99% CI 1·00–2·49, p=0·0103) and diclofenac (1·65, 0·95–2·85, p=0·0187), non-significantly increased by ibuprofen (1·90, 0·56–6·41, p=0·17), but not increased by naproxen (1·08, 0·48–2·47, p=0·80; figures 1–4). The risk of death from any cause was

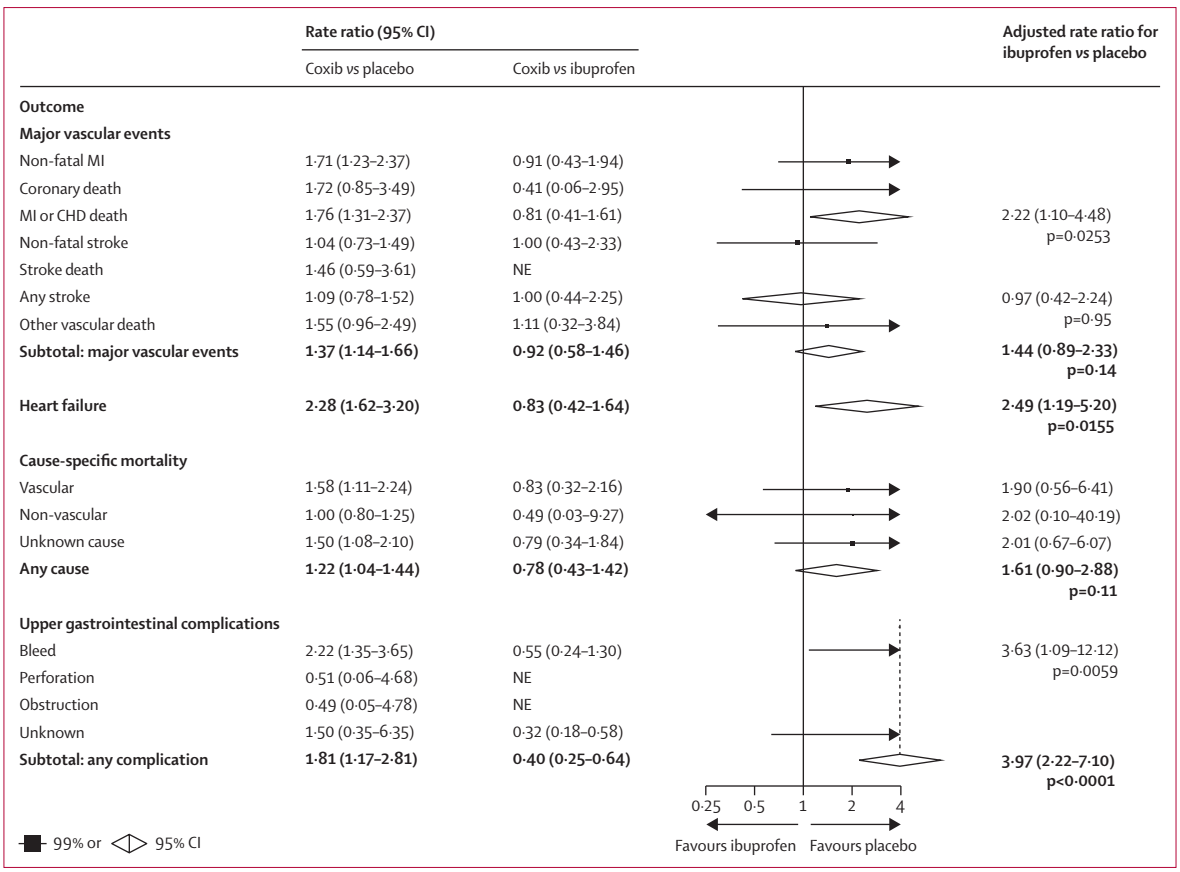

Figure 3: **Effects of ibuprofen on major vascular events, heart failure, cause-specific mortality, and upper gastrointestinal complications (indirect comparisons)**
MI=myocardial infarction. CHD=coronary heart disease. NE=not estimated.

significantly increased by around a quarter by allocation to a coxib (1·22, 1·04–1·44, p=0·0139), but despite a clear excess of vascular deaths the corresponding excess was not significant for diclofenac (1·20, 0·94–1·54, p=0·15), and nor were there significant excesses of death from any cause for ibuprofen (1·61, 0·90–2·88, p=0·11) or naproxen (1·03, 0·71–1·49, p=0·88).

Compared with placebo, there was an increased risk of upper gastrointestinal complications (most of which were bleeds) in association with allocation to a coxib (68 [0·38% per annum] coxib *vs* 29 [0·19% per annum] placebo; 1·81, 1·17–2·81, p=0·0070), diclofenac (1·89, 1·16–3·09, p=0·0106), ibuprofen (3·97, 2·22–7·10, p<0·0001), and naproxen (4·22, 2·71–6·56, p<0·0001; appendix p 3 and figures 1–4). Only 2% of upper gastrointestinal complications were recorded as being fatal.

There was very little power to assess variation in treatment effects on major vascular events or on symptomatic upper gastrointestinal events in patient subgroups; however, for each of the main categories of NSAIDs studied, after allowance for multiple comparisons, the proportional effects on each specific outcome seemed similar in different types of patients, including those at low, intermediate, and high risk of major vascular events and those at differing risk of symptomatic upper gastrointestinal events (Bonferroni-adjusted heterogeneity p values all >0·1; appendix pp 5–14).

There was only limited evidence for an increased risk of major vascular events during the first 6 months for coxibs (p=0·06) and diclofenac (p=0·0329), and no evidence that any proportional excess increased with greater exposure to treatment (p values all non-significant; appendix p 15). For symptomatic upper gastrointestinal ulcers, however, a more definite pattern of excess within the first 6 months was seen for coxibs (2·55, 99% CI 1·49–4·35), diclofenac (3·93, 2·16–7·13), ibuprofen (5·73, 3·24–10·14), and naproxen (6·31, 3·81–10·44; appendix p 16).

Overall, celecoxib and rofecoxib significantly increased the risks of major vascular events (celecoxib 1·36, 95% CI 1·00–1·84; rofecoxib 1·38, 1·07–1·80; appendix pp 17, 18). There was a smaller proportional excess risk of major vascular events with lower celecoxib doses in placebo-controlled trials (p for trend=0·0117; appendix p 18). Etoricoxib had not been extensively studied in placebo-controlled trials (appendix p 17), but the effects of etoricoxib, rofecoxib, and celecoxib seemed similar (heterogeneity p=0·21; appendix p 19) in trials of a coxib

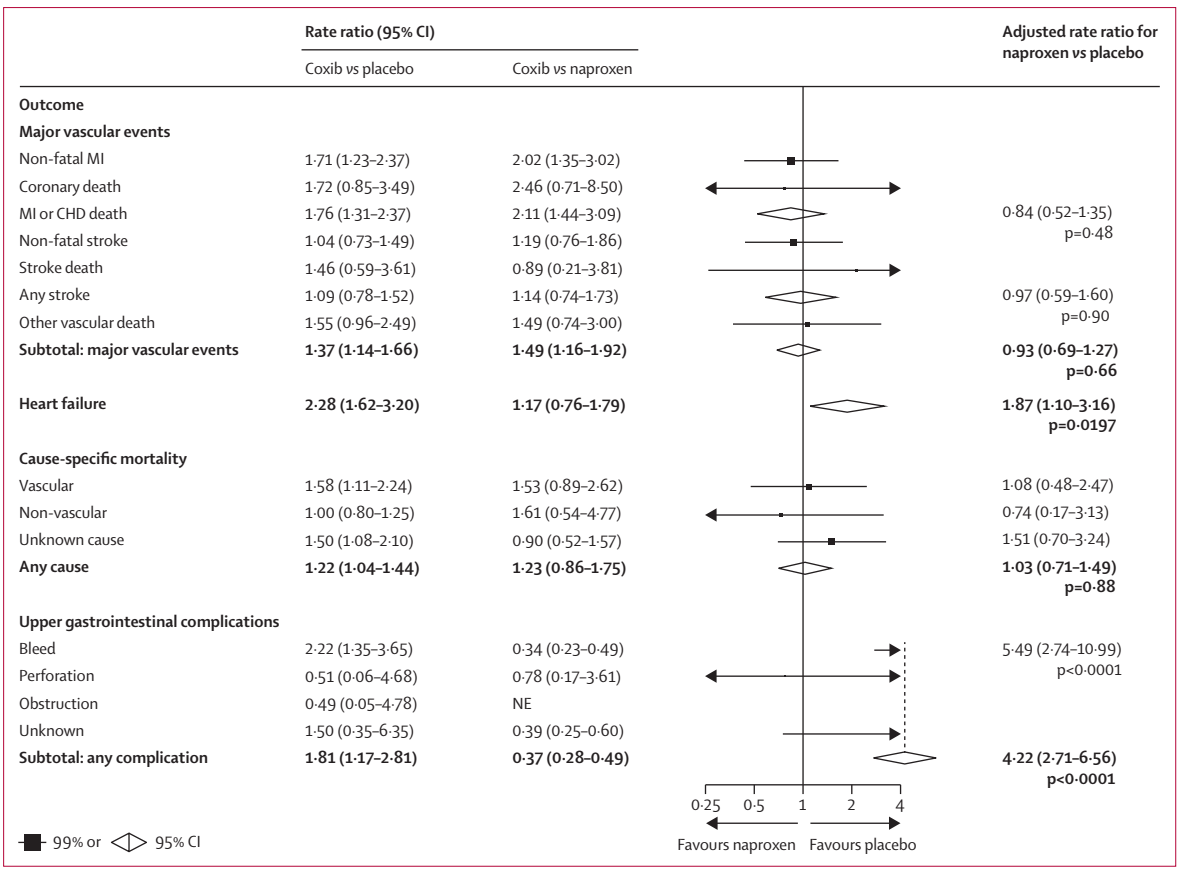

Figure 4: **Effects of naproxen on major vascular events, heart failure, cause-specific mortality, and upper gastrointestinal complications (indirect comparisons)**
MI=myocardial infarction. CHD=coronary heart disease.

versus diclofenac (where the same diclofenac regimen was used in each trial). Similarly, trials of lumiracoxib versus placebo provided little useful information, whereas trials of lumiracoxib versus ibuprofen or lumiracoxib versus naproxen (1000 mg in seven trials, 440 mg in one trial) were consistent with the vascular risks of lumiracoxib being similar to other coxibs (Bonferroni-adjusted heterogeneity p values all >0·1; appendix pp 20, 21).

In comparable analyses of symptomatic upper gastrointestinal events, there was also a lack of evidence of heterogeneity between coxibs in comparisons with placebo, diclofenac, ibuprofen, and naproxen (Bonferroni-adjusted heterogeneity p values all >0·1; appendix pp 22–26), suggesting that each of the coxibs yielded similar ulcer risks. For several of them, however, there was evidence that higher doses yielded larger proportional excesses in ulcer risk (celecoxib: p for trend=0·0043; rofecoxib: p for trend=0·0350; appendix p 25; etoricoxib: heterogeneity p=0·0135; appendix p 24).

Discussion

Meta-analyses of randomised trials and of observational studies have shown that coxibs and tNSAIDs are associated with an increased risk of cardiovascular disease and upper gastrointestinal complications,[5,6,8,18–20] but there has been uncertainty about the nature and magnitude of these risks, and the relative safety of different NSAID regimens, especially in those at increased risk of coronary heart disease.[10–12]

Our meta-analysis, which is unaffected by selection and other biases inherent in observational studies, showed clearly that the vascular risks of diclofenac, and possibly ibuprofen, are similar to coxibs, but that naproxen is not associated with an increased risk of major vascular events. However, it also showed that the excess risk of both vascular and gastrointestinal events can be predicted once the baseline risks of such hazards are known, which could help clinical decision-making.

Most of the information available for the estimation of vascular risks was derived from trials involving four coxibs (celecoxib, rofecoxib, etoricoxib, and lumiracoxib) and three high-dose tNSAID regimens (daily doses: diclofenac 150 mg, ibuprofen 2400 mg, and naproxen 1000 mg [table and appendix]). Overall, coxibs increased the risk of major vascular events by around a third, as previously reported in meta-analyses of summary trial data,[6] but these analyses show that the excess risk was mainly attributable to an increase of about three quarters in the risk of major

coronary events. These results are similar to those previously reported for coxibs, diclofenac, ibuprofen, and naproxen in observational studies[8] but, by contrast with the present meta-analysis of randomised trials, the observational studies used a wide range of vascular outcomes and tNSAID doses, so precise comparisons between these different types of studies are not possible.

This meta-analysis showed clearly that high-dose diclofenac has similar vascular risks to the average coxib regimen studied. The absolute excess risks were small but serious: compared with placebo, allocation to a coxib or diclofenac caused around three additional major vascular events per 1000 participants per year, with one such event causing death. High-dose ibuprofen also significantly increased the risk of major coronary events, but there were many fewer relevant events in trials of coxib versus ibuprofen, so its safety (including the possible relevance of its interaction with aspirin[21]) requires further study. Naproxen 500 mg twice a day did not seem to increase the risk of major vascular events, consistent with experimental studies showing that this naproxen regimen is capable of producing COX-1 inhibition that is sufficiently prolonged and intense to result in platelet inhibition in some individuals, which could attenuate any adverse vascular effects of COX-2 inhibition.[7]

There was no evidence of an increased risk of stroke for any of the NSAIDs studied, but few strokes were recorded and the absence of any stroke risk for drug regimens known to increase blood pressure is implausible. All NSAIDs doubled the risk of heart failure causing hospital admission (ie, not just ankle oedema), consistent with this being a COX-2 dependent hazard unrelated to variable platelet inhibition. As expected, NSAIDs increased the risk of upper gastrointestinal complications by around 2–4 times and, as previously shown by individual trials,[2,3] coxibs yielded the lowest risk of such complications.

Our analyses do not allow definite conclusions about whether particular NSAIDs increase vascular risk immediately after starting treatment, but evidence for an early hazard of coxibs would have been enhanced if data had been included from two trials that indicated vascular hazard from intravenous parecoxib followed by oral valdecoxib during a 2-week period after coronary artery bypass surgery.[22,23] There was, however, clear evidence that NSAIDs increase the early risk of upper gastrointestinal complications. Since the average trial duration was less than 1 year, our analyses do not provide reliable information about whether the risks of NSAIDs persist with prolonged treatment (and since events occurring more than a few weeks after patients discontinued treatment were not generally recorded, our analyses might underestimate those risks).

Overall, at the daily doses studied most frequently, the vascular risks of different coxib regimens seemed similar. Little information was available on whether the vascular hazards of coxibs were dose-dependent. Although there was a trend towards less risk with lower celecoxib doses, the vascular effects of celecoxib 200 mg daily (the most widely used coxib regimen) were statistically uncertain. The tNSAID regimens studied were all high-dose, with little variation between trials, so comparable analyses of tNSAIDs were not possible. However, since vascular hazard is probably related to the degree of COX-2 inhibition, which increases with dose,[9] such dose-dependency seems likely.[24]

The potential for bias has been minimised in this meta-analysis by obtaining access to detailed individual data from most trials recording vascular and gastrointestinal outcomes (including some that were unpublished). Since most events occurred in a small number of recent trials

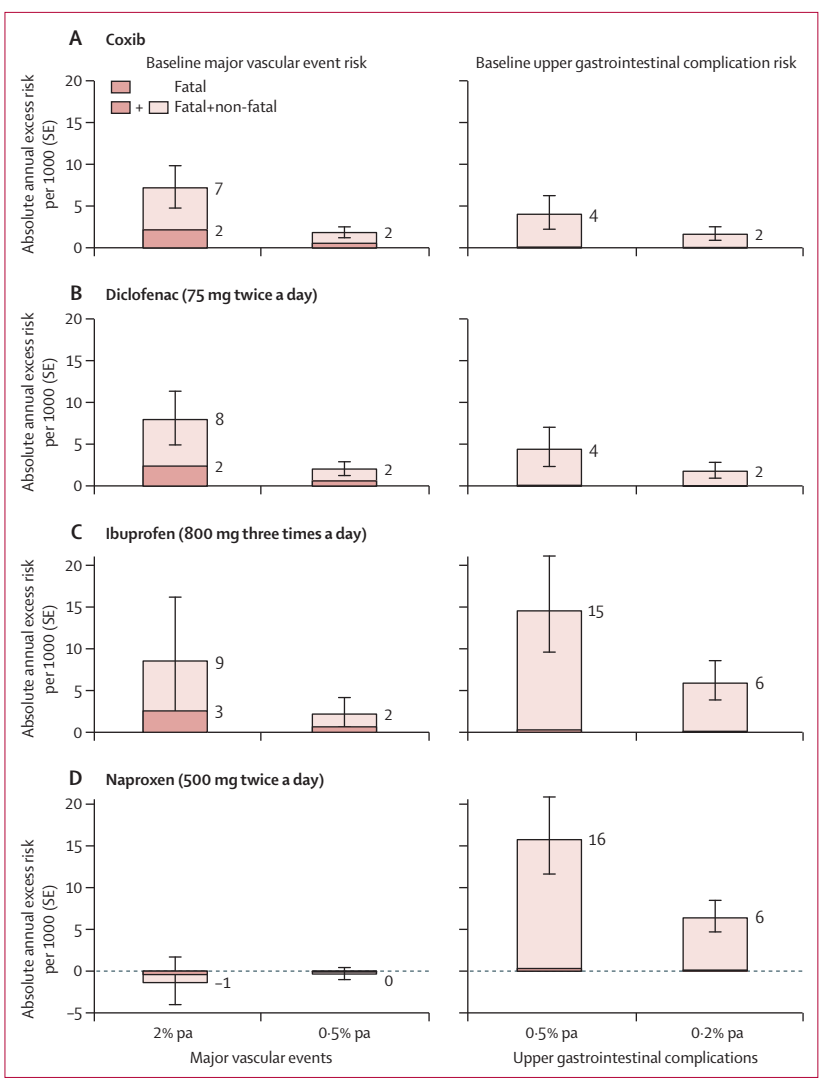

Figure 5: **Annual absolute effects per 1000 of coxibs and tNSAIDs at different baseline risks of major vascular events and upper gastrointestinal complications**

For each category of drug (coxib, diclofenac, ibuprofen, and naproxen), the predicted annual absolute risks of major vascular events (±1 SE) are shown (left) for patients with predicted risk of 2·0% or 0·5% per annum of a major vascular event. For comparison, predicted annual absolute risks of upper gastrointestinal complications (±1 SE) are shown for patients with predicted risks of 0·5% or 0·2% per annum (right). Absolute annual risks for placebo-allocated patients are assumed to be those of a hypothetical patient after all appropriate forms of prophylactic treatment (eg, antihypertensive therapy, statin therapy, proton-pump inhibitors) have been instituted.

that used secure randomisation methods and treatment blinding, sensitivity analyses (available on request) indicated that our results were not materially influenced by uncertainties about the quality of older trials. There was also no evidence that our results depended on whether participating trials had been published, although some unpublished trials of which we were unaware might have affected particular findings. A novel element of our analyses was that treatment effects were estimated by comparing the results of trials of a coxib versus placebo and trials of a coxib versus tNSAID. The conditions under which such indirect comparisons might be expected to yield valid results[25] are satisfied, since the two sets of trials involved similar doses of coxibs and similar populations, and different studies used the same (high-dose) tNSAID regimens as comparators.

A key objective was to quantify the hazards of NSAIDs in patients with an increased risk of vascular disease. The results of a previous meta-analysis suggested that the proportional increase in vascular risk might be highest for celecoxib in those at greatest risk of coronary heart disease.[26] In our meta-analysis, however, the proportional effects of coxibs and tNSAIDs seemed similar irrespective of baseline characteristics, and in particular were similar at all levels of risk of major vascular events (<5%, 5–10%, >10% over 5 years), although there were limited data among patients with a history of atherosclerosis. Assuming that proportional effects are indeed similar in different patients, we undertook hypothetical calculations (appendix) of the annual excess risks of each of the main NSAIDs as compared with placebo (figure 5). Excess risks were calculated for major vascular events in patients at high (2% per annum) or low (0·5%) risk of major vascular events (left panel), and for upper gastrointestinal complications in patients at moderate (0·5% a year) or low (0·2% a year) risk of such complications (right panel). For each outcome, the fraction of fatal events is shown in darker shading. Among those at low risk of vascular disease (the majority of participants in these trials), the predicted absolute risks of major vascular events were small irrespective of the particular regimen chosen. For high-risk individuals (about 40% of whom were taking aspirin), for every 1000 patients allocated to a year of treatment with a coxib regimen or high-dose diclofenac regimen, about seven or eight more would have a major vascular event, of which two would be fatal. High-dose ibuprofen may be associated with a similar risk, but is also likely to yield a higher risk of upper gastrointestinal complications than either a coxib or diclofenac.

Our analyses suggest that naproxen might not be associated with an increased risk of major vascular events, but this result should be interpreted with caution. First, we do not know whether this would be true in patients treated with aspirin, in whom naproxen will not result in any additional inhibition of COX-1 and might actually interfere with the antiplatelet effect of low-dose aspirin.[27,28] Secondly, the effects of lower naproxen doses, such as those typically used in over-the-counter preparations (eg, 220 mg twice a day), are uncertain since they would be less likely to mimic the aspirin-like effect of 500 mg twice a day.[29] Thirdly, the apparent advantage of naproxen regimens might not be preserved after longer term use. Finally, naproxen substantially increases the risk of upper gastrointestinal complications (although such bleeds are less likely than vascular events to result in disability[30] and such hazards could be mitigated with proton-pump inhibitors[31]).

This meta-analysis of individual participant data helps to characterise and quantify the vascular and gastrointestinal hazards of coxibs and tNSAIDs. It shows that high-dose diclofenac has vascular risks similar to coxibs, but also raises the possibility that high-dose ibuprofen has similar vascular effects. High-dose naproxen seems to be associated with less vascular hazard, although whether this is true of the lower doses most commonly used in clinical practice is unclear. Although NSAIDs increase vascular and gastrointestinal risks to a varying extent, our analyses indicate that the effects of different regimens in particular patients can be predicted, which could help in guiding decisions about the clinical management of inflammatory disorders.

Contributors

The writing committee accepts full responsibility for the content of this paper. All of the members contributed to the collection and analysis of the data, and to the preparation of the manuscript. All collaborators had an opportunity to contribute to the interpretation of the results and to drafting the manuscript. The pharmaceutical companies providing data were invited to comment on the study results and draft manuscripts, but the Writing Committee had full control of all editorial decisions.

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Others (not already listed) present at the initial presentation of results in January, 2011: E Hall, P McGettigan, R Midgley, R A Moore, GSK: R Philipson; Merck: S Curtis, A Reicin; Novartis: J Bond, A Moore; Pfizer: M Essex, J Fabule, B Morrison, L Tive.
Secretariat: C Baigent, N Bhala, K Davies, J Emberson, H Halls, L E Holland, P M Kearney, A Merhi, C Patrono, K Wilson, and F Yau.

Conflicts of interest

The Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), where the CNT Secretariat (C Baigent, N Bhala, J Emberson, H Halls, L Holland, A Merhi, K Wilson) is located, has a policy of staff not accepting fees, honoraria, or paid consultancies. CTSU staff are, however, involved in clinical trials of lipid-modifying therapy funded by research grants from Merck to the University of Oxford, with the University the trial sponsor in all cases. In particular, C Baigent was chief investigator of

the Study of Heart and Renal Protection of ezetimibe/simvastatin prior to 2011. N Arber, M Farkouh, P M Kearney, P Lance and S Solomon declare that they have no conflicts of interest. S Abramson serves as a consultant to Abbott and Pfizer. J A Baron was formerly a consultant to Merck and is currently a consultant to Bayer and to Pfizer (as a member of a safety and data monitoring committee). C Bombardier is a consultant to Abbott, AstraZeneca, Bristol-Myers Squibb (Canada and USA), and UCB, and receives research support from Abbott, Amgen, Bristol-Myers Squibb, Janssen, Hoffman La-Roche, Pfizer, and UCB Canada. C Cannon reports receiving research grants or support from Accumetrics, AstraZeneca, CSL Behring, Essentialis, GlaxoSmithKline, Merck, Regeneron, Sanofi, and Takeda. He is clinical advisor to, and holds equity in, Automedics Medical Systems. He also sits on advisory boards (but donates funds to charity) for Alnylam, Bristol-Myers Squibb, Lipimedix, and Pfizer. G FitzGerald has consulted for Boehringer Ingelheim, Lilly, Merck, BMS, Johnson and Johnson, Genentech, and Takeda. P Goss has received speaker honoraria from GlaxoSmithKline and Novartis. E Hawk reports a paid consultancy from Pozen Pharmaceuticals and is an unpaid consultant to Cancer Prevention Pharmaceuticals and PLx Pharmaceuticals. C Hawkey reports previously having received grants or honoraria from Merck, Pfizer, and AstraZeneca and at present advises Bayer, GlaxoSmithKline, and Novartis. C Hennekens reports serving on data and safety monitoring boards for Actelion, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, British Heart Foundation, Cadila, Canadian Institutes of Health Research, Lilly, Sunovion, and the Wellcome Foundation, and also serves as an advisor to legal counsel for Stryker. M Hochberg serves as a consultant or member of an advisory board for Abbott, Bioiberica SA, Boehringer Ingelheim, Bristol-Myers Squibb, Covidien, Eli Lilly, Genentech/Roche, Iroko Pharmaceuticals, Merck, Pfizer, and Regeneron. He chaired a data and safety monitoring board for Novartis and has received speaker honoraria from Bioiberica SA and IBSA. L Laine reports serving on data and safety monitoring boards for Bayer, Merck, and Eisai and has previously consulted for Pfizer, AstraZeneca, and Horizon. A Lanas is an advisor to Bayer and AstraZeneca Spain. A Laupacis reports serving on data and safety monitoring boards for Novartis and advisory boards for Pfizer and Eli Lilly, but none of these activities involve discussions about non-steroidal anti-inflammatory drugs. J Oates was a member of the scientific advisory board of Merck, concluding in 2006. C Patrono has received, during the past 2 years, consultant and speaker fees from Astra Zeneca, Bayer, Eli Lilly, Merck, NicOx, Novartis, and Servier, as well as an institutional grant from Bayer for investigator-initiated research. T Schnitzer reports paid consultancies with Merck, Janssen, Regeneron, Abbott, and McNeil, as well as research support (to Northwestern University) from Novartis, Merck, Eli Lilly, and Nuvo. P Tugwell reports paid consultancies with Bristol-Myers Squibb, Chelsea, and UCB, reports that OMERACT (Outcomes measures in Rheumatology), whose Executive he serves on in an unpaid capacity, receives support from Actellion, Alderbio, Amgen, Ardea Biosciences, Astra Zeneca, Bristol-Myers Squibb, Celgene, Centocor, Cypress/Forest, Eli Lilly, Boehringer Ingelheim, Genentech, Genzyme, Jass Pharmaceuticals, Merck, Novartis, Novo Nordisk, Pfizer, Regeneron, Savient, Takeda, UCB, and reports that the Ontario Biologics Research Initiative (OBRI) Industry Council receives support from Abbott, Roche, Schering Plough/Merck, UCB, and Bristol-Myers Squibb. J Wittes reports that Statistics Collaborative, a company in which she holds majority ownership, has consulting agreements with Merck, Bristol-Myers Squibb, AbbVie, Amgen, and Pfizer.

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THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013; published online May 30. http://dx.doi.org/10.1016/S0140-6736(13)60900-9.

Webmaterial: Vascular and upper gastrointestinal effect of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

Webtables

Webfigures

Webtable 1: Dose range and pharmacological properties of the main NSAIDs studied in randomised trials

(a) Traditional NSAIDs

	DICLOFENAC	IBUPROFEN	NAPROXEN
Daily dose studied	150mg (rarely 100mg)	2400mg	1000mg (rarely 440mg)
Half life	1 to 2 hours	2 to 4 hours	14 hours
COX1:COX2 IC50*	29	0.5	0.7
Excretion	Biliary	Renal	Renal

(b) Coxibs

	CELECOXIB	ROFECOXIB	LUMIRACOXIB	ETORICOXIB	VALDECOXIB
Daily dose studied (typical dose[s] †)	100-800mg (400mg)	12.5-125mg (25mg)	100-800mg (200mg)	5-120mg (60/90mg)	1-80mg (20mg)
Half life	6 to 12 hours	17 hours	4 hours	22 hours	10 hours
COX1:COX2 IC50*	30	267	515	344	62
Excretion	Renal and Faecal	Renal and Biliary	Renal and Faecal	Renal and Faecal	Mainly Renal

* COX-1:COX-2 IC50 refers to the ratio of half maximal inhibitory concentrations for COX-1 and COX-2, and is a measure of COX-2 selectivity (with higher numbers implying greater COX-2 selectivity)

† Defined as the dose or doses contributing the majority of information on major vascular events

Webtable 2: Baseline characteristics of trials that supplied individual patient data, overall and by comparison type

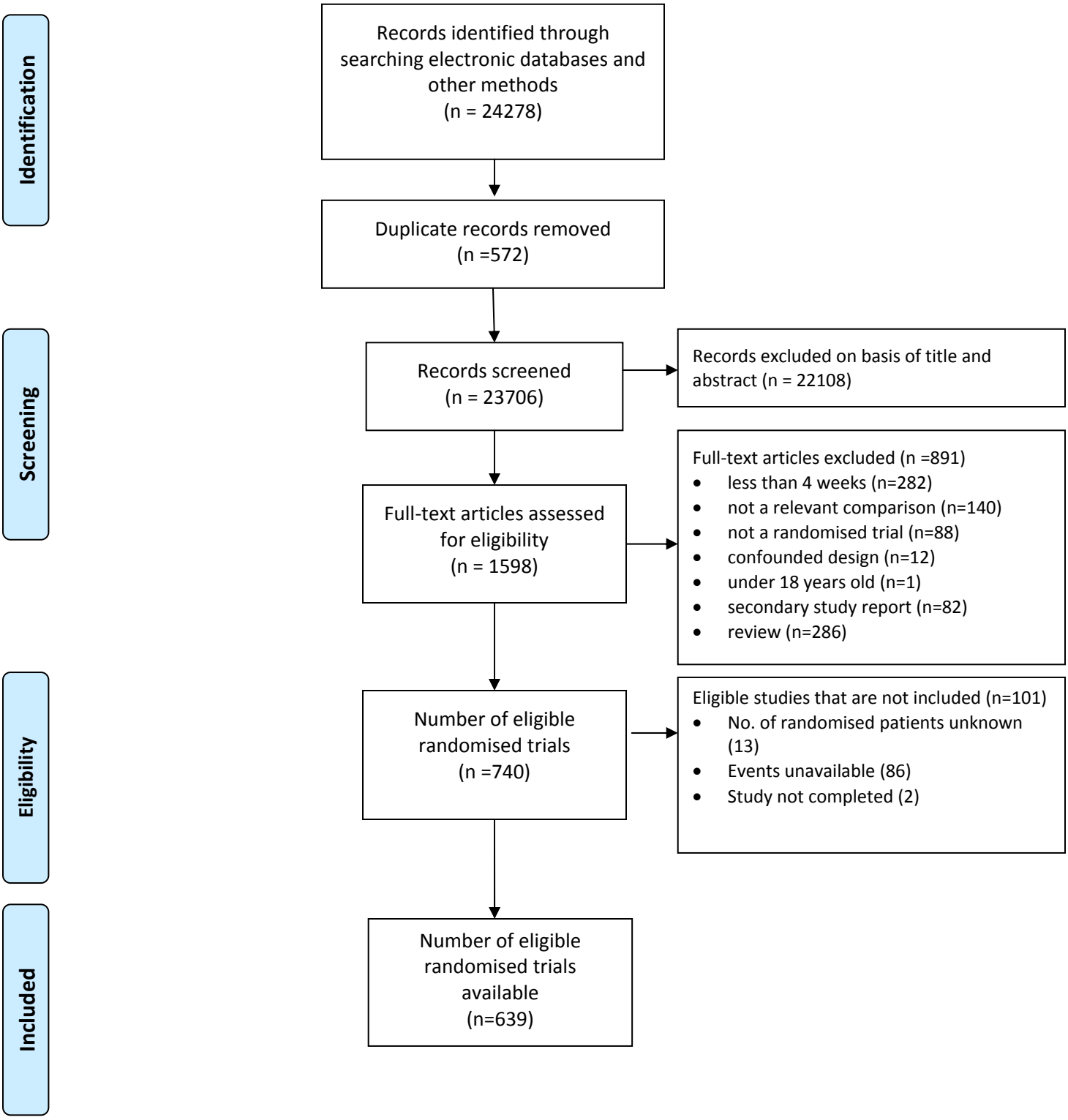
	Overall	Coxib vs placebo	tNSAID vs placebo	Coxib vs naproxen	Coxib vs other tNSAID
No. randomised	192981	73635	18018	42222	84680
No. trials	157	113	47	34	54
Age, years	61.2 (11.3)	60.1 (12.4)	59.7 (13.6)	60.6 (11.3)	61.6 (10.6)
Female, %	68	59	67	73	73
Caucasian, %	79	82	72	76	77
Indication for treatment, %					
Rheumatoid arthritis	20	20	28	36	17
Osteoarthritis	63	44	52	57	77
Cancer prevention/treatment	7	19	0	0	0
Alzheimers	3	7	11	4	0
Other known indication	5	10	9	2	4
Unknown	1	0	0	1	2
Prior disease, %					
Diabetes	9	8	6	9	8
Atherosclerotic disease	9	10	9	8	9
Upper GI ulcer	7	7	9	7	7
Medication, %					
Aspirin	20	14	15	14	27
Proton pump inhibitor	17	5	3	2	33
Other/multiple gastroprotectants	3	5	5	6	1
Current smoker, %	13	14	13	15	12
Physical measurements					
BMI, kg/m^2	29.3 (6.2)	29.2 (6.3)	28.9 (6.5)	29.1 (6.4)	29.3 (6.1)
Systolic blood pressure, mmHg	132 (16)	131 (16)	131 (17)	132 (17)	132 (16)
Diastolic blood pressure, mmHg	79 (9)	79 (9)	79 (9)	79 (9)	79 (9)
Laboratory measurements					
Total cholesterol, mmol/L	5.3 (1.0)	5.3 (1.0)	5.2 (0.8)	5.2 (0.8)	5.4 (1.0)
Creatinine, umol/L	79 (21)	81 (19)	80 (19)	76 (20)	79 (23)
Haemoglobin, g/dL	13.7 (1.3)	13.9 (1.4)	13.7 (1.3)	13.6 (1.3)	13.6 (1.3)

Mean (SD) or % shown

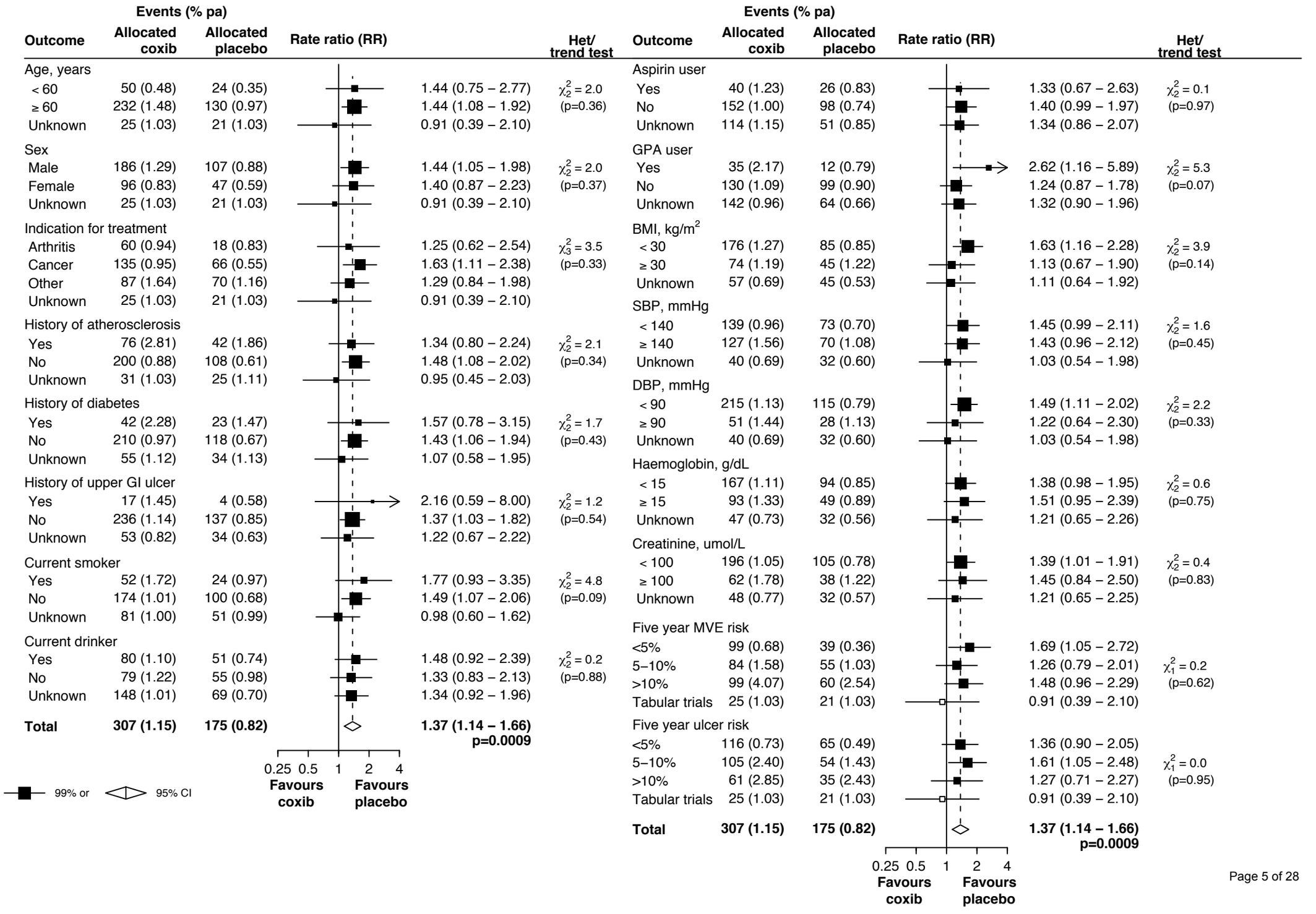
Webtable 3: Effects of coxibs and tNSAIDs on major vascular events and upper GI complications

	Summary RR (95% CI) for comparison	
NSAID	**Coxib vs NSAID**	**NSAID vs placebo**
Major vascular events		
Coxib	-	1.37 (1.14, 1.66)
Naproxen	1.49 (1.16, 1.92)	0.93 (0.69, 1.27)
Other tNSAID	0.98 (0.86, 1.13)	1.38 (1.10, 1.72)
Diclofenac	0.97 (0.84, 1.12)	1.41 (1.12, 1.78)
Ibuprofen	0.92 (0.58, 1.46)	1.44 (0.89, 2.33)
Other regimen	NE	0.93 (0.32, 2.70)
Upper GI complications		
Coxib	-	1.81 (1.17, 2.81)
Naproxen	0.37 (0.28, 0.49)	4.22 (2.71, 6.56)
Other tNSAID	0.75 (0.59, 0.94)	2.24 (1.46, 3.43)
Diclofenac	0.94 (0.72, 1.24)	1.89 (1.16, 3.09)
Ibuprofen	0.40 (0.25, 0.64)	3.97 (2.22, 7.10)
Other regimen	NE	2.66 (0.89, 7.99)

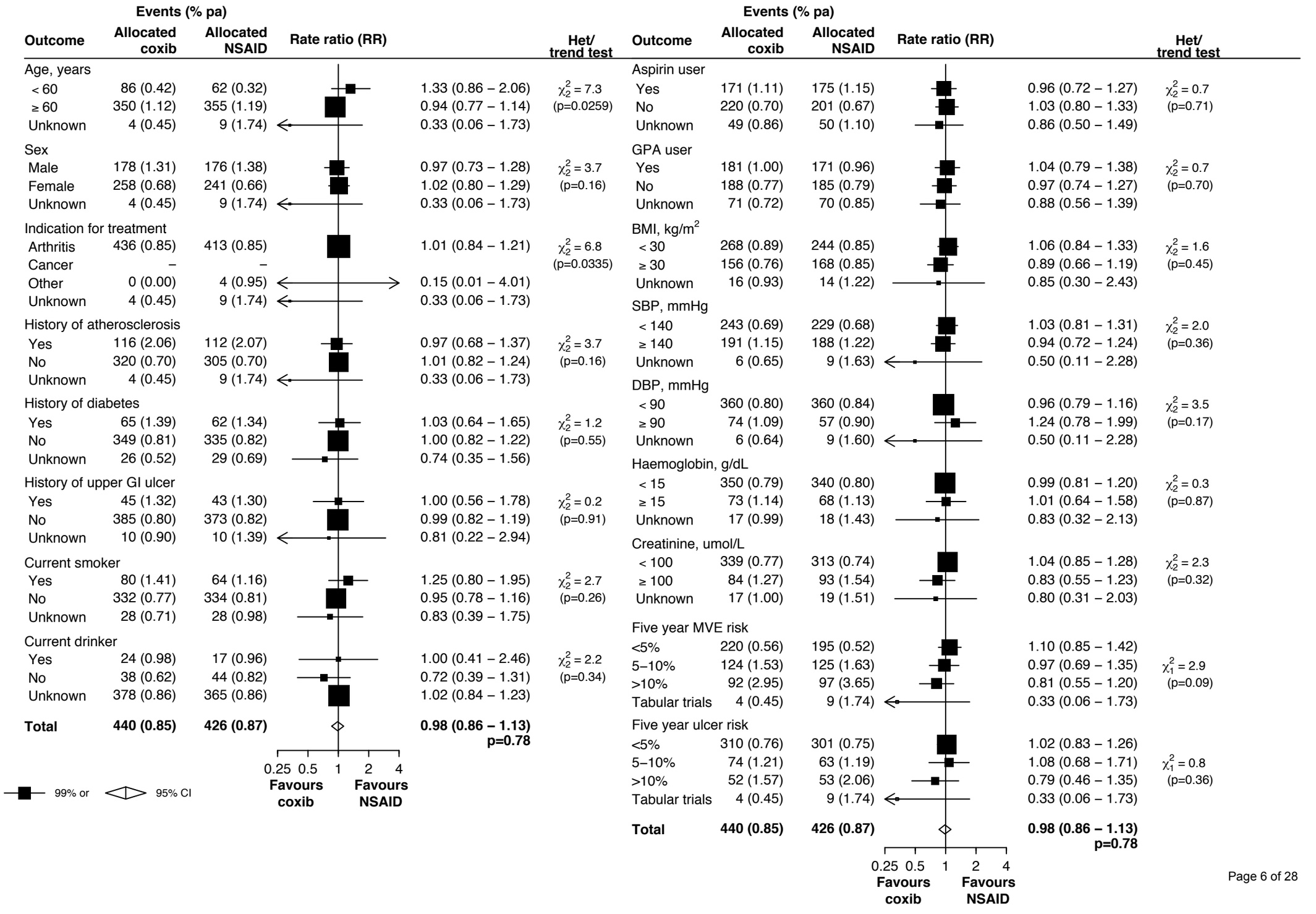
Webfigure 1: PRISMA flow diagram



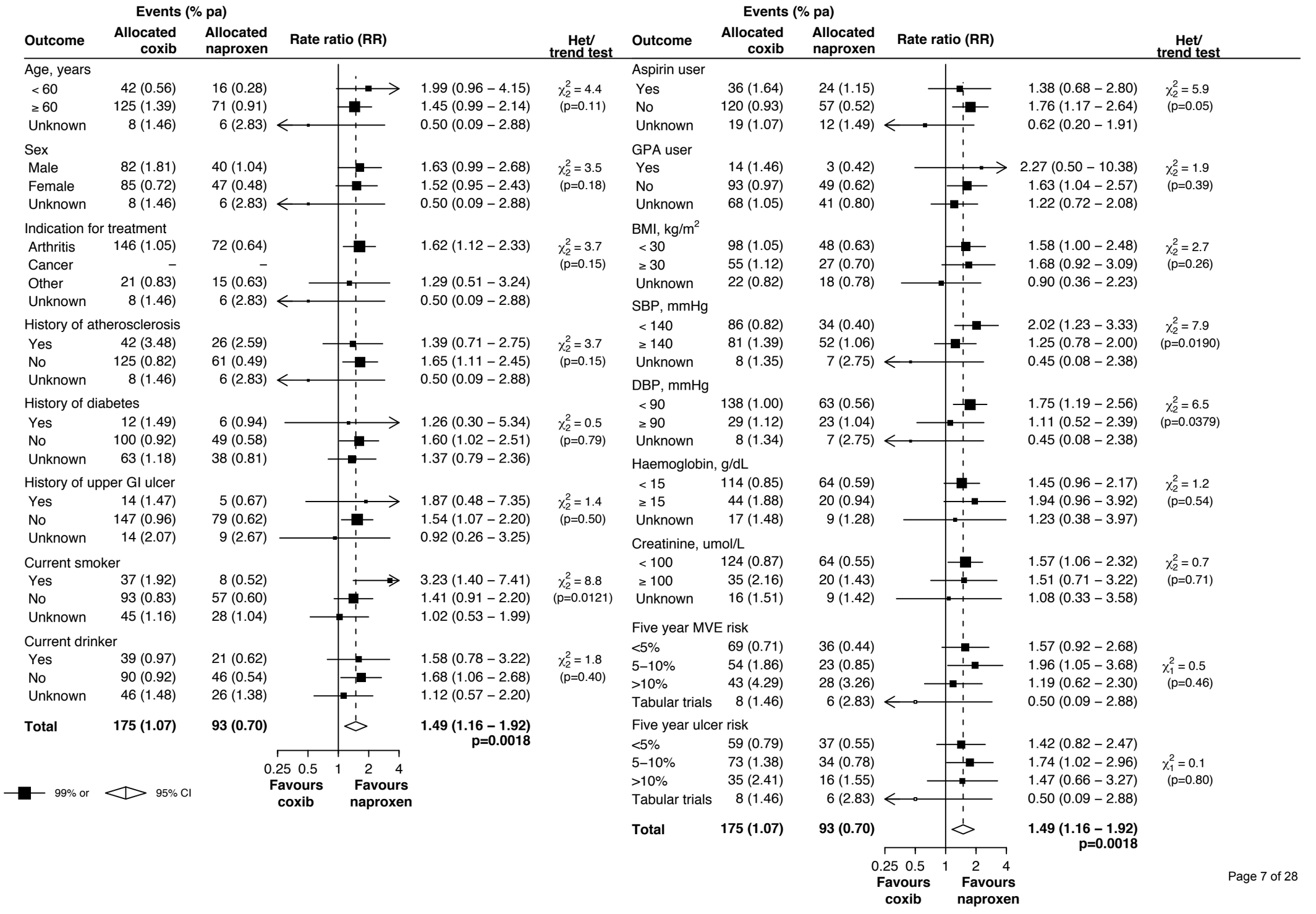
Webfigure 2: Effect of coxib therapy on major vascular events, by baseline characteristics



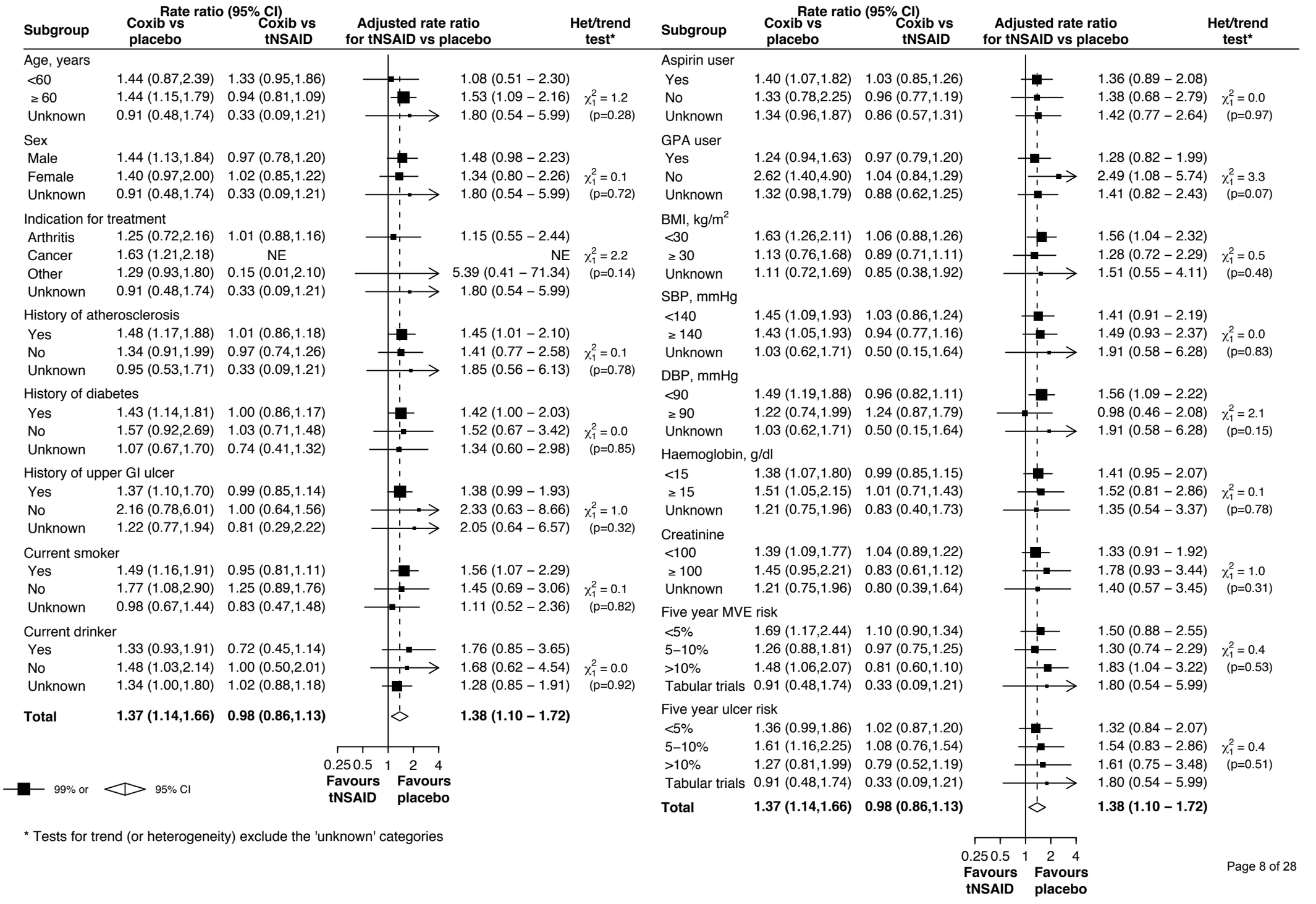
Webfigure 3: Comparisons of coxibs vs non–naproxen NSAIDs. Effect on major vascular events by baseline characteristics



Webfigure 4: Comparisons of coxibs vs naproxen. Effect on major vascular events by baseline characteristics

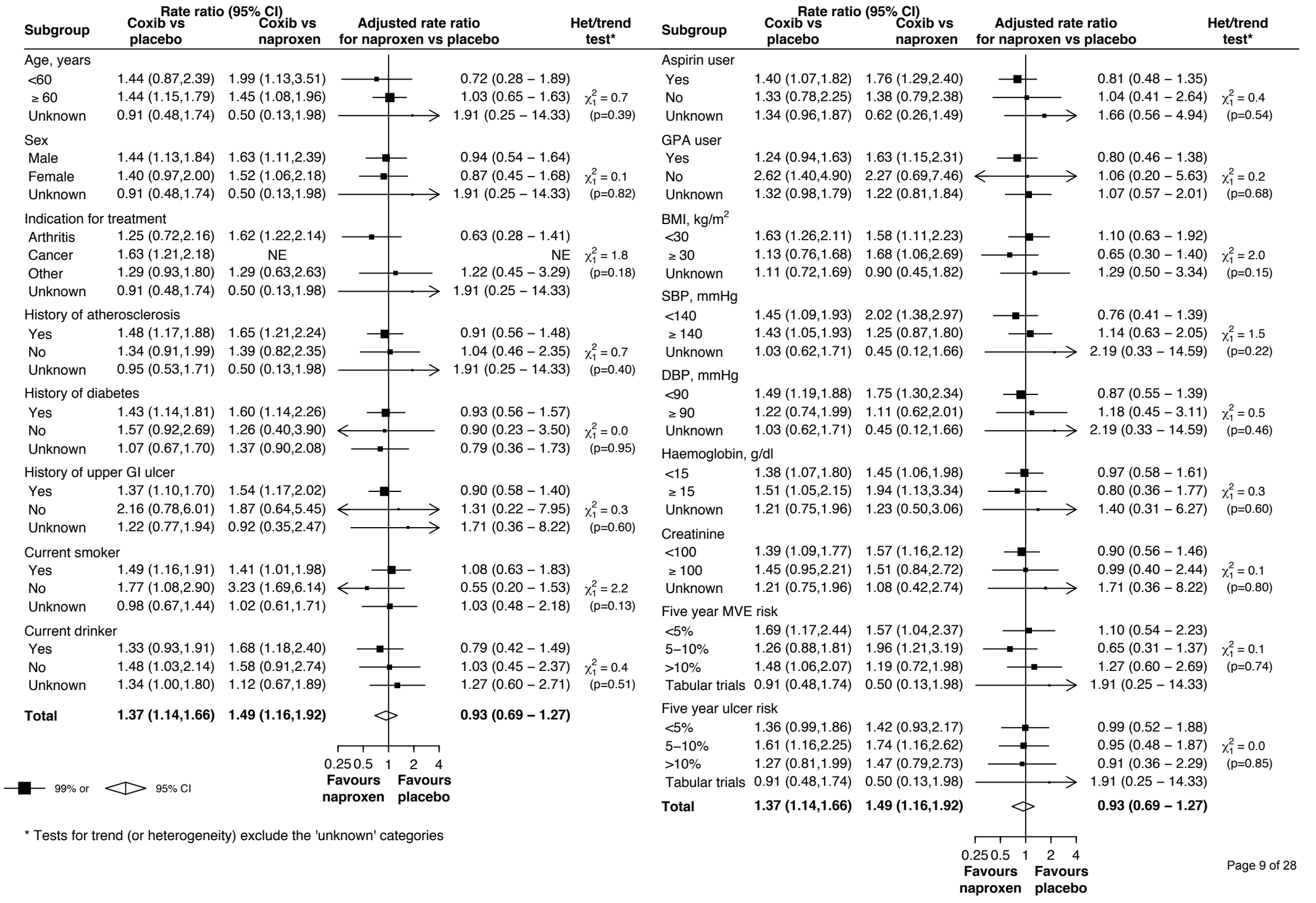


Webfigure 5: Effect of non–naproxen tNSAIDs on major vascular events, by baseline characteristics



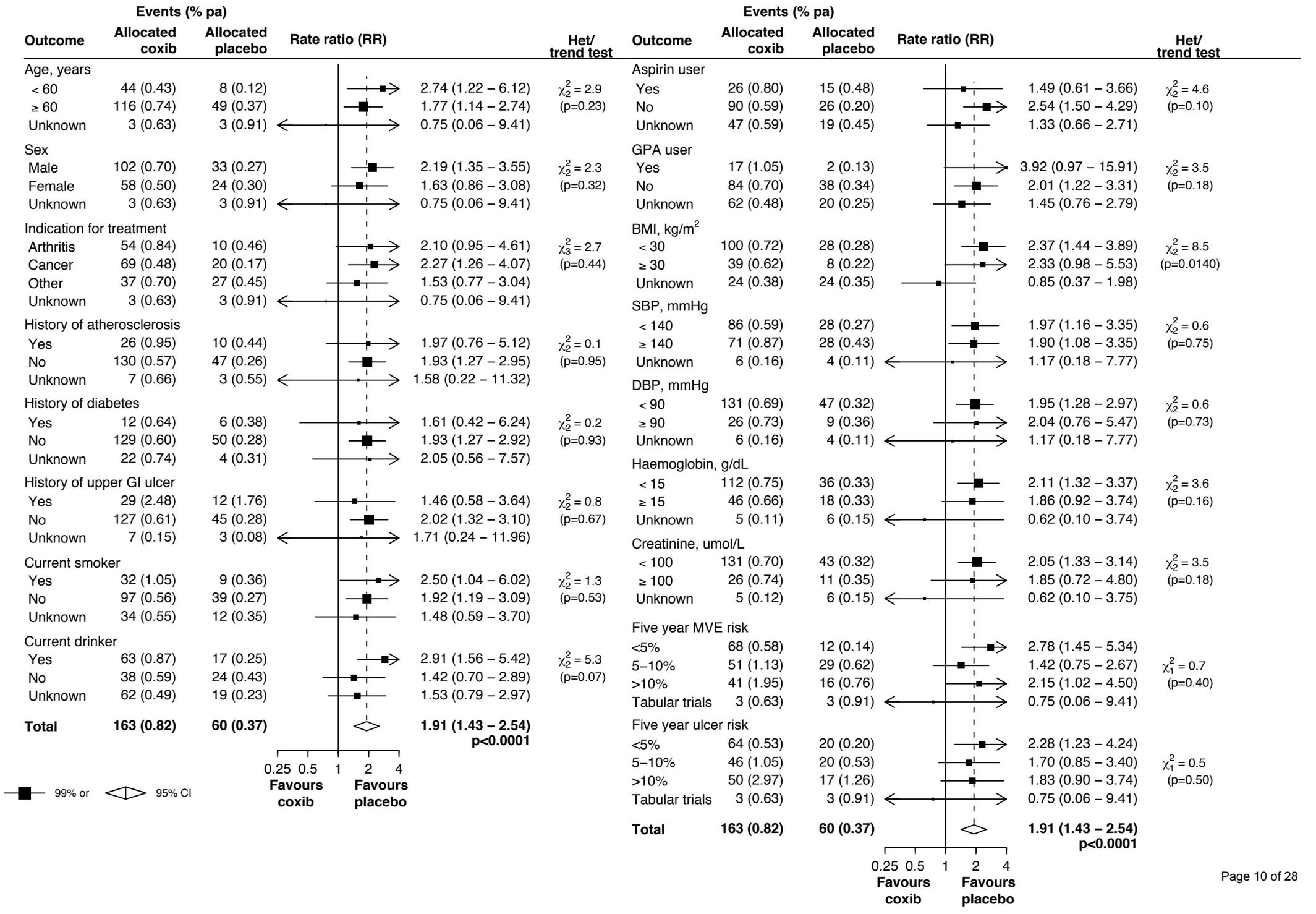
* Tests for trend (or heterogeneity) exclude the 'unknown' categories

Webfigure 6: Effect of naproxen on major vascular events, by baseline characteristics

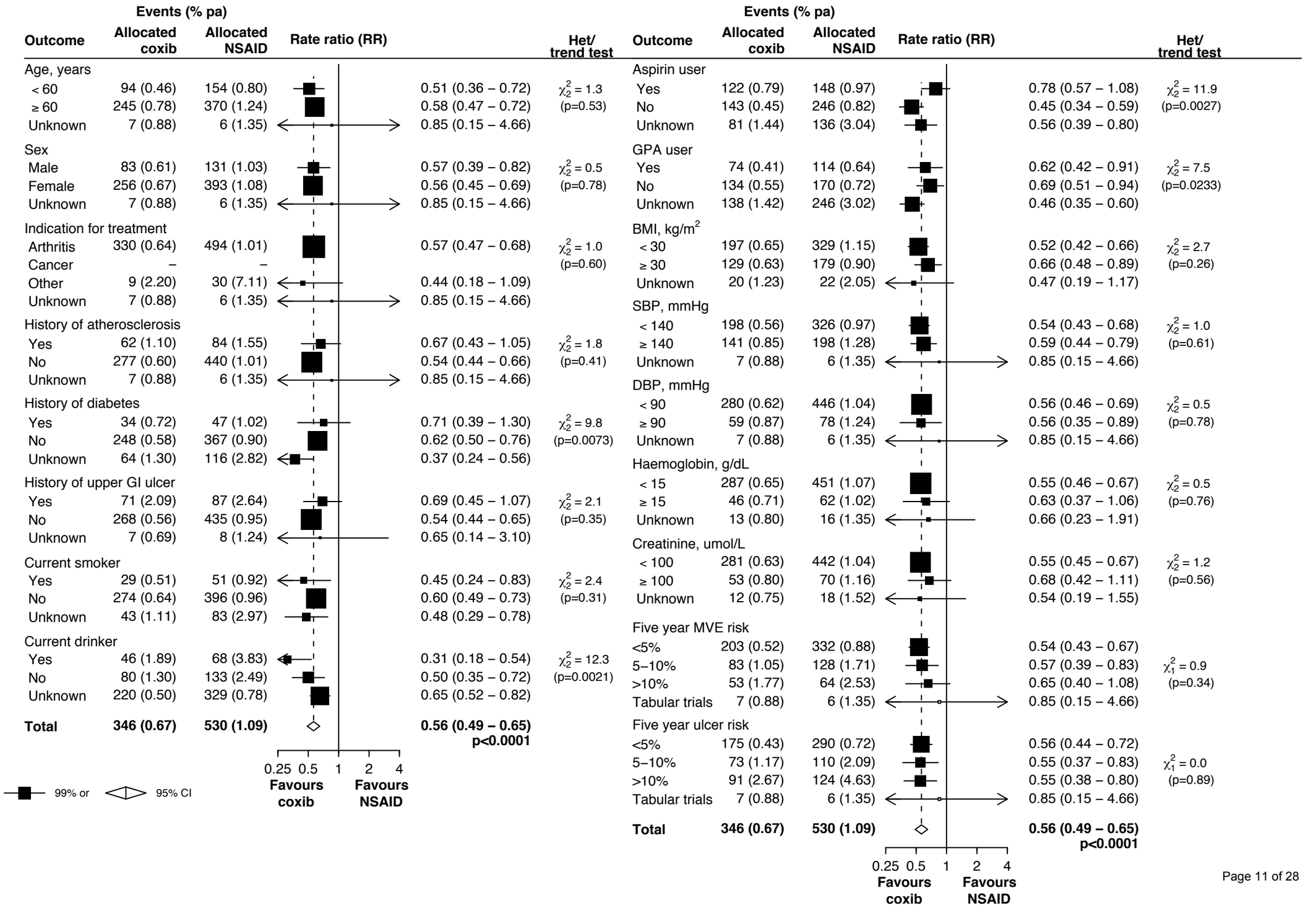


* Tests for trend (or heterogeneity) exclude the 'unknown' categories

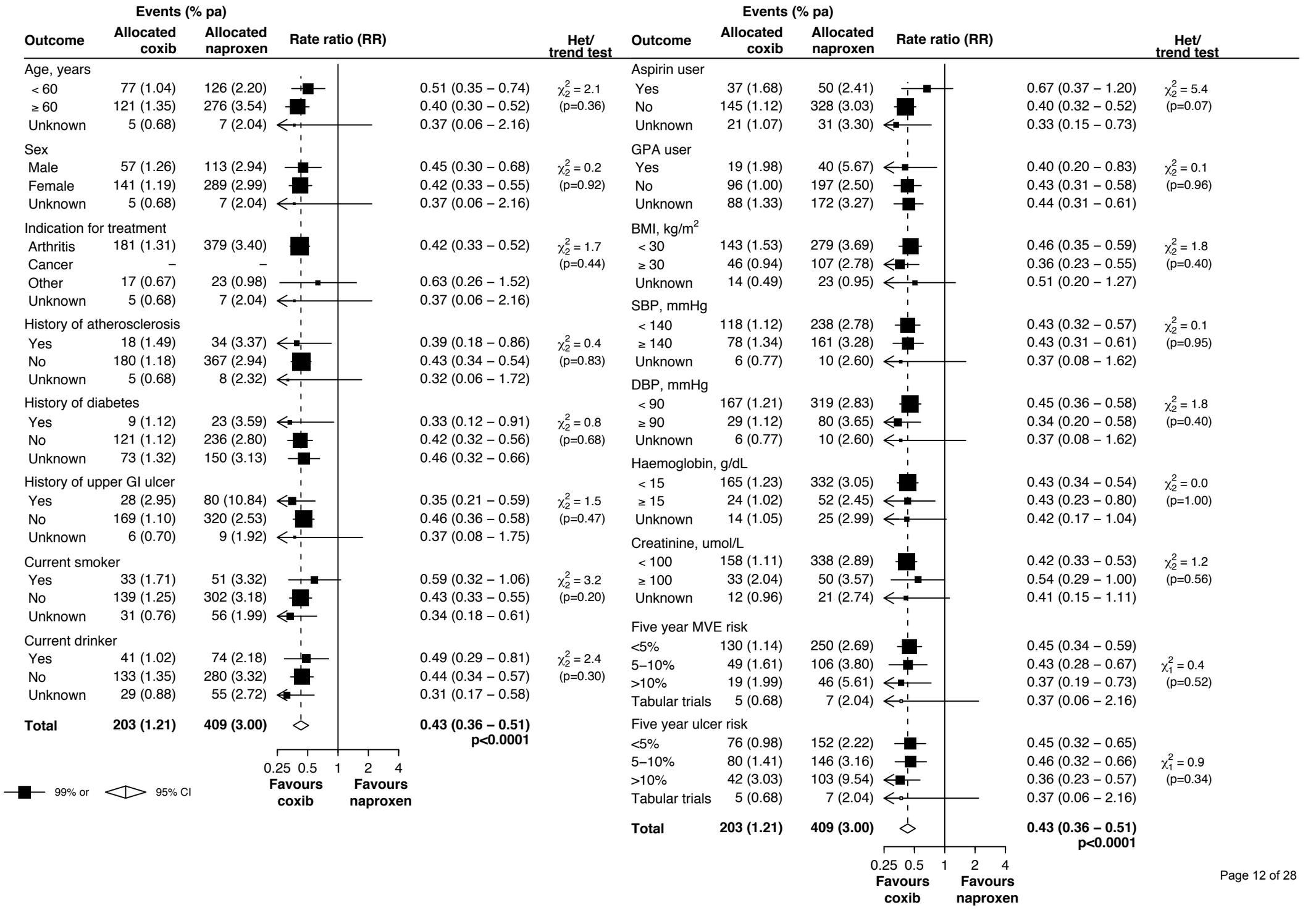
Webfigure 7: Effect of coxib therapy on any symptomatic upper GI event, by baseline characteristics



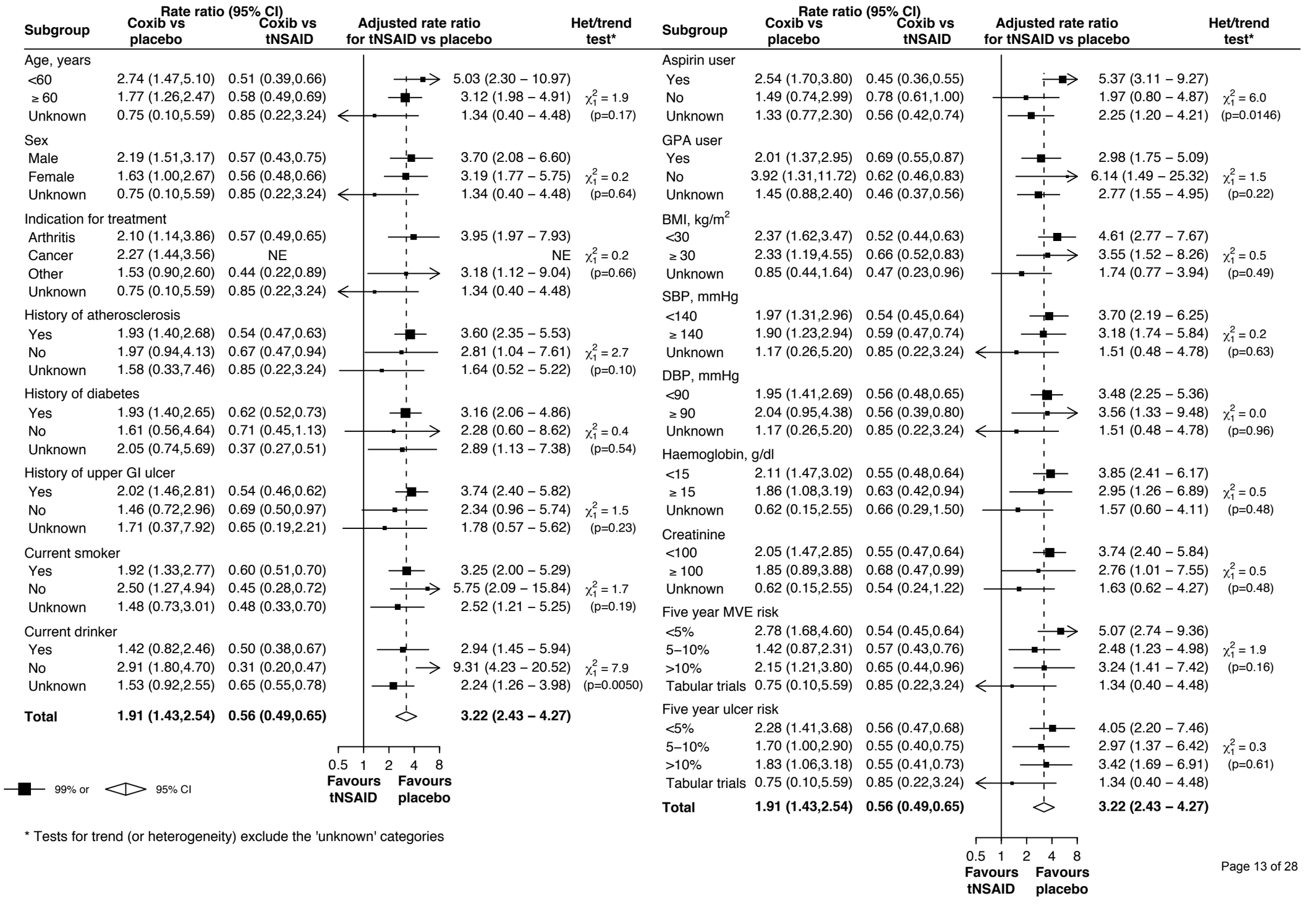
Webfigure 8: Comparisons of coxibs vs non–naproxen NSAIDs. Effect on any symptomatic upper GI event by baseline characteristics



Webfigure 9: Comparisons of coxibs vs naproxen. Effect on any symptomatic upper GI event by baseline characteristics

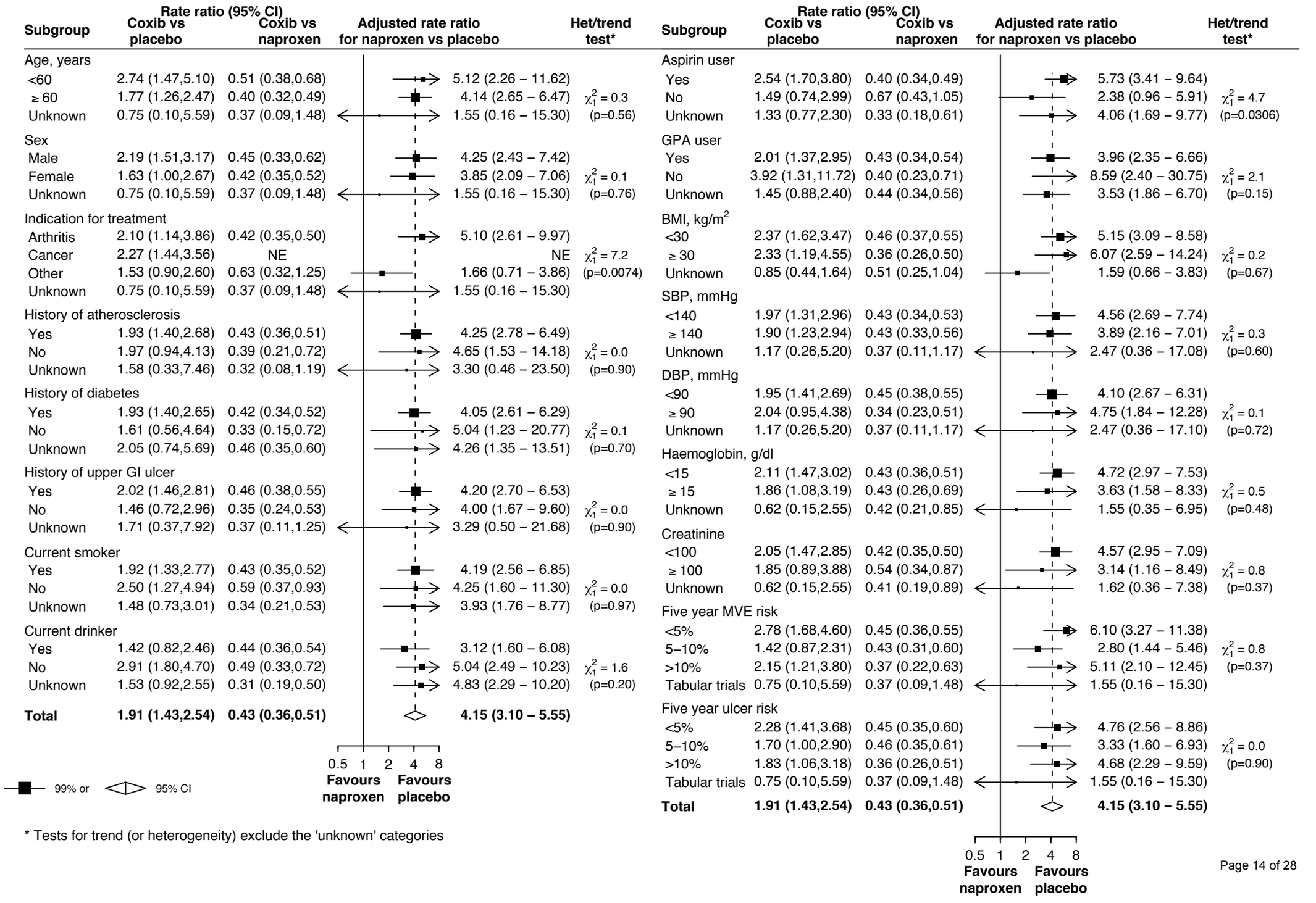


Webfigure 10: Effect of non–naproxen tNSAIDs on any symptomatic upper GI event, by baseline characteristics



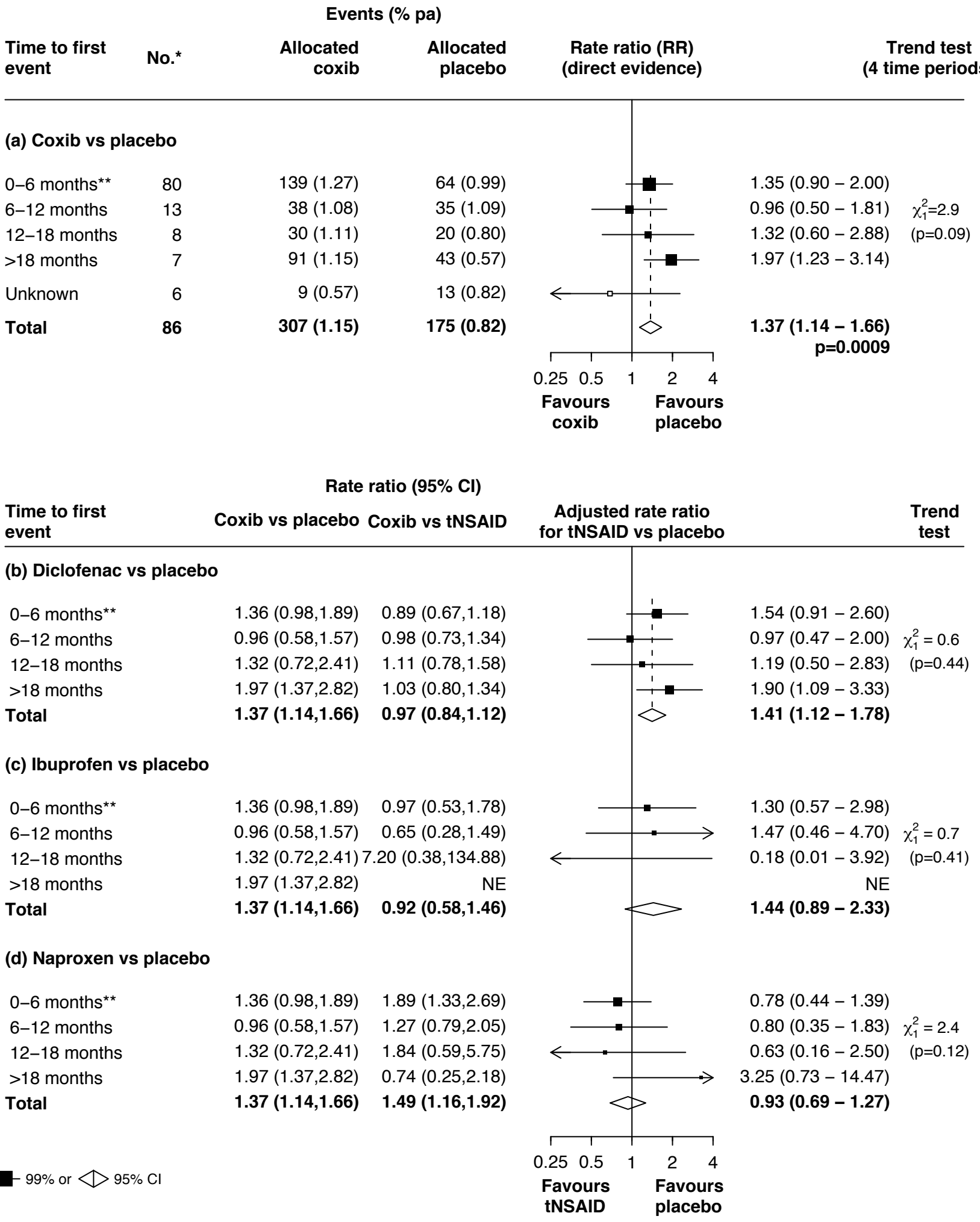
* Tests for trend (or heterogeneity) exclude the 'unknown' categories

Webfigure 11: Effect of naproxen on any symptomatic upper GI event, by baseline characteristics



* Tests for trend (or heterogeneity) exclude the 'unknown' categories

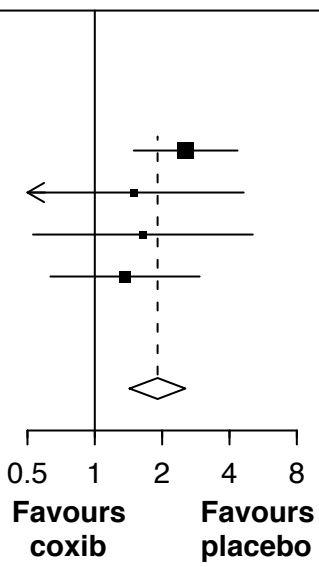
Webfigure 12: Effect of coxibs, non–naproxen tNSAIDs and naproxen on major vascular events, by duration of treatment



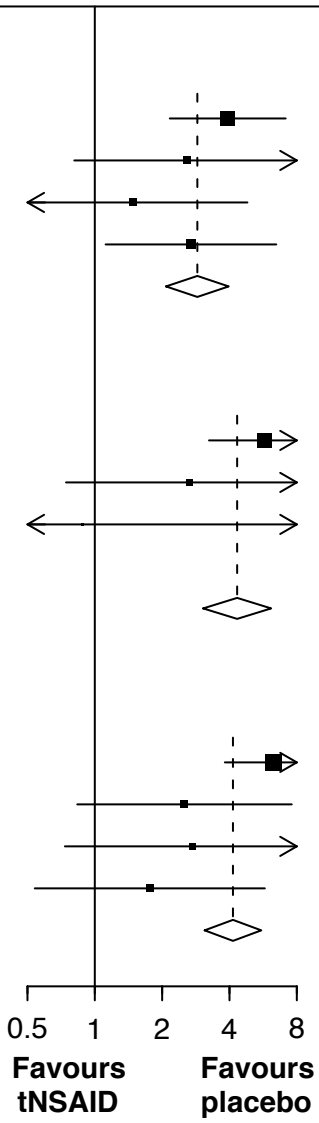
* Number of comparisons with at least one event in that period
** Includes tabular data from trials known to be <6 months duration. Other tabular trials for which events dates are unknown only contribute to the summary diamond.

Webfigure 13: Effect of coxibs, non–naproxen tNSAIDs and naproxen on any symptomatic upper GI event, by duration of treatment

Time to first event	No.*	Events (% pa) Allocated coxib	Allocated placebo	Rate ratio (RR) (direct evidence)	Trend test (4 time periods)
(a) Coxib vs placebo					
0–6 months**	44	99 (1.28)	20 (0.42)	2.55 (1.49 – 4.35)	
6–12 months	9	16 (0.58)	9 (0.36)	1.50 (0.48 – 4.63)	χ^2_1=3.4
12–18 months	5	16 (0.76)	9 (0.47)	1.64 (0.53 – 5.08)	(p=0.06)
>18 months	5	32 (0.48)	21 (0.33)	1.36 (0.63 – 2.94)	
Unknown	1	0 (0.00)	1 (0.47)		
Total	**46**	**163 (0.82)**	**60 (0.37)**	**1.91 (1.43 – 2.54) p<0.0001**	



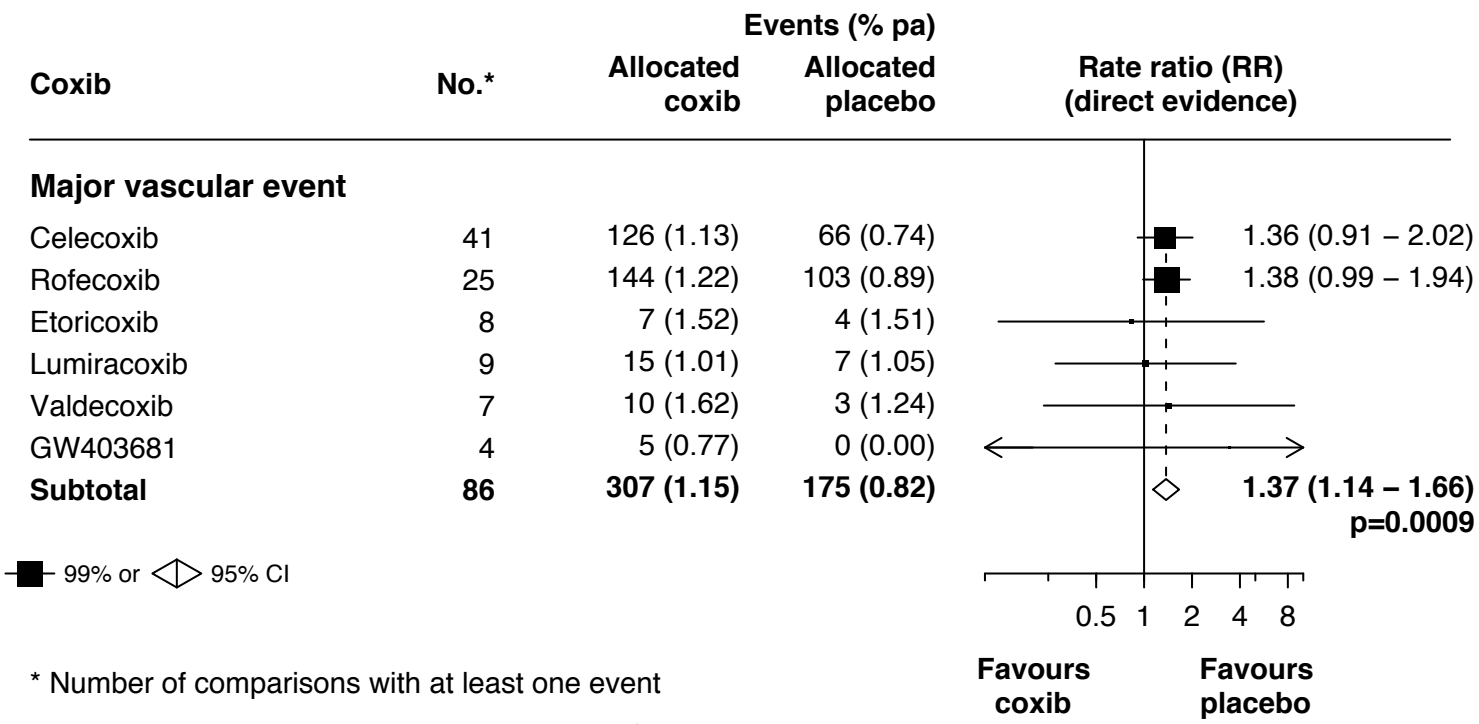
Time to first event	Rate ratio (95% CI) Coxib vs placebo	Coxib vs tNSAID	Adjusted rate ratio for tNSAID vs placebo	Trend test
(b) Diclofenac vs placebo				
0–6 months**	2.65 (1.74,4.05)	0.64 (0.50,0.83)	3.93 (2.16 – 7.13)	
6–12 months	1.50 (0.62,3.60)	0.58 (0.39,0.86)	2.59 (0.81 – 8.26)	χ^2_1 = 1.8
12–18 months	1.64 (0.68,3.96)	1.11 (0.72,1.71)	1.48 (0.46 – 4.81)	(p=0.18)
>18 months	1.36 (0.75,2.47)	0.51 (0.34,0.75)	2.69 (1.12 – 6.47)	
Total	**1.91 (1.43,2.54)**	**0.66 (0.56,0.78)**	**2.87 (2.08 – 3.97)**	
(c) Ibuprofen vs placebo				
0–6 months**	2.65 (1.74,4.05)	0.36 (0.27,0.48)	5.73 (3.24 – 10.14)	
6–12 months	1.50 (0.62,3.60)	0.56 (0.31,1.01)	2.65 (0.74 – 9.47)	χ^2_1 = 4.0
12–18 months	1.64 (0.68,3.96)	1.86 (0.10,34.85)	0.88 (0.04 – 20.70)	(p=0.0469)
>18 months	1.36 (0.75,2.47)	NE	NE	
Total	**1.91 (1.43,2.54)**	**0.40 (0.31,0.52)**	**4.33 (3.05 – 6.14)**	
(d) Naproxen vs placebo				
0–6 months**	2.65 (1.74,4.05)	0.35 (0.29,0.43)	6.31 (3.81 – 10.44)	
6–12 months	1.50 (0.62,3.60)	0.64 (0.46,0.90)	2.52 (0.83 – 7.59)	χ^2_1 = 8.8
12–18 months	1.64 (0.68,3.96)	0.49 (0.21,1.14)	2.73 (0.73 – 10.11)	(p=0.0030)
>18 months	1.36 (0.75,2.47)	0.71 (0.29,1.74)	1.76 (0.54 – 5.75)	
Total	**1.91 (1.43,2.54)**	**0.43 (0.36,0.51)**	**4.15 (3.10 – 5.55)**	



99% or 95% CI

* Number of comparisons with at least one event in that period
** Includes tabular data from trials known to be <6 months duration. Other tabular trials for which events dates are unknown only contribute to the summary diamond.

Webfigure 14: Effect of coxib therapy on major vascular events, by type of coxib

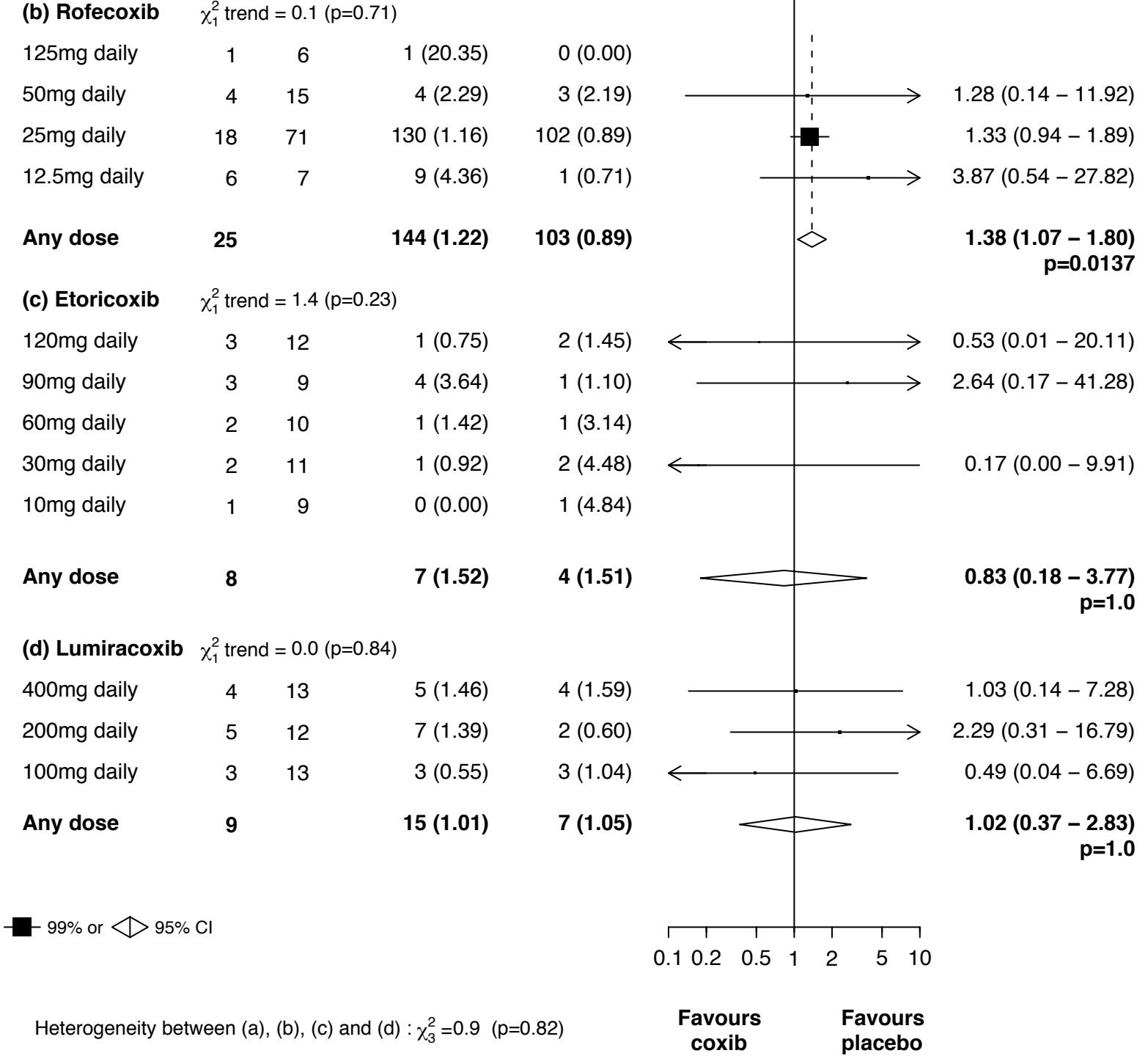


* Number of comparisons with at least one event

Heterogeneity between celecoxib and rofecoxib: χ^2_1 =0.0 (p=0.91)

Webfigure 15: Effect of different coxib regimens on major vascular events, by dose: trials of a coxib vs placebo

Dose	No.*	Mean FU (weeks)	Events (% pa) Allocated coxib	Events (% pa) Allocated placebo	Rate ratio (RR) (direct evidence)
(a) Celecoxib	χ^2_1 trend = 6.4 (p=0.0117)				
800mg daily	5	83	30 (1.65)	8 (0.46)	2.96 (1.21 – 7.25)
400mg daily	22	74	81 (1.01)	56 (0.70)	1.29 (0.81 – 2.04)
200mg daily	17	10	14 (1.26)	11 (1.45)	0.95 (0.30 – 3.00)
100mg daily	2	8	1 (1.63)	1 (1.97)	
Any dose	**41**		**126 (1.13)**	**66 (0.74)**	**1.36 (1.00 – 1.84) p=0.05**
(b) Rofecoxib	χ^2_1 trend = 0.1 (p=0.71)				
125mg daily	1	6	1 (20.35)	0 (0.00)	
50mg daily	4	15	4 (2.29)	3 (2.19)	1.28 (0.14 – 11.92)
25mg daily	18	71	130 (1.16)	102 (0.89)	1.33 (0.94 – 1.89)
12.5mg daily	6	7	9 (4.36)	1 (0.71)	3.87 (0.54 – 27.82)
Any dose	**25**		**144 (1.22)**	**103 (0.89)**	**1.38 (1.07 – 1.80) p=0.0137**
(c) Etoricoxib	χ^2_1 trend = 1.4 (p=0.23)				
120mg daily	3	12	1 (0.75)	2 (1.45)	0.53 (0.01 – 20.11)
90mg daily	3	9	4 (3.64)	1 (1.10)	2.64 (0.17 – 41.28)
60mg daily	2	10	1 (1.42)	1 (3.14)	
30mg daily	2	11	1 (0.92)	2 (4.48)	0.17 (0.00 – 9.91)
10mg daily	1	9	0 (0.00)	1 (4.84)	
Any dose	**8**		**7 (1.52)**	**4 (1.51)**	**0.83 (0.18 – 3.77) p=1.0**
(d) Lumiracoxib	χ^2_1 trend = 0.0 (p=0.84)				
400mg daily	4	13	5 (1.46)	4 (1.59)	1.03 (0.14 – 7.28)
200mg daily	5	12	7 (1.39)	2 (0.60)	2.29 (0.31 – 16.79)
100mg daily	3	13	3 (0.55)	3 (1.04)	0.49 (0.04 – 6.69)
Any dose	**9**		**15 (1.01)**	**7 (1.05)**	**1.02 (0.37 – 2.83) p=1.0**

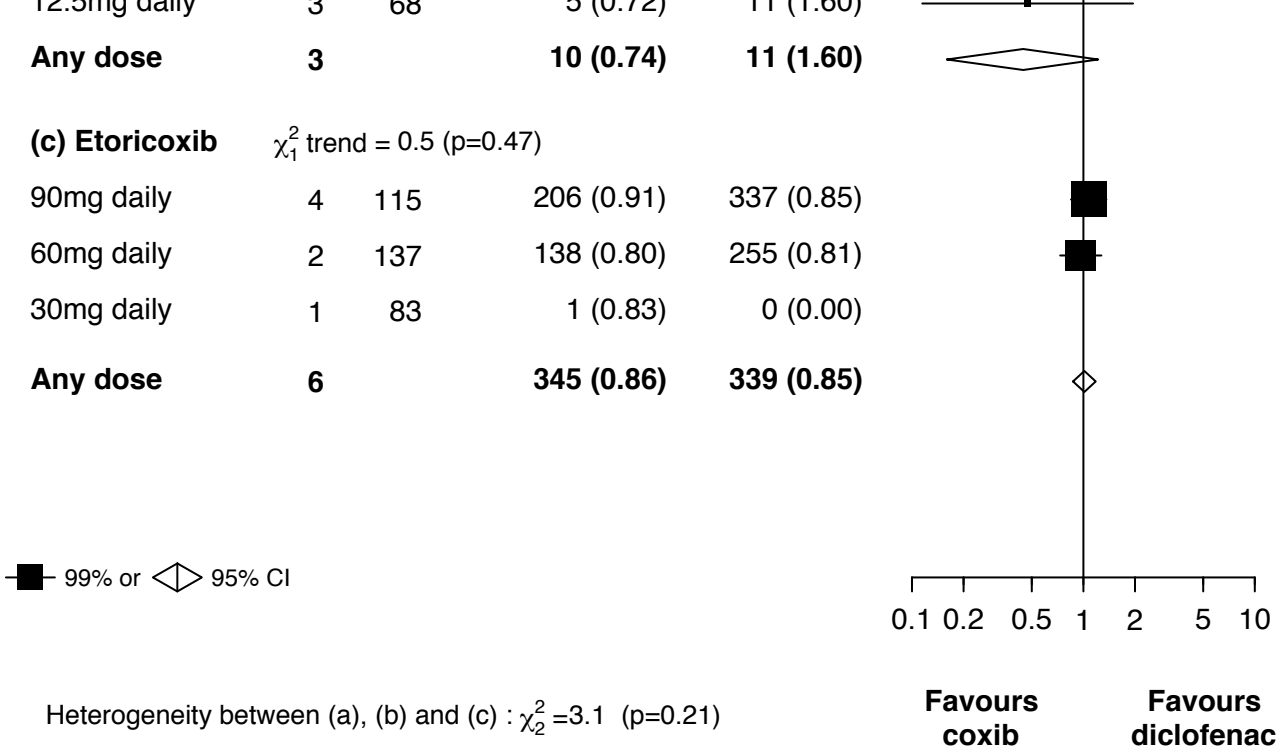


Heterogeneity between (a), (b), (c) and (d) : χ^2_3 =0.9 (p=0.82)

* Number of comparisons with at least one event

Webfigure 16: Effect of different coxib regimens on major vascular events, by dose: trials of a coxib vs diclofenac

Dose	No.*	Mean FU (weeks)	Events (% pa) Allocated coxib	Events (% pa) Allocated diclofenac	Rate ratio (RR) (direct evidence)
(a) Celecoxib	χ^2_1 trend = 0.0 (p=0.94)				
800mg daily	1	28	11 (0.97)	12 (1.12)	0.87 (0.27 – 2.78)
400mg daily	4	12	7 (0.73)	7 (0.73)	1.00 (0.22 – 4.59)
200mg daily	5	15	13 (1.09)	15 (1.23)	0.90 (0.32 – 2.55)
Any dose	**8**		**31 (0.95)**	**28 (1.12)**	**0.94 (0.54 – 1.63) p=0.71**
(b) Rofecoxib	χ^2_1 trend = 0.0 (p=0.93)				
25mg daily	3	67	5 (0.75)	11 (1.60)	0.50 (0.12 – 2.09)
12.5mg daily	3	68	5 (0.72)	11 (1.60)	0.47 (0.11 – 1.95)
Any dose	**3**		**10 (0.74)**	**11 (1.60)**	**0.45 (0.16 – 1.22) p=0.0472**
(c) Etoricoxib	χ^2_1 trend = 0.5 (p=0.47)				
90mg daily	4	115	206 (0.91)	337 (0.85)	1.07 (0.85 – 1.36)
60mg daily	2	137	138 (0.80)	255 (0.81)	0.97 (0.73 – 1.27)
30mg daily	1	83	1 (0.83)	0 (0.00)	
Any dose	**6**		**345 (0.86)**	**339 (0.85)**	**1.01 (0.87 – 1.18) p=0.90**

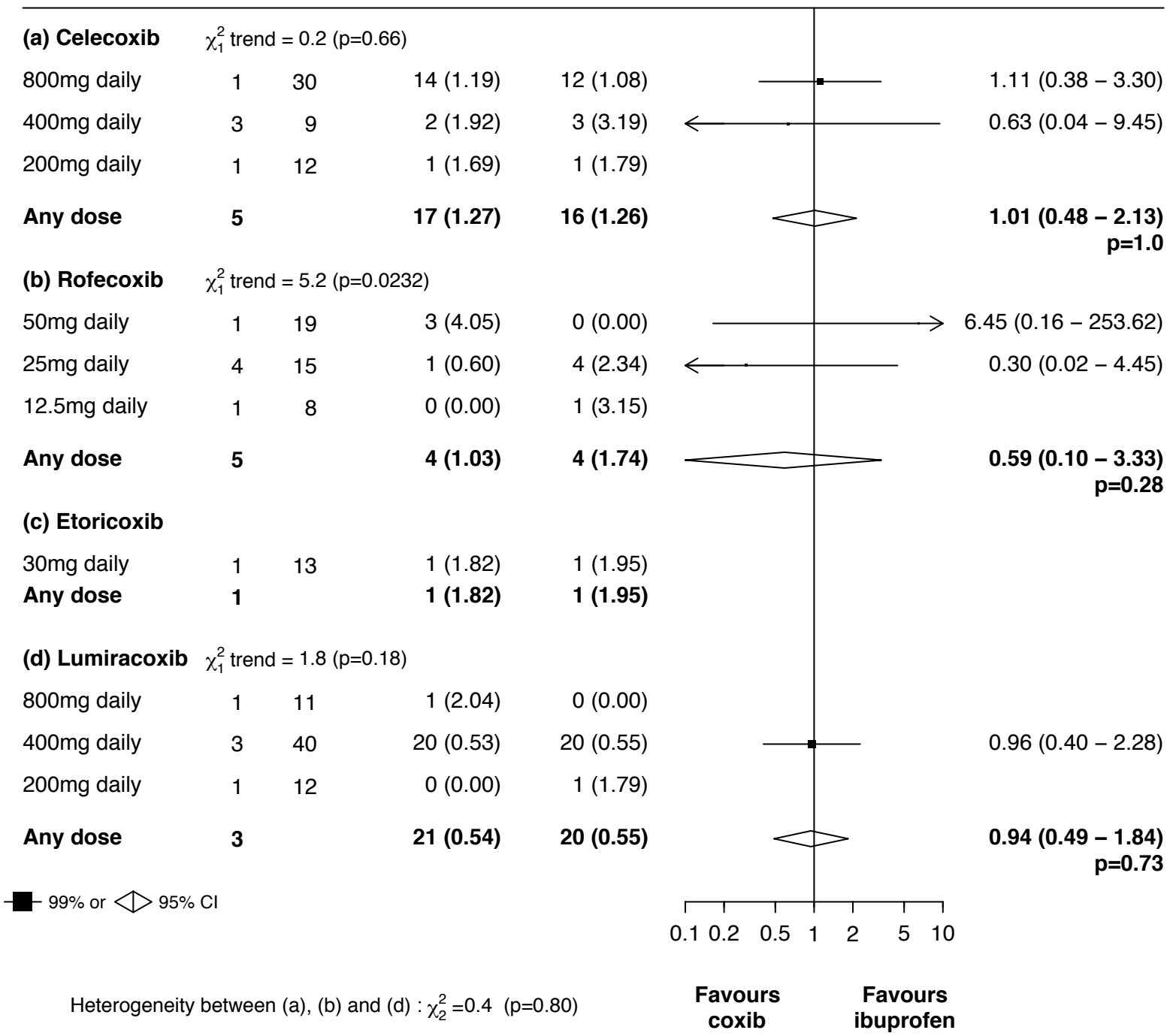


Heterogeneity between (a), (b) and (c) : χ^2_2 =3.1 (p=0.21)

* Number of comparisons with at least one event

Webfigure 17: Effect of different coxib regimens on major vascular events, by dose: trials of a coxib vs ibuprofen

Dose	No.*	Mean FU (weeks)	Events (% pa) Allocated coxib	Events (% pa) Allocated ibuprofen	Rate ratio (RR) (direct evidence)
(a) Celecoxib	χ^2_1 trend = 0.2 (p=0.66)				
800mg daily	1	30	14 (1.19)	12 (1.08)	1.11 (0.38 – 3.30)
400mg daily	3	9	2 (1.92)	3 (3.19)	0.63 (0.04 – 9.45)
200mg daily	1	12	1 (1.69)	1 (1.79)	
Any dose	**5**		**17 (1.27)**	**16 (1.26)**	**1.01 (0.48 – 2.13) p=1.0**
(b) Rofecoxib	χ^2_1 trend = 5.2 (p=0.0232)				
50mg daily	1	19	3 (4.05)	0 (0.00)	6.45 (0.16 – 253.62)
25mg daily	4	15	1 (0.60)	4 (2.34)	0.30 (0.02 – 4.45)
12.5mg daily	1	8	0 (0.00)	1 (3.15)	
Any dose	**5**		**4 (1.03)**	**4 (1.74)**	**0.59 (0.10 – 3.33) p=0.28**
(c) Etoricoxib					
30mg daily	1	13	1 (1.82)	1 (1.95)	
Any dose	**1**		**1 (1.82)**	**1 (1.95)**	
(d) Lumiracoxib	χ^2_1 trend = 1.8 (p=0.18)				
800mg daily	1	11	1 (2.04)	0 (0.00)	
400mg daily	3	40	20 (0.53)	20 (0.55)	0.96 (0.40 – 2.28)
200mg daily	1	12	0 (0.00)	1 (1.79)	
Any dose	**3**		**21 (0.54)**	**20 (0.55)**	**0.94 (0.49 – 1.84) p=0.73**

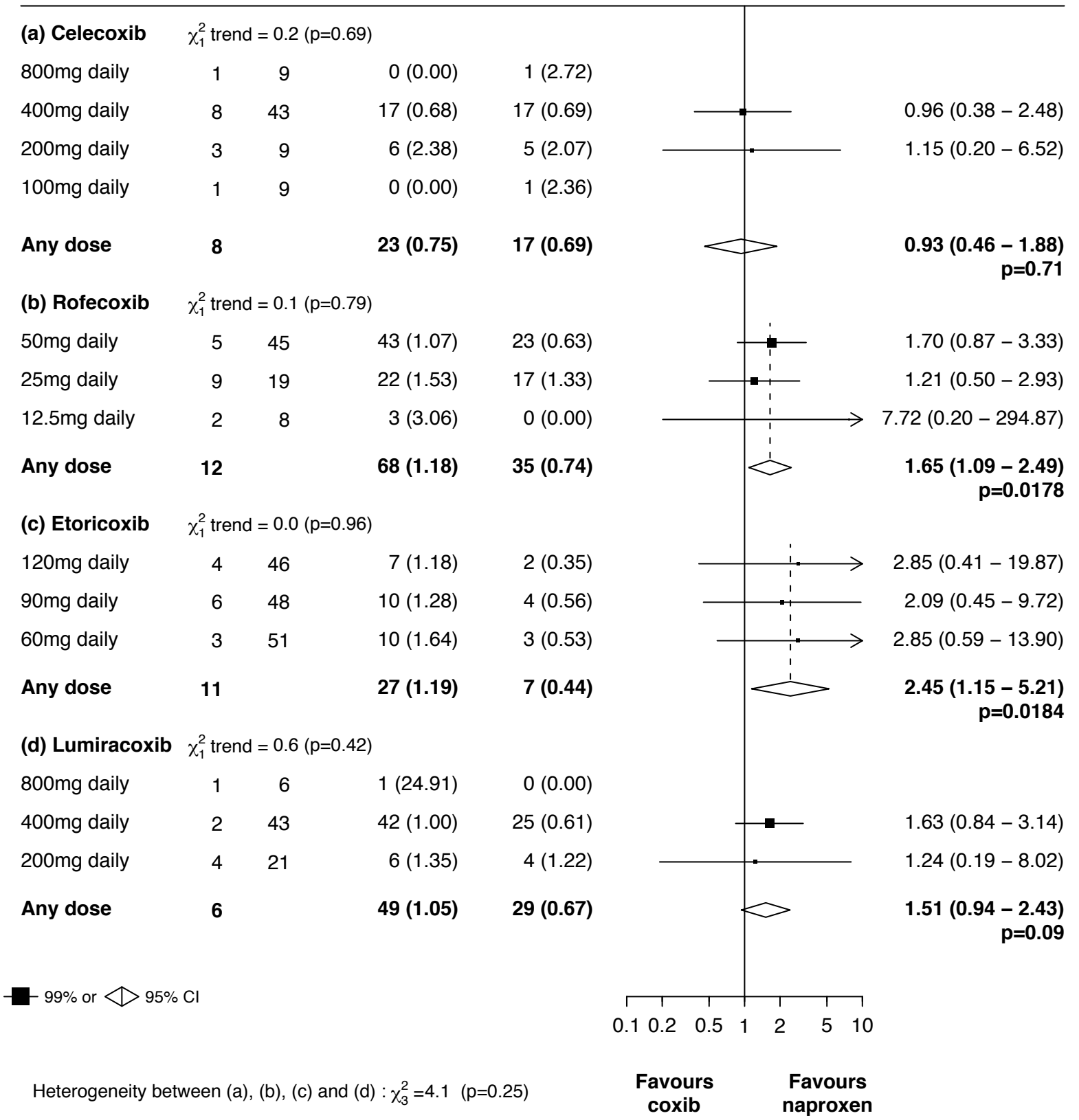


Heterogeneity between (a), (b) and (d) : χ^2_2 =0.4 (p=0.80)

* Number of comparisons with at least one event

Webfigure 18: Effect of different coxib regimens on major vascular events, by dose: trials of a coxib vs naproxen

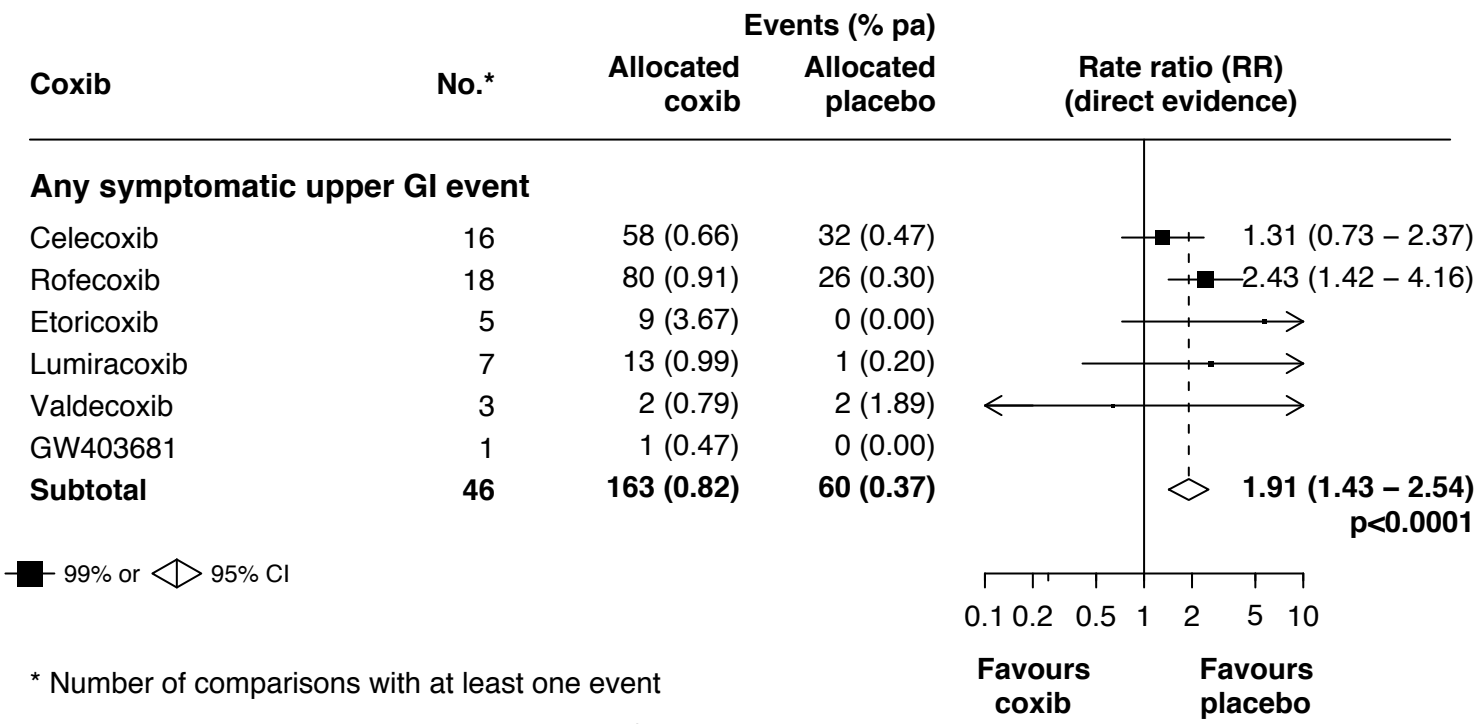
Dose	No.*	Mean FU (weeks)	Events (% pa) Allocated coxib	Events (% pa) Allocated naproxen	Rate ratio (RR) (direct evidence)
(a) Celecoxib	χ^2_1 trend = 0.2 (p=0.69)				
800mg daily	1	9	0 (0.00)	1 (2.72)	
400mg daily	8	43	17 (0.68)	17 (0.69)	0.96 (0.38 – 2.48)
200mg daily	3	9	6 (2.38)	5 (2.07)	1.15 (0.20 – 6.52)
100mg daily	1	9	0 (0.00)	1 (2.36)	
Any dose	**8**		**23 (0.75)**	**17 (0.69)**	**0.93 (0.46 – 1.88) p=0.71**
(b) Rofecoxib	χ^2_1 trend = 0.1 (p=0.79)				
50mg daily	5	45	43 (1.07)	23 (0.63)	1.70 (0.87 – 3.33)
25mg daily	9	19	22 (1.53)	17 (1.33)	1.21 (0.50 – 2.93)
12.5mg daily	2	8	3 (3.06)	0 (0.00)	7.72 (0.20 – 294.87)
Any dose	**12**		**68 (1.18)**	**35 (0.74)**	**1.65 (1.09 – 2.49) p=0.0178**
(c) Etoricoxib	χ^2_1 trend = 0.0 (p=0.96)				
120mg daily	4	46	7 (1.18)	2 (0.35)	2.85 (0.41 – 19.87)
90mg daily	6	48	10 (1.28)	4 (0.56)	2.09 (0.45 – 9.72)
60mg daily	3	51	10 (1.64)	3 (0.53)	2.85 (0.59 – 13.90)
Any dose	**11**		**27 (1.19)**	**7 (0.44)**	**2.45 (1.15 – 5.21) p=0.0184**
(d) Lumiracoxib	χ^2_1 trend = 0.6 (p=0.42)				
800mg daily	1	6	1 (24.91)	0 (0.00)	
400mg daily	2	43	42 (1.00)	25 (0.61)	1.63 (0.84 – 3.14)
200mg daily	4	21	6 (1.35)	4 (1.22)	1.24 (0.19 – 8.02)
Any dose	**6**		**49 (1.05)**	**29 (0.67)**	**1.51 (0.94 – 2.43) p=0.09**



Heterogeneity between (a), (b), (c) and (d) : χ^2_3 =4.1 (p=0.25)

* Number of comparisons with at least one event

Webfigure 19: Effect of coxib therapy on any symptomatic upper GI event, by type of coxib

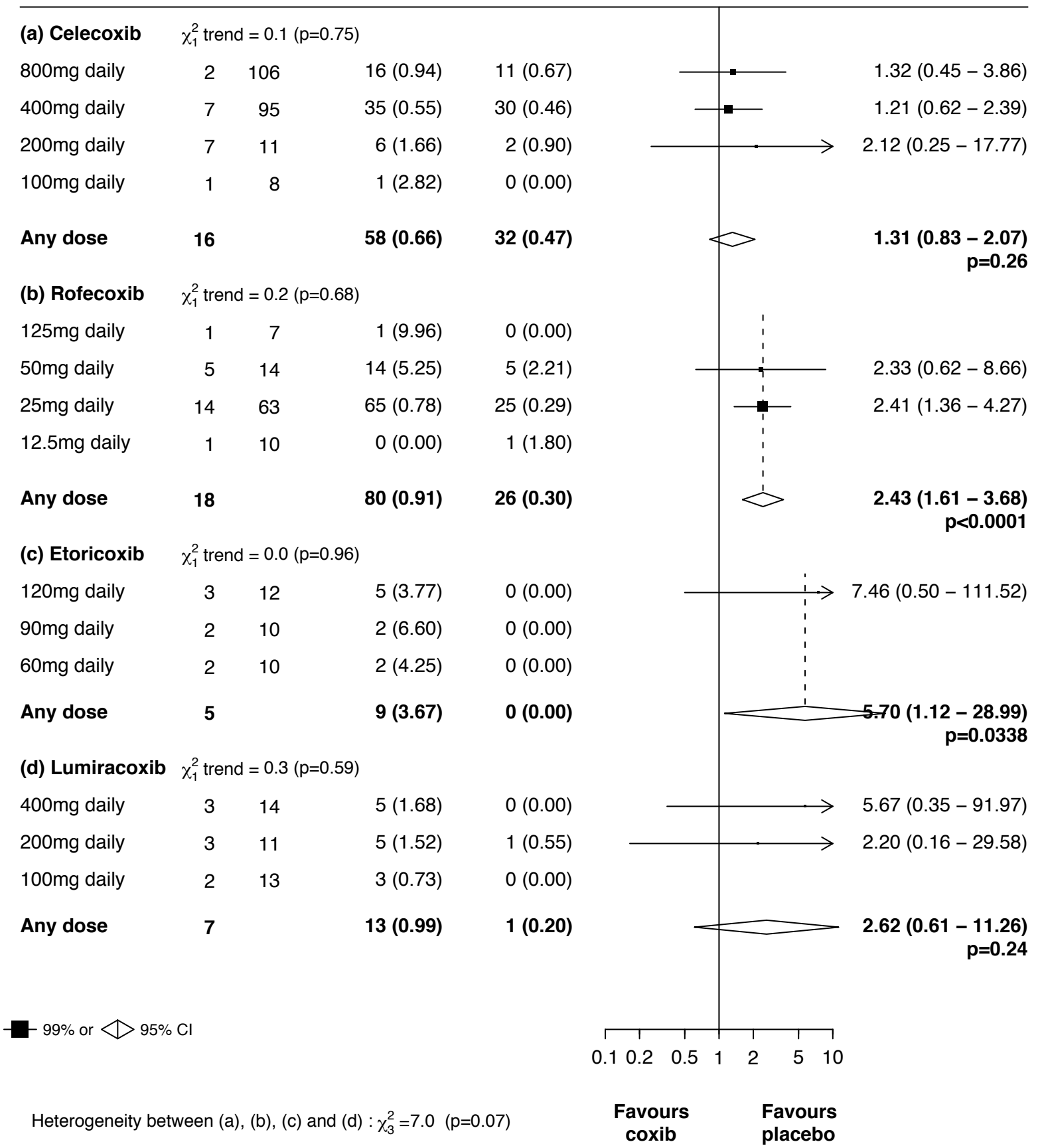


* Number of comparisons with at least one event

Heterogeneity between celecoxib and rofecoxib: χ^2_1 =4.3 (p=0.0380)

Webfigure 20: Effect of different coxib regimens on any symptomatic upper GI event, by dose: trials of a coxib vs placebo

Dose	No.*	Mean FU (weeks)	Events (% pa) Allocated coxib	Events (% pa) Allocated placebo	Rate ratio (RR) (direct evidence)
(a) Celecoxib	χ^2_1 trend = 0.1 (p=0.75)				
800mg daily	2	106	16 (0.94)	11 (0.67)	1.32 (0.45 – 3.86)
400mg daily	7	95	35 (0.55)	30 (0.46)	1.21 (0.62 – 2.39)
200mg daily	7	11	6 (1.66)	2 (0.90)	2.12 (0.25 – 17.77)
100mg daily	1	8	1 (2.82)	0 (0.00)	
Any dose	**16**		**58 (0.66)**	**32 (0.47)**	**1.31 (0.83 – 2.07) p=0.26**
(b) Rofecoxib	χ^2_1 trend = 0.2 (p=0.68)				
125mg daily	1	7	1 (9.96)	0 (0.00)	
50mg daily	5	14	14 (5.25)	5 (2.21)	2.33 (0.62 – 8.66)
25mg daily	14	63	65 (0.78)	25 (0.29)	2.41 (1.36 – 4.27)
12.5mg daily	1	10	0 (0.00)	1 (1.80)	
Any dose	**18**		**80 (0.91)**	**26 (0.30)**	**2.43 (1.61 – 3.68) p<0.0001**
(c) Etoricoxib	χ^2_1 trend = 0.0 (p=0.96)				
120mg daily	3	12	5 (3.77)	0 (0.00)	7.46 (0.50 – 111.52)
90mg daily	2	10	2 (6.60)	0 (0.00)	
60mg daily	2	10	2 (4.25)	0 (0.00)	
Any dose	**5**		**9 (3.67)**	**0 (0.00)**	**5.70 (1.12 – 28.99) p=0.0338**
(d) Lumiracoxib	χ^2_1 trend = 0.3 (p=0.59)				
400mg daily	3	14	5 (1.68)	0 (0.00)	5.67 (0.35 – 91.97)
200mg daily	3	11	5 (1.52)	1 (0.55)	2.20 (0.16 – 29.58)
100mg daily	2	13	3 (0.73)	0 (0.00)	
Any dose	**7**		**13 (0.99)**	**1 (0.20)**	**2.62 (0.61 – 11.26) p=0.24**

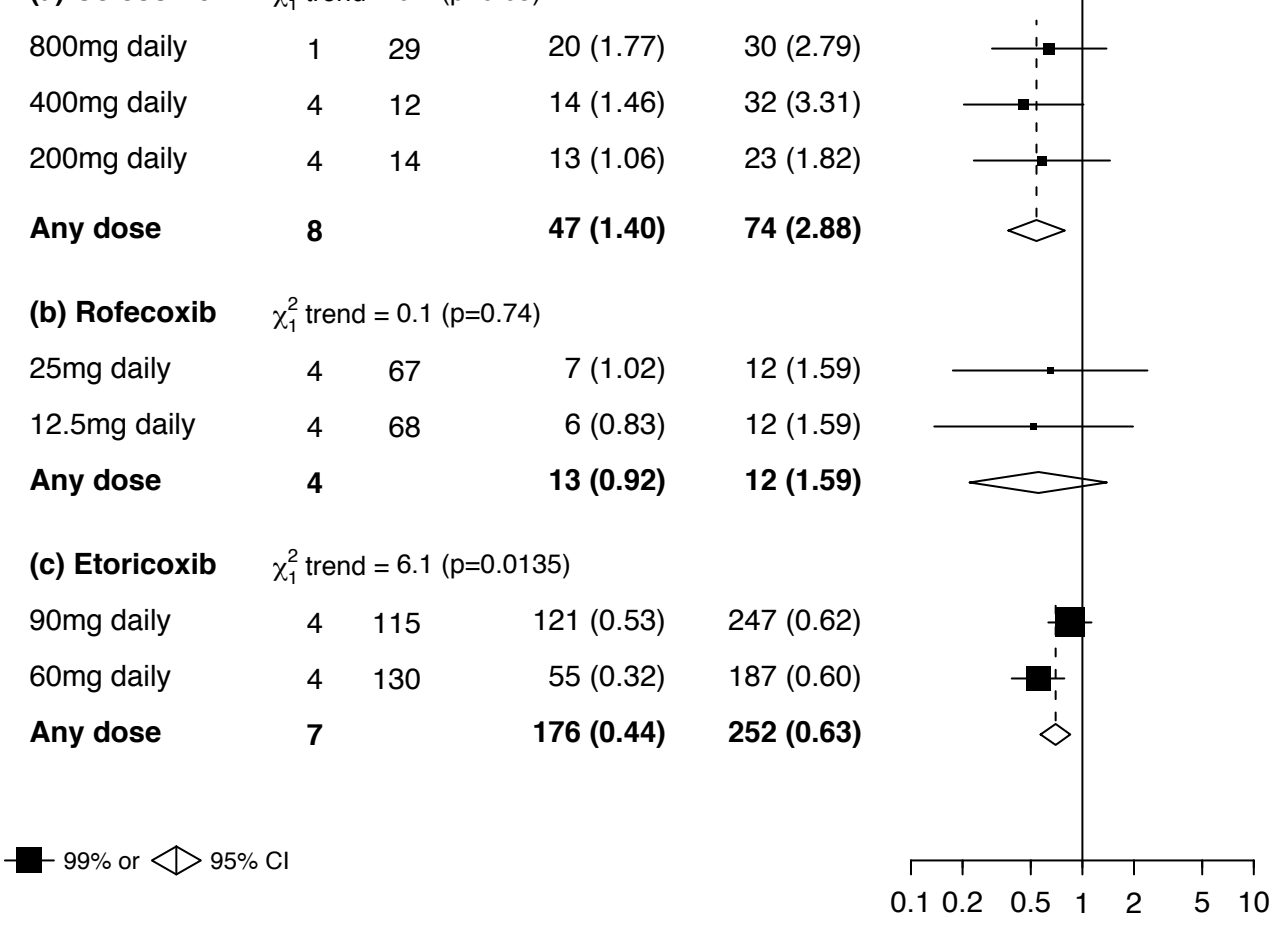


Heterogeneity between (a), (b), (c) and (d) : χ^2_3 =7.0 (p=0.07)

* Number of comparisons with at least one event

Webfigure 21: Effect of different coxib regimens on any symptomatic upper GI event, by dose: trials of a coxib vs diclofenac

Dose	No.*	Mean FU (weeks)	Events (% pa) Allocated coxib	Events (% pa) Allocated diclofenac	Rate ratio (RR) (direct evidence)
(a) Celecoxib	χ^2_1 trend = 0.2 (p=0.65)				
800mg daily	1	29	20 (1.77)	30 (2.79)	0.64 (0.30 – 1.38)
400mg daily	4	12	14 (1.46)	32 (3.31)	0.45 (0.20 – 1.01)
200mg daily	4	14	13 (1.06)	23 (1.82)	0.58 (0.23 – 1.45)
Any dose	**8**		**47 (1.40)**	**74 (2.88)**	**0.54 (0.37 – 0.79) p=0.0006**
(b) Rofecoxib	χ^2_1 trend = 0.1 (p=0.74)				
25mg daily	4	67	7 (1.02)	12 (1.59)	0.65 (0.18 – 2.40)
12.5mg daily	4	68	6 (0.83)	12 (1.59)	0.52 (0.14 – 1.97)
Any dose	**4**		**13 (0.92)**	**12 (1.59)**	**0.55 (0.22 – 1.39) p=0.11**
(c) Etoricoxib	χ^2_1 trend = 6.1 (p=0.0135)				
90mg daily	4	115	121 (0.53)	247 (0.62)	0.85 (0.63 – 1.13)
60mg daily	4	130	55 (0.32)	187 (0.60)	0.55 (0.39 – 0.78)
Any dose	**7**		**176 (0.44)**	**252 (0.63)**	**0.70 (0.57 – 0.85) p=0.0002**

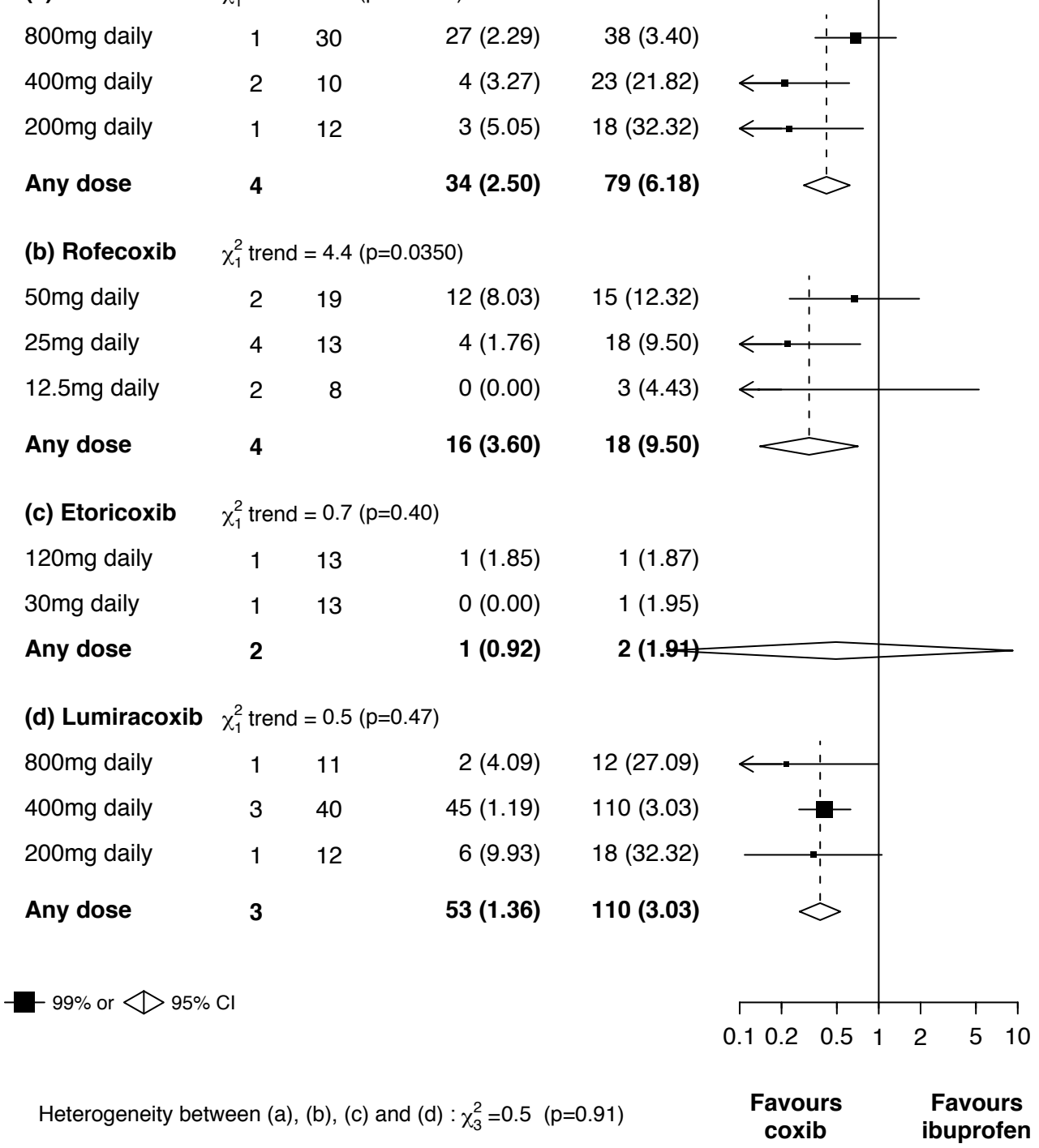


Heterogeneity between (a), (b) and (c) : χ^2_2 =1.7 (p=0.43)

* Number of comparisons with at least one event

Webfigure 22: Effect of different coxib regimens on any symptomatic upper GI event, by dose: trials of a coxib vs ibuprofen

Dose	No.*	Mean FU (weeks)	Events (% pa) Allocated coxib	Events (% pa) Allocated ibuprofen	Rate ratio (RR) (direct evidence)
(a) Celecoxib	χ^2_1 trend = 8.1 (p=0.0043)				
800mg daily	1	30	27 (2.29)	38 (3.40)	0.68 (0.35 – 1.33)
400mg daily	2	10	4 (3.27)	23 (21.82)	0.21 (0.07 – 0.61)
200mg daily	1	12	3 (5.05)	18 (32.32)	0.23 (0.07 – 0.77)
Any dose	**4**		**34 (2.50)**	**79 (6.18)**	**0.42 (0.29 – 0.62) p<0.0001**
(b) Rofecoxib	χ^2_1 trend = 4.4 (p=0.0350)				
50mg daily	2	19	12 (8.03)	15 (12.32)	0.67 (0.23 – 1.96)
25mg daily	4	13	4 (1.76)	18 (9.50)	0.22 (0.07 – 0.74)
12.5mg daily	2	8	0 (0.00)	3 (4.43)	0.14 (0.00 – 5.26)
Any dose	**4**		**16 (3.60)**	**18 (9.50)**	**0.32 (0.14 – 0.71) p=0.0012**
(c) Etoricoxib	χ^2_1 trend = 0.7 (p=0.40)				
120mg daily	1	13	1 (1.85)	1 (1.87)	
30mg daily	1	13	0 (0.00)	1 (1.95)	
Any dose	**2**		**1 (0.92)**	**2 (1.91)**	**0.49 (0.03 – 9.23) p=0.23**
(d) Lumiracoxib	χ^2_1 trend = 0.5 (p=0.47)				
800mg daily	1	11	2 (4.09)	12 (27.09)	0.22 (0.05 – 0.99)
400mg daily	3	40	45 (1.19)	110 (3.03)	0.41 (0.27 – 0.63)
200mg daily	1	12	6 (9.93)	18 (32.32)	0.34 (0.11 – 1.05)
Any dose	**3**		**53 (1.36)**	**110 (3.03)**	**0.38 (0.27 – 0.53) p<0.0001**

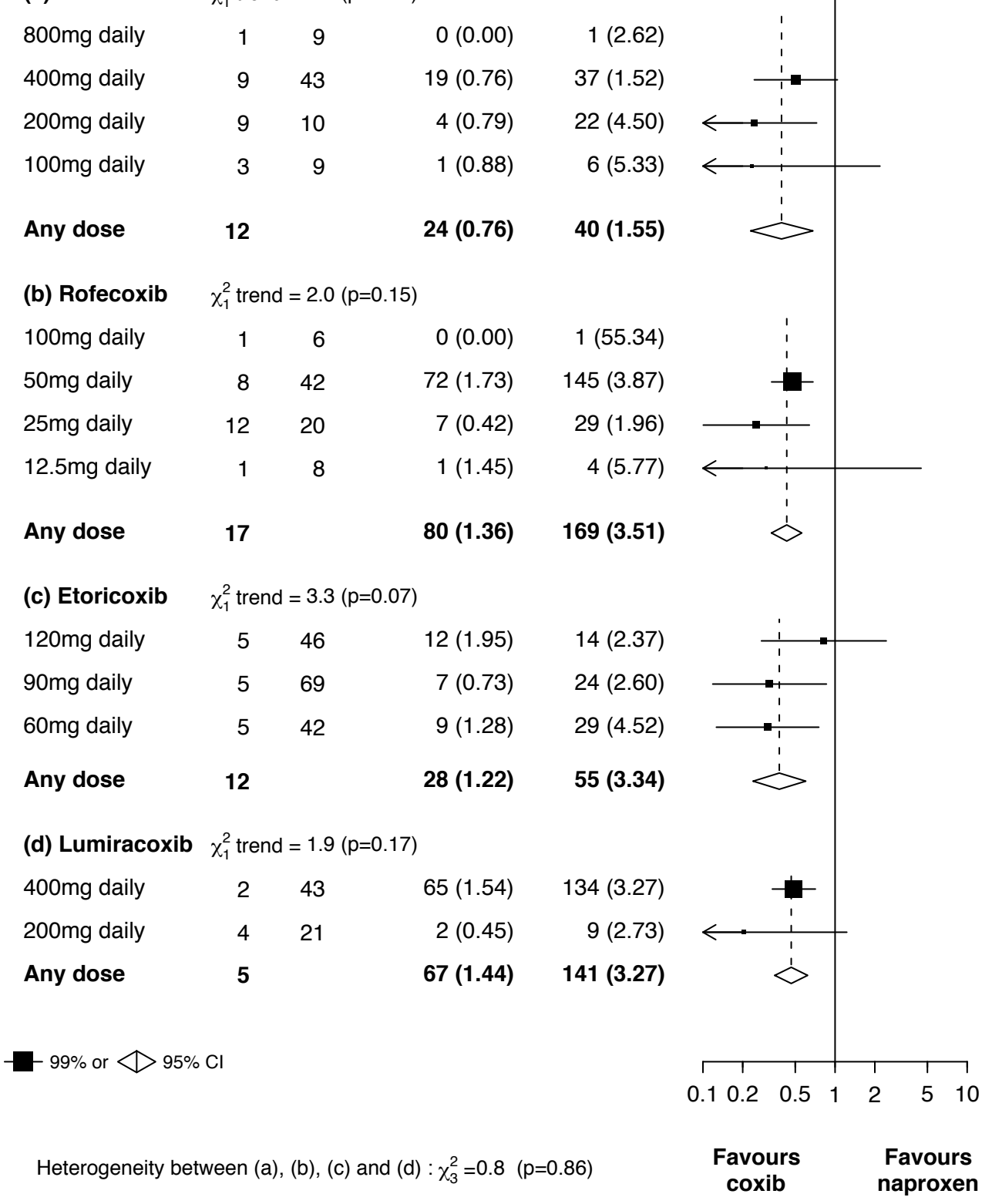


Heterogeneity between (a), (b), (c) and (d) : χ^2_3 =0.5 (p=0.91)

* Number of comparisons with at least one event

Webfigure 23: Effect of different coxib regimens on any symptomatic upper GI event, by dose: trials of a coxib vs naproxen

Dose	No.*	Mean FU (weeks)	Events (% pa) Allocated coxib	Events (% pa) Allocated naproxen	Rate ratio (RR) (direct evidence)
(a) Celecoxib	χ^2_1 trend = 1.8 (p=0.17)				
800mg daily	1	9	0 (0.00)	1 (2.62)	
400mg daily	9	43	19 (0.76)	37 (1.52)	0.50 (0.24 – 1.04)
200mg daily	9	10	4 (0.79)	22 (4.50)	0.24 (0.08 – 0.73)
100mg daily	3	9	1 (0.88)	6 (5.33)	0.23 (0.03 – 2.19)
Any dose	**12**		**24 (0.76)**	**40 (1.55)**	**0.39 (0.23 – 0.68) p=0.0002**
(b) Rofecoxib	χ^2_1 trend = 2.0 (p=0.15)				
100mg daily	1	6	0 (0.00)	1 (55.34)	
50mg daily	8	42	72 (1.73)	145 (3.87)	0.47 (0.33 – 0.68)
25mg daily	12	20	7 (0.42)	29 (1.96)	0.25 (0.10 – 0.64)
12.5mg daily	1	8	1 (1.45)	4 (5.77)	0.30 (0.02 – 4.48)
Any dose	**17**		**80 (1.36)**	**169 (3.51)**	**0.43 (0.33 – 0.56) p<0.0001**
(c) Etoricoxib	χ^2_1 trend = 3.3 (p=0.07)				
120mg daily	5	46	12 (1.95)	14 (2.37)	0.82 (0.28 – 2.44)
90mg daily	5	69	7 (0.73)	24 (2.60)	0.32 (0.12 – 0.86)
60mg daily	5	42	9 (1.28)	29 (4.52)	0.31 (0.13 – 0.75)
Any dose	**12**		**28 (1.22)**	**55 (3.34)**	**0.38 (0.24 – 0.60) p<0.0001**
(d) Lumiracoxib	χ^2_1 trend = 1.9 (p=0.17)				
400mg daily	2	43	65 (1.54)	134 (3.27)	0.49 (0.34 – 0.71)
200mg daily	4	21	2 (0.45)	9 (2.73)	0.20 (0.03 – 1.23)
Any dose	**5**		**67 (1.44)**	**141 (3.27)**	**0.47 (0.35 – 0.62) p<0.0001**



Heterogeneity between (a), (b), (c) and (d) : χ^2_3 =0.8 (p=0.86)

* Number of comparisons with at least one event

Electronic Search Strategy

Medline (1946 -1 January 2009) and EMBASE (1974 - 1 January 2009) were searched (using OVIDsp) for all trial publications (including protocols, results papers, abstracts, conference proceedings and reviews) by adapting the first Cochrane Search Strategy design (Dickersin 1994[1]). No language restrictions were applied to the search. Eligible studies were randomised trials of at least four weeks' daily treatment in which there was 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. All trial participants were at least 18 years old at the point of randomization.

1. randomized controlled trial.mp. OR Randomized Controlled Trial/
2. controlled clinical trial.mp. OR Controlled Clinical Trial/
3. random allocation.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
4. double-blind method.mp. OR Double-Blind Method/
5. single-blind method.mp. OR Single-Blind Method/
6. clinical trial.mp. OR Clinical Trial/
7. clinical trials.mp. OR Clinical Trial/
8. ((singl$ OR doubl$ OR trebl$ OR tripl$) adj (blind$ OR mask$)).ti.
9. ((singl$ OR doubl$ OR trebl$ OR tripl$) adj (blind$ OR mask$)).ab.
10. latin square.mp.
11. placebo$1.mp.
12. random$7.mp.
13. comparative study.mp.
14. evaluation studies.mp. OR Evaluation Studies/
15. prospective studies.mp. OR Prospective Studies/
16. follow-up studies.mp.
17. cross-over studies.mp. OR Cross-Over Studies/
18. Case-Control Studies/

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

20. celecoxib.mp. OR etoricoxib.mp. OR lumiracoxib.mp. OR parecoxib.mp. OR rofecoxib.mp. OR tiracoxib.mp. OR valdecoxib.mp. OR aceclofenac.mp. OR AZD3582.mp. OR alclofenac.mp. OR apazone.mp. OR benoxaprofen.mp. OR carprofen.mp. OR diclofenac.mp. OR diflunisal.mp. OR dipyrone (metamizole).mp. OR etodolac.mp. OR fenbufen.mp. OR fenoprofen.mp. OR feprazone.mp. OR floctafenine.mp. OR flurbiprofen.mp. OR ibuprofen.mp. OR indobufen.mp. OR indomethacin.mp. OR isoxicam.mp. OR ketoprofen.mp. OR ketorolac.mp. OR lornoxicam.mp. OR meclofenamate.mp. OR meclofenamic acid.mp. OR mefenamic acid.mp. OR meloxicam.mp. OR nabumetone.mp. OR naproxen.mp. OR naproxcinod.mp. OR nimesulide.mp. OR oxyphenbutazone.mp. OR oxyprozin/oxaprozin.mp. OR phenylbutazone.mp. OR piroxicam.mp. OR pirprofen.mp. OR proquazone.mp. OR sulindac.mp. OR tenoxicam.mp. OR tiaprofenic acid.mp. OR tiroxicam.mp. OR tolfenamic acid.mp. OR tolmetin.mp.

21. 19 AND 20

Further drugs were identified during publication processing that were found to be suitable. Trials of these drugs were included: Amtolmetin, Droxicam, Fenclofenac, GW403681, Licofelone, Lonazolac, Loxoprofen, Proglumetacin and Suprofen.

In addition, www.clinicalstudyresults.org was searched and all four of the manufacturers of the different coxibs were contacted to provide information on all of their trials (both published and unpublished). To further ensure that no potentially eligible studies had been missed, reference lists of systematic reviews, meta-analyses and review articles were searched and contact was made with numerous experts in the field. Overall these searches resulted in 24,278 records to be examined, and all decisions on trial inclusion were reviewed by at least 2 authors.

1. BMJ 1994; 309 doi: http://dx.doi.org/10.1136/bmj.309.6964.1286 (Published 12 November 1994)

Statistical appendix

1. Poisson model for predicting risk of particular outcomes

For patient *i* in study *j*, let *Yij* denote the occurrence (*Yij* = 1) or otherwise (*Yij* = 0) of an outcome of interest (eg, major vascular event, upper GI ulcer) and let *Tij* denote the number of years of follow-up (ie, time to event/censoring). Poisson regression was used to model the logarithm of the expected annual event rate as follows

$$\ln\left(\frac{E(Y_{ij})}{T_{ij}}\right) = x_{ij}^{T}\beta$$

where x_{ij} is the vector of baseline characteristics for patient *i* in study *j* and β is the vector of unknown regression coefficients associated with the individual baseline characteristics. For each patient, the baseline predicted 5-year probability of the outcome was then estimated by:

$$P_{ij} = 1 - \left(1 - \exp\left(x_{ij}^{T}\hat{\beta}\right)\right)^{5}$$

Patients were then separated into three baseline risk groups (5-year risk <5%, 5%-10%, >10%) for both their predicted risk of a major vascular event and their predicted risk of a symptomatic upper gastrointestinal event.

2. Calculation of annual absolute excess risks for particular outcomes

The annual excess risk of a primary outcome per 1000 attributable to an NSAID in a patient with a given annual probability (p_0) of that outcome (in the absence of any NSAID regimen) was calculated as $1000 \times (p_1 - p_0)$, where:

$$p_1 = 1 - \frac{1 - p_0}{rp_0 + (1 - p_0)}$$

and *r* is the estimated odds ratio (approximately the same as the rate ratio for rare outcomes) for NSAID versus placebo.